

# Bilag til Medicinrådets anbefaling vedrørende acalabrutinib som monoterapi og acalabrutinib i kombination med obinutuzumab til behandling af kronisk lymfatisk leukæmi

*Vers. 1.0*



# Bilagsoversigt

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# Medicinrådets sundheds- økonomiske afrapportering

## Acalabrutinib

*Tidligere behandlede patienter med kronisk  
lymfatisk leukæmi*



## Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

## Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

### Dokumentoplysninger

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# 1. Begreber og forkortelser

<b>AIP</b>	Apotekernes indkøbspris
<b>BSA</b>	Kropsoverfladeareal
<b>CLL</b>	Kronisk lymfatisk leukæmi
<b>DKK</b>	Danske kroner
<b>DRG</b>	Diagnose Relaterede Grupper
<b>HR</b>	Hazard ratio
<b>I.V.</b>	Intravenøst
<b>KM</b>	Kaplan-Meier
<b>MAIC</b>	<i>Matching-adjusted indirect comparisons</i>
<b>NMA</b>	Netværksmetaanalyse
<b>OS</b>	Samlet overlevelse
<b>PFS</b>	Progressionsfri overlevelse
<b>PPS</b>	Post-progressions overlevelse
<b>SAIP</b>	Sygehusapotekernes indkøbspris
<b>SPC</b>	Produkters produktresuméer
<b>TTD</b>	Tid til død



## 2. Konklusion

### **Inkrementelle omkostninger og budgetkonsekvenser**

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for acalabrutinib ca. [REDACTED] DKK pr. patient sammenlignet med ibrutinib. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 4.000 DKK pr. patient. De inkrementelle omkostninger er udelukkende drevet af lægemiddelomkostningerne for acalabrutinib

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af acalabrutinib som mulig standardbehandling vil være ca. [REDACTED] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 15 mio. DKK i det femte år.





## 3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af acalabrutinib monoterapi som mulig standardbehandling til 2. linjebehandling på danske hospitaler til patienter, som har modtaget mindst én tidligere behandling (2. linje eller mere) med kronisk lymfatisk leukæmi.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca. Vi modtog ansøgningen den 30. april 2021.

Denne sundhedsøkonomiske afrapportering er den ene af to afrapporteringer tilhørende vurderingen af acalabrutinib. Den anden behandler vurderingens første fire kliniske spørgsmål.

### 3.1 Patientpopulation

Kronisk lymfatisk leukæmi (CLL) er en kræftsygdom i blodet, som opstår i kroppens B-celler og påvirker deres regulering af celledeling og celledød. Det fører til en ophobning af B-celler bl.a. i knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket.

Fagudvalget vurderer, at der er ca. 65-70 tidligere behandlede patienter med CLL om året, der kræver 2. linjebehandling. Fagudvalgets estimering af patientantal er baseret på informationer fra den landsdækkende LYFO-database, viden om tid til første tilbagefald [1–4].

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

#### 3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af acalabrutinib på baggrund af følgende kliniske spørgsmål:

*Klinisk spørgsmål 5:*

Hvilken værdi har acalabrutinib som monoterapi sammenlignet med dansk standardbehandling (ibrutinib) til 2. linjebehandling af patienter med kronisk lymfatisk leukæmi?



## 4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsminimeringsanalyse og en budgetkonsekvensanalyse. De inkrementelle omkostninger pr. patient estimeres for acalabrutinib monoterapi til tidligere behandlede patienter med CLL sammenlignet med ibrutinib.

Medicinerådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

### 4.1 Antagelser og forudsætninger for modellen

Sammenligningen af acalabrutinib med ibrutinib er lavet på baggrund af data fra studiet ELEVATE-RR, som er et non-inferiority, open-label, randomiseret, fase III-studie [5]. Studiet undersøger effekten af acalabrutinib monoterapi overfor ibrutinib hos tidligere behandlede patienter med kronisk lymfatisk leukæmi (CLL) med deletion17p eller deletion11q, der oplever behandlingskrævende relaps eller behandlingssvigt efter mindst én tidligere behandling. Jf. Medicinerådets vurderingsrapport afsnit 5.6.2, noterer fagudvalget sig, at patienterne i ELEVATE-RR alle har enten del(17p) og/eller del(11q), men fagudvalget forventer, at effekten af acalabrutinib observeret i studiet kan genfindes ved behandling af danske patienter.

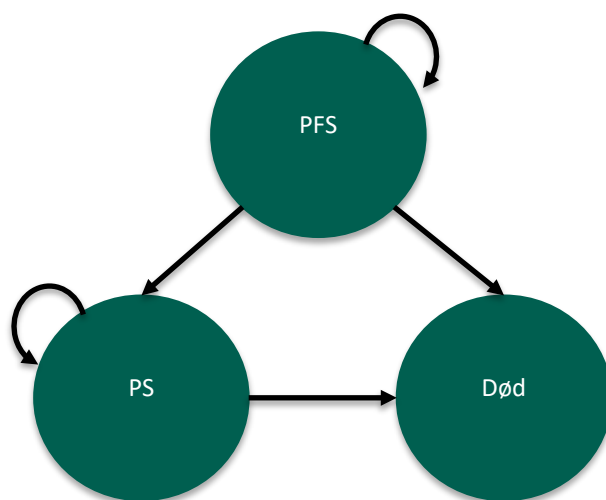
Yderligere information om sygdomsområdet kan findes i Medicinerådets vurderingsrapport.

#### 4.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival* model til at estimere omkostningerne forbundet med acalabrutinib monoterapi. Modellen består af tre sygdomsstadier, som patienten skifter mellem i takt med, at sygdommen forværres: progressionsfri overlevelse, post-progression og død. Se Figur 1 for modellens opbygning, de forskellige helbredsstadier, og hvordan patienten kan bevæge sig mellem de forskellige stadier.

Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen afhænger af sygdomsprogression, som estimeres ud fra ekstrapoleret time-to-event-data fra ansøgers anvendte studie.

Ansøger har anvendt en cykluslængde på 28 dage og *half-cycle correction*.



**Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen. PFS, progressionsfri overlevelse, PS, progredieret sygdom og død**

#### **Medicinrådets vurdering af ansøgers model**

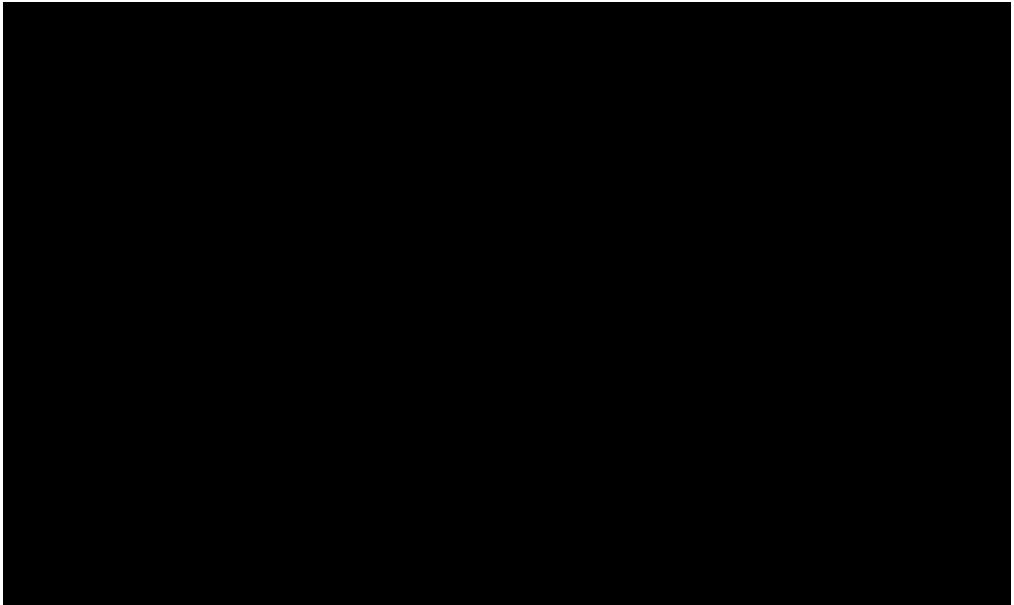
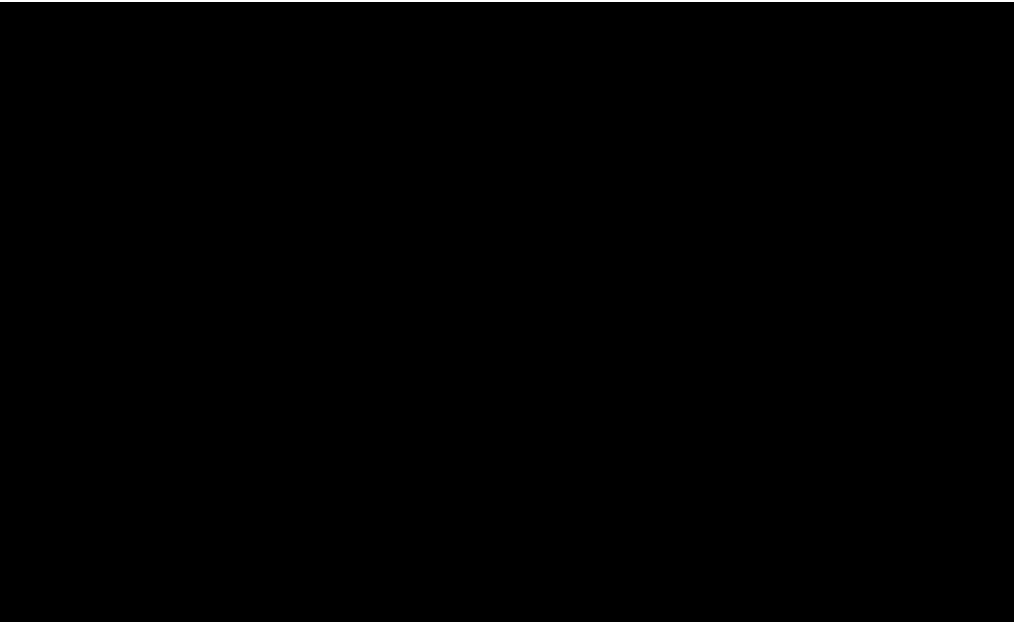
*Medicinrådet accepterer ansøgers tilgang vedr. ansøgers modeller.*

#### **4.1.2 Modelantagelser og beskrivelse for tidligere behandlet CLL-patienter**

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i ELEVATE-RR-studiet er kortere end den anvendte tidshorisont. På baggrund af ELEVATE-RR-studiet antager ansøger, at der ikke er forskel i effekt mellem acalabrutinib og ibrutinib, hvorfor ansøger vælger at poole data for begge arme.

Ansøger har anvendt den parametriske funktion generaliseret gamma til at ekstrapolere PFS for acalabrutinib og ibrutinib monoterapi, se Figur 2. For OS har ansøger valgt at ekstrapolere data med den parametriske funktion eksponentiel for acalabrutinib og ibrutinib monoterapi, se Figur 3. Disse parametriske funktioner er valgt, da de, jf. AIC- og BIC-værdierne, har det bedste statistiske fit.

Ansøger antager, at behandlingsvarighed for acalabrutinib og ibrutinib monoterapi er lig tiden til progression fra ELEVATE-RR-studiet. Ansøger argumenterer for, at dette stemmer overens med dansk klinisk praksis, fordi progression er et udtryk for, at behandlingen ikke virker, og man vil derfor skifte patienten til en anden behandling som følge af progression.



#### **Medicinerådets vurdering af ansøgers modelantagelser**

Fagudvalget accepterer ansøgers antagelser omkring ingen forskel i effekt mellem acalabrutinib og ibrutinib. Fagudvalget vurderer, at ansøgers valg af ekstrapolering for PFS underestimerer den gennemsnitlige tid til PFS, som observeret i dansk klinisk praksis. Fagudvalget bemærker, at patientpopulationen fra ELEVATE-RR er behæftet med en dårligere prognose end de patienter i dansk klinisk praksis. Fagudvalget vurderer, at den log-logistiske funktion repræsenterer patienterne set i dansk klinisk praksis i højere grad, hvorfor Medicinerådet anvender denne ekstrapolering i sin hovedanalyse. Fagudvalget vurderer samtidig, at den log-normale ekstrapolering også kunne repræsentere patienterne i dansk klinisk praksis, hvorfor Medicinerådet vælger at præsentere en følsomhedsanalyse med den log-normale funktion.

Fagudvalget vurderer, at ansøgers valg af ekstrapolering for OS repræsenterer dansk klinisk praksis, hvorfor Medicinerådet accepterer ansøgers valg af ekstrapolering.



Medicinerådet vælger at foretage to følsomhedsanalyser for valg af funktion til ekstrapolering af OS, for at undersøge betydningen det har på de samlede omkostninger. Medicinerådet præsenterer derfor to følsomhedsanalyser med hhv. Gompertz-funktionen og den log-logistiske funktion.

Medicinerådet accepterer ansøgers estimater for behandlingsvarighed. Estimaterne er præsenteret i Tabel 1.

**Tabel 1. Gennemsnitlig tid i behandling og i stadierne PFS og OS**

Behandling	Behandlingsvarighed [år]	PFS [år]	OS [år]
Acalabrutinib	5,1	5,1	10,9
Ibrutinib	5,1	5,1	10,9

\*Progressionsfri overlevelse (PFS), samlet overlevelse (OS).

*Medicinerådet accepterer ansøgers tilgang vedr. modelantagelser og ændrer valget af ekstrapolering for PFS til den log-logistiske og foretager en følsomhedsanalyse med den log-normale funktion og to følsomhedsanalyser, hvor hhv. Gompertz og den log-logistiske ekstrapolering anvendes.*

#### 4.1.3 Analyseperspektiv

I overensstemmelse med Medicinerådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 30 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

#### Medicinerådets vurdering af ansøgers analyseperspektiv

Medicinerådet accepterer ansøgers valgte tidshorisont. Tidshorisonten er valgt, da ansøger argumenterer, at den gennemsnitlige behandlingslængde (af både 1., 2. og 3. linjebehandling) ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med acalabrutinib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem acalabrutinib og komparatorer set over en tidshorisont på 30 år.

*Medicinerådet accepterer ansøgers valg vedr. analyseperspektiv.*

## 4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af acalabrutinib monoterapi sammenlignet med ibrutinib. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, efterfølgende behandling og patientomkostninger. Medicinerådet vælger at ekskludere omkostninger til administration, monitorering, efterfølgende behandling og patientomkostninger i Medicinerådets hovedanalyse, fordi formålet med analysen er at estimere de inkrementelle omkostninger pr. patient ved behandling med acalabrutinib og ibrutinib,



og da patientomkostninger og efterfølgende behandlingsforløb vurderes at være ens for de to lægemidler ekskluderes omkostningerne hertil.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne akkumuleres for hver cyklus, patienten befinder sig i et givent stadie.

#### 4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren*, estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive lægemidlers produktresuméer (SPC'er).

- Acalabrutinib administreres oralt to gange dagligt af 100 mg.
- Ibrutinib administreres oralt en gang dagligt af 420 mg.

Ansøger har ikke inkluderet spild i deres hovedanalyse.

#### Medicinerådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger

Medicinerådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 2.

**Tabel 2. Anvendte lægemiddelpriser, SAIP (september, 2021)**

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Acalabrutinib	100 mg	60 stk.	■	Amgros
Ibrutinib	420 mg	28 stk.	■	Amgros

*Medicinerådet accepterer ansøgers valg vedr. lægemiddelomkostninger.*

#### 4.2.2 Hospitalsomkostninger

Til beregning af hospitalsomkostningerne har ansøger inkluderet omkostninger forbundet med lægemiddeladministration, monitorering og bivirkninger.

Medicinerådet vælger at ekskludere omkostninger forbundet med lægemiddeladministration og monitorering i Medicinerådets hovedanalyse, da lægemiddeladministration og monitorering antages at være ens ved behandling med acalabrutinib og ibrutinib. Medicinerådet inkluderer derfor omkostninger forbundet med bivirkninger i deres hovedanalyse.

#### Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger. De benytter frekvenser for uønskede hændelser (AE) af grad  $\geq 3$  med en forekomst på mindst 2 %. Enhedsomkostningerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på 2021 DRG-takster, hvor AE enten behandles ambulant eller via indlæggelse.



Ansøger anvender de rapporterede bivirkningsfrekvenser fra ELEVATE-RR-studiet for både acalabrutinib og ibrutinib og anvender en fordeling mellem indlæggelse og ambulante behandling til estimering af behandling for de rapporterede bivirkninger.

#### **Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger**

Medicinrådet accepterer ansøgers antagelser vedr. bivirkningsfrekvenser fra ELEVATE-RR, se Tabel 11. Fagudvalget vurderer, at fordelingen mellem indlæggelse og ambulante behandling for anæmi bør være 5 % for indlæggelse og 95 % for ambulante behandling. Derfor ændrer Medicinrådet fordelingen mellem indlæggelse og ambulante behandling for anæmi, se Tabel 12. Medicinrådet vælger at opdatere ansøgers anvendte DRG 2021-takster til DRG 2022-takster

*Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ændrer fordelingen mellem indlæggelse og ambulante behandling for anæmi og opdaterer anvendte DRG-takster.*

### 4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en lang række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Ansøger har udarbejdet de samme typer følsomhedsanalyser for hvert klinisk spørgsmål. Ansøger har undersøgt for følsomheden for administrations-, monitorerings-, bivirknings- og patientomkostningerne  $\pm 20\%$ , men da det vurderes at have mindre betydning for de samlede omkostninger, vælger Medicinrådet ikke at præsentere det. I stedet præsenteres de følsomhedsanalyser med størst indflydelse på resultaterne, se Tabel 3:

**Tabel 3. Følsomhedsanalyser og beskrivelse**

Følsomhedsanalyse	Beskrivelse
Diskonteringsrente	Ændrer diskonteringsrenten $\pm 20\%$
DRG-Takst	Ændrer omkostningsestimaterne for alle DRG-takster anvendt i analyse
Behandlingsvarighed efterfølgende behandling	Ændrer behandlingsvarigheden for efterfølgende behandling
Pris for acalabrutinib	Ændrer prisen $\pm 20\%$

#### **Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser**

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser vedr. diskonteringsrenten, DRG-takster, behandlingsvarighed for efterfølgende behandling og prisen for acalabrutinib, fordi Medicinrådet vurderer, at følsomhedsanalyserne ikke repræsenterer dansk klinisk praksis. I stedet vælger Medicinrådet at udarbejde egne følsomhedsanalyser. Medicinrådet præsenterer en følsomhedsanalyse for valg af



ekstrapolering ved PFS, hvor den log-normale ekstrapolering anvendes frem for den log-logistiske ekstrapolering. Medicinrådet præsenterer yderligere to følsomhedsanalyser for valg af ekstrapolering ved OS, hvor hhv. Gompertz og den log-logistiske ekstrapolering anvendes i stedet for den eksponentielle.

*Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, men præsenterer følsomhedsanalyser for både PFS og OS.*

## 4.4 Opsummering af basisantagelser

I Tabel 4 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

**Tabel 4. Basisantagelser for ansøgers og Medicinrådets hovedanalyse**

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	30 år	30 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemedielomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger	Lægemedielomkostninger Hospitalsomkostninger
Behandlingslinje	2. linjebehandling	2. linjebehandling
<b>Behandlingslængde</b>		
Acalabrutinib:	2,9 år	5,1 år
Ibrutinib:	2,9 år	5,1 år
<b>Parametriske funktioner for PFS</b>		
Acalabrutinib & Ibrutinib	Pooled data: Generaliseret gamma	Pooled data: Log-logistiske
<b>Parametriske funktioner for OS</b>		
Acalabrutinib & Ibrutinib	Pooled data: Eksponentiel	Pooled data: Eksponentiel





## 5. Resultater

### 5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 4.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [REDACTED] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 4.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 5.

**Tabel 5. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ibrutinib, DKK, diskonterede tal**

	Acalabrutinib	Ibrutinib	Inkrementelle omkostninger
Lægemedielomkostninger	[REDACTED]	[REDACTED]	[REDACTED]
Hospitalsomkostninger	11.829	12.798	-970
<b>Totale omkostninger</b>	[REDACTED]	[REDACTED]	[REDACTED]

#### 5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 6.

**Tabel 6. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK**

Scenarie	Inkrementelle omkostninger
<b>Resultatet af hovedanalysen</b>	[REDACTED]
Anvender den log-normale funktion til ekstrapolering af PFS	[REDACTED]
Anvender Gompertz-funktionen til ekstrapolering af OS	[REDACTED]
Anvender den log-logistiske funktion til ekstrapolering af OS	[REDACTED]



## 6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at acalabrutinib monoterapi og acalabrutinib + obinutuzumab vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Acalabrutinib bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Acalabrutinib bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

### 6.1 Estimat af patientantal og markedsandel

Ansøger anvender et estimat for patientantal baseret på historisk data, hvor der i år 1 vil være 65 patienter og i år 5 vil være 69 patienter, der er kandidater til behandling med acalabrutinib monoterapi. Heraf antager ansøger, at acalabrutinib vil have et stigende markedsoptag til fra 20 % i år 1 til 40 % i år 5. Ansøger har valgt at inddrage en supplerende komparator, venetoclax + obinutuzumab, i deres budgetkonsekvensanalyse

#### **Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse**

Fagudvalget er blevet konsulteret i forhold til patientantal hvis acalabrutinib anbefales som mulig standardbehandling og hvis ikke acalabrutinib anbefales. Jf. *Medicinrådets protokol for acalabrutinib +/- obinutuzumab* har fagudvalget angivet, at der er 65 patienter pr. år, som vil være kandidater til behandling med acalabrutinib. Derfor ændrer Medicinrådet patientantallet til 65 patienter pr. år i Medicinrådets budgetkonsekvensanalyse. Fagudvalget vurderer ansøgers antagelse omkring markedsoptag usandsynlig og vurderer i stedet, at acalabrutinib vil have et stigende markedsoptag til 20 % i år 5, mens ibrutinib vil have et markedsoptag på 5 % i år 5 og venetoclax + rituximab vil have 75 % af markedet i år 5, se Tabel 7.

Fagudvalget vurderer, at man på nuværende tidspunkt anvender venetoclax + rituximab i dansk klinisk praksis. Fagudvalget forventer yderligere, at markedsoptaget for venetoclax + rituximab stiger hen over de kommende år. Da Medicinrådet ikke har vurderet den kliniske værdi af venetoclax + rituximab overfor acalabrutinib, er det ikke muligt at inkludere venetoclax + obinutuzumab i budgetkonsekvensanalysen. Derfor ekskluderer Medicinrådet markedsandelen for venetoclax + obinutuzumab i Medicinrådets budgetkonsekvensanalyse.



**Tabel 7. Medicinrådets estimat af antal nye patienter pr. år for tidligere behandlede CLL-patienter**

	År 1	År 2	År 3	År 4	År 5
<b>Anbefales</b>					
Acalabrutinib	6	10	13	13	13
Ibrutinib	20	13	6	3	3
<b>Anbefales ikke</b>					
Acalabrutinib	0	0	0	0	0
Ibrutinib	26	13	6	6	6

Medicinrådet ændrer markedsoptaget for acalabrutinib, ændrer patientantallet pr. år og ekskluderer venetoclax + rituximab fra budgetkonsekvensanalysen.

## 6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har accepteret ansøgers patientantal i sin budgetkonsekvensanalyse, hvorfor der vil være 65 patienter, der kandiderer til behandling med acalabrutinib monoterapi årligt.

Medicinrådet estimerer, at anvendelse af acalabrutinib vil resultere i budgetkonsekvenser på ca. [REDACTED] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 8.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 15 mio. DKK i år 5.

**Tabel 8. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Anbefales ikke	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Totale budgetkonsekvenser</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



## 7. Diskussion

Behandling med acalabrutinib er forbundet med inkrementelle omkostninger på [REDACTED] DKK sammenlignet med behandling med ibrutinib. De inkrementelle omkostninger er udelukkende drevet af lægemiddelomkostningerne for acalabrutinib.

Jf. Medicinrådets vurderingsrapport afsnit 5.6.2, noterer fagudvalget sig, at patienterne i ELEVATE-RR alle har enten del(17p) og/eller del(11q), da dette var et inklusionskriterie i studiet. Fagudvalget vurderer, at ELEVATE-RR inkluderer mange patienter med dårlige prognostika, som generelt har dårligere prognose end patientpopulationen, ansøgningen ligger til grund for (patienter med og uden mutationer). Derfor har Medicinrådet ændret valget af ekstrapolering til den log-logistiske, som fagudvalget vurderede at repræsentere dansk klinisk praksis i højere grad. De inkrementelle omkostninger er [REDACTED], mens de ved anvendelsen af den log-normale funktion er [REDACTED].

Medicinrådet præsenterer samtidig to følsomhedsanalyser for valg af ekstrapolering af OS, for at undersøge betydningen af ekstrapoleringerne for omkostningerne. Følsomhedsanalyserne har ikke betydning for de inkrementelle omkostninger, fordi behandlingsvarigheden for acalabrutinib og ibrutinib i Medicinrådets hovedanalyse er den samme.

Fagudvalget forventer, at effekten af acalabrutinib observeret i studiet kan genfindes ved behandling af danske patienter.



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## 9. Versionslog

### Versionslog

Version	Dato	Ændring
1.0	15. juni 2022	Godkendt af Medicinrådet.



## 10. Bilag

### 10.1 Resultatet af ansøgers hovedanalyse

Patienter, der oplever behandlingskrævende relaps eller behandlingssvigt efter mindst en tidligere behandling.

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient for sammenligning med acalabrutinib og ibrutinib [REDACTED] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 9.

**Tabel 9. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal**

	Acalabrutinib	Ibrutinib	Inkrementelle omkostninger
Lægemiddelomkostninger	[REDACTED]	[REDACTED]	[REDACTED]
Hospitalsomkostninger	1.037.063	1.037.958	-895
Efterfølgende behandling	[REDACTED]	[REDACTED]	[REDACTED]
Patientomkostninger	39.277	39.277	0
<b>Totale omkostninger</b>	[REDACTED]	[REDACTED]	[REDACTED]

### 10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Patienter uden deletion17p/p53-mutation

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af acalabrutinib monoterapi vil resultere i budgetkonsekvenser på ca. [REDACTED] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 10.

**Tabel 10. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal: Acalabrutinib monoterapi**

	År 1	År 2	År 3	År 4	År 5
Anbefales	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Anbefales ikke	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Totale budgetkonsekvenser</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



### 10.3 Ansøgers anvendte bivirkningsfrekvenser for patienter med tidligere behandlet kronisk lymfatisk leukæmi

**Tabel 11. Rapporterede bivirkningsfrekvenser ved behandling med acalabrutinib og ibrutinib for patienter, der oplever behandlingskrævende relaps eller behandlingssvigt efter mindst en tidligere behandling**

	Acalabrutinib [%]	Ibrutinib [%]
Anæmi	11,7	12,9
Cataract	2,3	2,7
Atrial Fibrillation	4,5	3,4
Syncope	2,3	1,1
Congestive Heart Failure	1,5	2,7
Diarrhoea	1,1	4,9
Dyspnoea	2,3	0,4
Fatigue	3,4	0,0
Febrile Neutropenia	1,5	1,9
Hyperglycemia	0,0	0,0
Hypertension	4,1	8,7
Urinary Tract Infection	1,1	2,3
Infusion-Related Reaction	0,0	0,0
Hypogammaglobulinemia	0,0	0,0
Acute Kidney injury	1,5	2,3
Neutropenia	19,5	22,8
Pyrexia	3,0	0,8
Thrombocytopenia	9,8	6,8
Tumour Lysis Syndrome	0,4	0,4
Sepsis	1,5	2,7
Hyperuricaemia	1,1	3,4
Pneumonia	10,5	8,7





## 10.4 Ansøgers anvendte fordeling af bivirkningsbehandling og estimering af bivirkningsomkostning for patienter med tidligere behandlet kronisk lymfatisk leukæmi

**Tabel 12. Fordeling af bivirkningsbehandling og estimering af bivirkningsomkostning for patienter, der oplever behandlingskrævende relaps eller behandlingssvigt efter mindst en tidligere behandling**

	Indlæggelse		Ambulant	
	Frekvens	DRG-takst	Frekvens	DRG- takst
Anaemia	20 %	16MA10	80 %	16MA98
Cataract	100 %	02MP21	-	-
Atrial Fibrillation	100 %	05MA07	-	-
Syncope	100 %	05MA07	-	-
Congestive Heart Failure	100 %	05MA04	-	-
Diarrhoea	70 %	06MA98	30 %	06MA98
Dyspnoea	-	-	100 %	04MA98
Fatigue	-	-	100 %	04MA98
Febrile Neutropenia	100 %	16MA03	-	-
Hyperglycemia	-	-	100 %	10MA98
Hypertension	100 %	05MA11	-	-
Urinary Tract Infection	10 %	11MA07	90 %	11MA98
Infusion-Related Reaction	-	-	100 %	18MA98
Hypogammaglobulinemia	-	-	100 %	16MA98
Acute Kidney injury	100 %	11MA01	-	-
Neutropenia	10 %	16MA03	90 %	16MA98
Pyrexia	100 %	18MA04		
Thrombocytopenia	10 %	16MA09	90 %	16MA98
Tumour Lysis Syndrome	100 %	10MA06	-	-
Sepsis	100 %	18MA01	-	-



	Indlæggelse		Ambulant	
	Frekvens	DRG-takst	Frekvens	DRG- takst
Hyperuricaemia	-	-	100 %	23MA98
Pneumonia	100 %	04MA13	-	-

# Medicinrådets sundheds- økonomiske afrapportering

## Acalabrutinib +/- obinutuzumab

*Tidligere ubehandlede patienter med kronisk  
lymfatisk leukæmi*



## Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

## Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

### Dokumentoplysninger

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# 1. Begreber og forkortelser

<b>AIP</b>	Apotekernes indkøbspris
<b>BSA</b>	Kropsoverfladeareal
<b>CLL</b>	Kronisk lymfatisk leukæmi
<b>DKK</b>	Danske kroner
<b>DRG</b>	Diagnose Relaterede Grupper
<b>HR</b>	Hazard ratio
<b>I.V.</b>	Intravenøst
<b>MAIC</b>	<i>Matching-adjusted indirect comparisons</i>
<b>NMA</b>	Netværksmetaanalyse
<b>OS</b>	Samlet overlevelse
<b>PFS</b>	Progressionsfri overlevelse
<b>PS</b>	Progredieret sygdom
<b>SAIP</b>	Sygehusapotekernes indkøbspris
<b>SPC</b>	Produkters produktresuméer
<b>TTD</b>	Tid til død



## 2. Konklusion

### **Inkrementelle omkostninger og budgetkonsekvenser**

#### Klinisk spørgsmål 1

##### *Acalabrutinib monoterapi vs. chlorambucil + obinutuzumab*

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for acalabrutinib ca. [REDACTED] DKK pr. patient sammenlignet med chlorambucil + obinutuzumab. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 2.340.000 DKK pr. patient

##### *Acalabrutinib monoterapi vs. bendamustin + rituximab*

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for acalabrutinib ca. [REDACTED] DKK pr. patient sammenlignet med chlorambucil + obinutuzumab. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 2.600.000 DKK pr. patient

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af acalabrutinib som mulig standardbehandling vil være ca. [REDACTED] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 149 mio. DKK i det femte år.

#### Klinisk spørgsmål 2

##### *Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab*

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for acalabrutinib + obinutuzumab ca. [REDACTED] DKK pr. patient sammenlignet med chlorambucil + obinutuzumab. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 2.500.000 DKK pr. patient

##### *Acalabrutinib + obinutuzumab vs. bendamustin + rituximab*

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for acalabrutinib + obinutuzumab ca. [REDACTED] DKK pr. patient sammenlignet med chlorambucil + obinutuzumab. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 2.900.000 DKK pr. patient

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af acalabrutinib som mulig standardbehandling vil være ca. [REDACTED] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 190 mio. DKK i det femte år.





### Klinisk spørgsmål 3

#### *Acalabrutinib vs. ibrutinib*

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for acalabrutinib ca. [REDACTED] DKK pr. patient sammenlignet med ibrutinib. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. -2.215 DKK pr. patient

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af acalabrutinib som mulig standardbehandling vil være ca. [REDACTED] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 5 mio. DKK i det femte år.

### Klinisk spørgsmål 4

#### *Acalabrutinib + obinutuzumab vs. ibrutinib*

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for acalabrutinib ca. [REDACTED] DKK pr. patient sammenlignet med ibrutinib. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 245.000 DKK pr. patient

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af acalabrutinib som mulig standardbehandling vil være ca. [REDACTED] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 6 mio. DKK i det femte år.

Analyserne i Medicinrådets vurdering af acalabrutinib +/- obinutuzumab er baseret på umodne data fra ELEVATE-TN-studiet, hvor medianen ikke er opnået. Dette medfører ekstrapolering på baggrund af umodent PFS- og OS-data, hvilket har stor betydning på analysens resultat. Især fordi acalabrutinib +/- obinutuzumab behandles indtil progression har valget af ekstrapolering for PFS stor betydning for analysen, og da der er stor variation internt mellem ekstrapoleringerne for PFS bør resultaterne tolkes med stor usikkerhed. Selvom 4 års *follow-up* fra ELEVATE-TN, der ikke er inkluderet i modellen, men underbygger, at valget af ekstrapolering for TP1 for acalabrutinib +/- obinutuzumab er det mest klinisk plausible valg af ekstrapolering for dansk klinisk praksis.



## 3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af acalabrutinib monoterapi og kombinationsbehandling med obinutuzumab som mulig standardbehandling til 1. linjebehandling til patienter med tidligere ubehandlet kronisk lymfatisk leukæmi.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca. Vi modtog ansøgningen den 30. april 2021.

Denne sundhedsøkonomiske afrapportering er den ene af to afrapporteringer tilhørende vurderingen af acalabrutinib. Den anden behandler vurderingen af sidste kliniske spørgsmål.

### 3.1 Patientpopulation

Kronisk lymfatisk leukæmi (CLL) er en kræftsygdom i blodet, som opstår i kroppens B-celler og påvirker deres regulering af celledeling og celledød. Det fører til en ophobning af B-celler bl.a. i knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket.

Der er ca. 150 patienter om året med behandlingsbehov i 1. linje [1], hvoraf ca. 90 % (ca. 135 patienter) ikke har deletion17p/p53-mutation og derfor behandles med cytostatika i kombination med et anti-CD20-antistof [2]. De resterende 10 % (ca. 15 patienter) med deletion17p/p53-mutation behandles med ibrutinib.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

#### 3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af acalabrutinib på baggrund af følgende kliniske spørgsmål:

*Klinisk spørgsmål 1:*

Hvilken værdi har acalabrutinib som monoterapi sammenlignet med kemoimmunoterapi (chlorambucil + obinutuzumab og bendamustin + rituximab) for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion17p/p53-mutation?

*Klinisk spørgsmål 2:*

Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med kemoimmunoterapi (chlorambucil + obinutuzumab og bendamustin + rituximab) for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion17p/p53-mutation?



*Klinisk spørgsmål 3:*

Hvilken værdi har acalabrutinib som monoterapi sammenlignet med dansk standardbehandling (ibrutinib) hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation?

*Klinisk spørgsmål 4:*

Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med dansk standardbehandling (ibrutinib) hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation?

## 4. Vurdering af den sundhedsøkonomiske analyse

Ansøgers sundhedsøkonomiske analyse består af en omkostningsanalyse og en budgetkonsekvensanalyse. De inkrementelle omkostninger pr. patient estimeres for:

- Acalabrutinib +/- obinutuzumab til patienter med tidligere ubehandlet CLL uden deletion17p/p53-mutationen sammenlignet med kemoimmunterapi i form af chlorambucil + obinutuzumab eller bendamustin + rituximab.
- Acalabrutinib +/- obinutuzumab til patienter med tidligere ubehandlet CLL med deletion17p/p53-mutationen sammenlignet med ibrutinib monoterapi.

Medicinerådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

### 4.1 Antagelser og forudsætninger for modellen

I den sundhedsøkonomiske sammenligning af acalabrutinib +/- obinutuzumab med dets komparatorer indgår både direkte sammenligninger og indirekte sammenligninger.

#### Patienter uden deletion17p/p53-mutation

For patienter uden deletion17p/p53-mutationen sammenlignes acalabrutinib +/- obinutuzumab med hhv. chlorambucil + obinutuzumab og bendamustin + rituximab.

Sammenligningen af acalabrutinib +/- obinutuzumab med chlorambucil + obinutuzumab er lavet på baggrund af data fra studiet ELEVATE-TN, der direkte sammenligner acalabrutinib +/- obinutuzumab med chlorambucil + obinutuzumab. ELEVATE-TN-studiet er et randomiseret, head-to-head, fase III-studie [3].

Sammenligningen af acalabrutinib +/- obinutuzumab med bendamustin + rituximab er lavet på baggrund af en indirekte sammenligning vha. en *matching-adjusted indirect comparisons* (MAIC)-analyse. Studier, der indgår i MAIC-analysen, er ELEVATE-TN-studiet for acalabrutinib +/- obinutuzumab og ALLIANCE [4] for bendamustin + rituximab.



#### Patienter med deletion17p/p53-mutation

For patienter med deletion17p/p53-mutationen sammenlignes acalabrutinib +/- obinutuzumab med ibrutinib monoterapi.

Sammenligningen af acalabrutinib +/- obinutuzumab med ibrutinib monoterapi er lavet på baggrund af en indirekte sammenligning via en MAIC-analyse. Studier, der indgår i MAIC-analysen, er ELEVATE-TN-studiet for acalabrutinib +/- obinutuzumab og RESONATE [5] og ILLUMINATE [6] for ibrutinib.

Yderligere information om de indirekte sammenligninger kan findes i Medicinrådets vurderingsrapport.

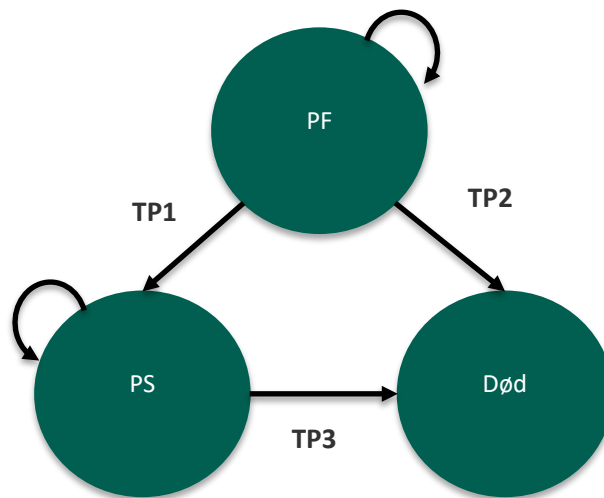
#### 4.1.1 Modelbeskrivelse

Ansøger har indsendt en *semi-markov-model* til at estimere omkostningerne forbundet med behandlingen med acalabrutinib +/- obinutuzumab.

Modellen består af en række sygdomsstadier, som patienten kan befinde sig i på et givet tidspunkt. Patientens bevægelse mellem disse sygdomsstadier bestemmes af transitionssandsynligheder. Modellen estimerer omkostninger baseret på det sygdomsstadie, patienten befinder sig i. Hvert sygdomsstadie er forbundet med en omkostning, der baserer sig på den behandling, patienten modtager i det pågældende stadie. Forskel i omkostninger mellem acalabrutinib og dets komparatorer opstår på baggrund af transitionssandsynlighederne, som varierer efter type af behandling, patienten modtager. Transitionssandsynlighederne benyttet i ansøgers model er baseret på studierne beskrevet i afsnit 4.1.2.

Modellen består af tre stadier: progressionsfri overlevelse, post-progression og stadiet død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.

Modellen har en cykluslængde på 28 dage og anvender *half-cycle correction*.



**Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen. PFS = progressionsfri overlevelse, PS = progredieret sygdom, Død = død, TP1 = transitionssandsynlighed fra PFS til PD, TP2 = transitionssandsynlighed fra PF til død, TP3 = transitionssandsynlighed fra PS til død**

#### Medicinerådets vurdering af ansøgers model

*Medicinerådet accepterer ansøgers tilgang vedr. ansøgers modeller.*

#### 4.1.2 Modelantagelser og -beskrivelse

I en *semi-markov-model* vil patienter altid befinde sig i ét helbredsstadie ad gangen på et givent tidspunkt, hvor begivenheder repræsenterer overgange fra ét helbredsstadie til et andet.

Ansøger anvender ekstrapoleret tid til progressionsdata fra ELEVATE-TN-studiet til at bestemme transitionssandsynligheden for bevægelsen fra helbredsstadiet progressionsfri overlevelse til sygdomsstadiet progredieret sygdom (TP1) for acalabrutinib +/- obinutuzumab og chlorambucil + obinutuzumab. For bendamustin + rituximab finder ansøger i sin MAIC-analyse en hazard ratio (HR) overfor både acalabrutinib +/- obinutuzumab, men anvender kun HR overfor kombinationsbehandlingen, fordi behandlingsalternativerne ligner hinanden. Ansøger anvender HR på ekstrapoleret tid til progressionsdata fra ELEVATE-TN-studiet til at estimere transitionssandsynligheden.

Til at bestemme transitionssandsynligheden fra helbredsstadiet progressionsfri overlevelse til sygdomsstadiet død (TP2) for acalabrutinib +/- obinutuzumab og chlorambucil + obinutuzumab, anvender ansøger ekstrapoleret tid til død (TTD)-data fra ELEVATE-TN-studiet. For bendamustin + rituximab finder ansøger i sin MAIC-analyse en HR overfor både acalabrutinib +/- obinutuzumab, som ansøger anvender på ekstrapoleret TTD-data fra ELEVATE-TN-studiet til at estimere transitionssandsynligheden.

Til at bestemme transitionssandsynligheden fra helbredsstadiet progredieret sygdom (PS) til sygdomsstadiet død (TP3) anvender ansøger ekstrapoleret OS-data fra ELEVATE



R/R-studiet [7] for alle behandlingsalternativerne. ELEVATE R/R-studiet er et open-label, randomiseret fase III-studie, der direkte sammenligner acalabrutinib med ibrutinib hos patienter med CLL med bl.a. deletion 17p/p53-mutation, der oplever behandlingskrævende relaps. Ansøger pooler OS-data for acalabrutinib og ibrutinib fra ELEVATE R/R-studiet, fordi data herfra er mere modne end overlevelsesdata fra ELEVATE-TN-studiet.

For at overlevelsen i modellen ikke overstiger den generelle befolknings overlevelse i Danmark, justerer ansøger data for den generelle befolknings dødelighed.

#### Patienter uden deletion 17p/p53-mutation

##### **For sammenligning mellem acalabrutinib monoterapi, chlorambucil + obinutuzumab og bendamustin + rituximab**

For acalabrutinib monoterapi anvender ansøger Gompertz-funktionen til at ekstrapolere data for TP1, den eksponentielle funktion for TP2 og den eksponentielle funktion for TP3. Ansøgers valg af ekstrapolering for hhv. TP1, TP2 og TP3 har betydning for patienternes forløb i modellen.

For chlorambucil + obinutuzumab anvender ansøger den log-normale funktion til at ekstrapolere data for TP1, den eksponentielle funktion for TP2 og den eksponentielle funktion for TP3. Ansøgers valg af ekstrapolering for hhv. TP1, TP2 og TP3 har betydning for patienternes forløb i modellen.

For bendamustin + rituximab finder ansøger i sin MAIC-analyse en HR på 4,76 (2,33 – 10,00) overfor acalabrutinib + obinutuzumab, der anvendes direkte på time-to-event-data for acalabrutinib monoterapi til at estimere tiden i modellen for bendamustin + rituximab. Ansøger anvender de samme ekstrapoleringer som ved acalabrutinib + obinutuzumab for hhv. TP1, TP2 og TP3.

##### **For sammenligning mellem acalabrutinib + obinutuzumab, chlorambucil + obinutuzumab og bendamustin + rituximab**

For acalabrutinib + obinutuzumab anvender ansøger Weibull-funktionen til at ekstrapolere data for TP1, den eksponentielle funktion for TP2 og den eksponentielle funktion for TP3.

For chlorambucil + obinutuzumab anvender ansøger den log-normale funktion til at ekstrapolere data for TP1, den eksponentielle funktion for TP2 og den eksponentielle funktion for TP3.

For bendamustin + rituximab finder ansøger i sin MAIC-analyse en HR på 4,76 (2,33 – 10,00) overfor acalabrutinib + obinutuzumab, der anvendes direkte på time-to-event-data for acalabrutinib + obinutuzumab til at estimere tiden i modellen for bendamustin + rituximab. Ansøger anvender de samme ekstrapoleringer som ved acalabrutinib + obinutuzumab for hhv. TP1, TP2 og TP3.

Ansøger antager, at behandlingsvarigheden for acalabrutinib +/- obinutuzumab er lig tid til progression fra ELEVATE-TN-studiet, hvor patienten maksimalt kan få obinutuzumab i op til 6 cykler. For chlorambucil + obinutuzumab anvender ansøger en maksimal



behandlingsvarighed på 6 cykler, som angivet i produktresuméer (SPC'er). For bendamustin + rituximab anvender ansøger en maksimal behandlingsvarighed på 6 cykler, som angivet i SPC'erne.

#### Patienter med deletion17p/p53-mutation

Ansøger vælger at poole data for acalabrutinib +/- obinutuzumab, fordi subgruppepopulationen med deletion17p/p53-mutation i ELEVATE-TN-studiet var lille. Ansøger anvender Gompertz-funktionen til at ekstrapolere data for TP1, den eksponentielle funktion for TP2 og den eksponentielle funktion for TP3.

For komparatoren, ibrutinib, finder ansøger i sin MAIC-analyse, at der ikke er statistisk signifikant forskel i sammenligningen med acalabrutinib +/- obinutuzumab. Derfor antager ansøger i stedet, at der er ens effekt mellem ibrutinib og acalabrutinib +/- obinutuzumab, hvorfor tiden i de forskellige sygdomsstadier og bevægelse gennem modellen er ens for begge behandlingsalternativer. Data fra den poolede acalabrutinib +/- obinutuzumabarm anvendes til at modellere patienternes bevægelse gennem modellen.

For acalabrutinib monoterapi og acalabrutinib + obinutuzumab vælger ansøger at basere den gennemsnitlige behandlingsvarighed på PFS-data fra ELEVATE-TN-studiet, hvor patienten maksimalt kan få obinutuzumab i op til 6 cykler, men fortsætter behandling med acalabrutinib efterfølgende. Ansøger antager, at ibrutinibs behandlingsvarighed er lig tiden til progression magen til acalabrutinib +/- obinutuzumab.

#### Medicinerådets vurdering af ansøgers modelantagelser

Medicinerådet accepterer ansøgers tilgang vedr. modelstruktur og ansøgers antagelser vedr. estimater for behandlingsvarighed.

I det kommende afsnit vil Medicinerådet vurdere ansøgers modelantagelser, der ligger til grund for vurderingen af acalabrutinib +/- obinutuzumab og dets komparatorer. I afsnittet vil fagudvalgets vurderinger, af ansøgers valgte ekstrapoleringer, blive vurderet ift. klinisk plausibilitet. Ekstrapoleringerne for TP1 og TP2 er foretaget på baggrund af data fra ELEVATE-TN-studiet, der jf. vurderingsrapporten vurderes umodent, hvorfor ekstrapoleringerne skal tolkes med stor usikkerhed. Derfor belyser Medicinerådet usikkerheden af ekstrapoleringernes betydning for analysens resultat ved følsomhedsanalyser.

Ekstrapoleringerne for TP3 er foretaget på baggrund af OS-data fra ELEVATE-RR-studiet, som må anskues at være mindre umodent end OS-data fra ELEVATE-TN-studiet, men stadig umodent, hvorfor ekstrapoleringerne skal tolkes med stor usikkerhed. Derfor belyser Medicinerådet usikkerheden af ekstrapoleringernes betydning for analysens resultat ved følsomhedsanalyser. Da data for TP3 er fra ELEVATE RR-studiet [7] og anvendes for alle behandlingsalternativerne, der vurderer Medicinerådets dem samlet her. Fagudvalget accepterer ansøgers valg af ekstrapolering for TP3, fordi den er klinisk repræsentativ for klinisk praksis, men fordi valget af ekstrapolering har stor betydning for patienternes overlevelse i modellen, præsenterer Medicinerådet følsomhedsanalyser, der undersøger alternative valg af ekstrapoleringer. Valget af ekstrapolering har indflydelse på, hvor lang tid der går, fra patienten er progredieret, til patienten dør.



Derfor præsenterer Medicinrådet to følsomhedsanalyser med hhv. Gompertz-funktionen og den log-logistiske funktion. De er mere optimistiske end ansøgers valg. I Figur 8 præsenteres ekstrapoleringerne af OS-data fra ELEVATE-RR-studiet.

Alle ansøgers ekstrapoleringer er præsenteret i bilag 10.1.

#### Patienter uden deletion17p/p53-mutation

##### **For sammenligning mellem acalabrutinib monoterapi, chlorambucil + obinutuzumab og bendamustin + rituximab**

For sammenligning mellem acalabrutinib monoterapi, chlorambucil + obinutuzumab og bendamustin + rituximab vurderer fagudvalget, at ansøgers valg af ekstrapolering for TP1 for acalabrutinib monoterapi virker rimelige og klinisk plausible ift. dansk klinisk praksis. Fagudvalget vurderer at ekstrapoleringen generaliseret gamma også virker klinisk plausibel. Den er et mere optimistisk valg end Gompertz-funktionen. Derfor præsenterer Medicinrådet en følsomhedsanalyse, hvor ekstrapoleringen for TP1 ændres til generaliseret gamma i stedet. I Figur 9 præsenteres ekstrapoleringen af TP1 fra ELEVATE-TN-studiet.

For valg af ekstrapolering for TP2 accepterer fagudvalget ansøgers valg. Dog præsenterer Medicinrådet en følsomhedsanalyse, der undersøger alternative valg af ekstrapoleringer, fordi valget har indflydelse på andelen af patienter, der dør, inden de progredierer, hvilket har betydning for patientens tid i modellen. Derfor præsenterer Medicinrådet to følsomhedsanalyser med hhv. den log-logistisk funktion og Weibull-funktionen, som begge er mere pessimistiske valg end den eksponentielle funktion. I Figur 10 præsenteres ekstrapoleringen af TP2 fra ELEVATE-TN-studiet. I Figur 2 præsenteres patienternes forløb i modellen for behandling med acalabrutinib monoterapi, baseret på de valgte ekstrapoleringer for hver transitionssandsynlighed.

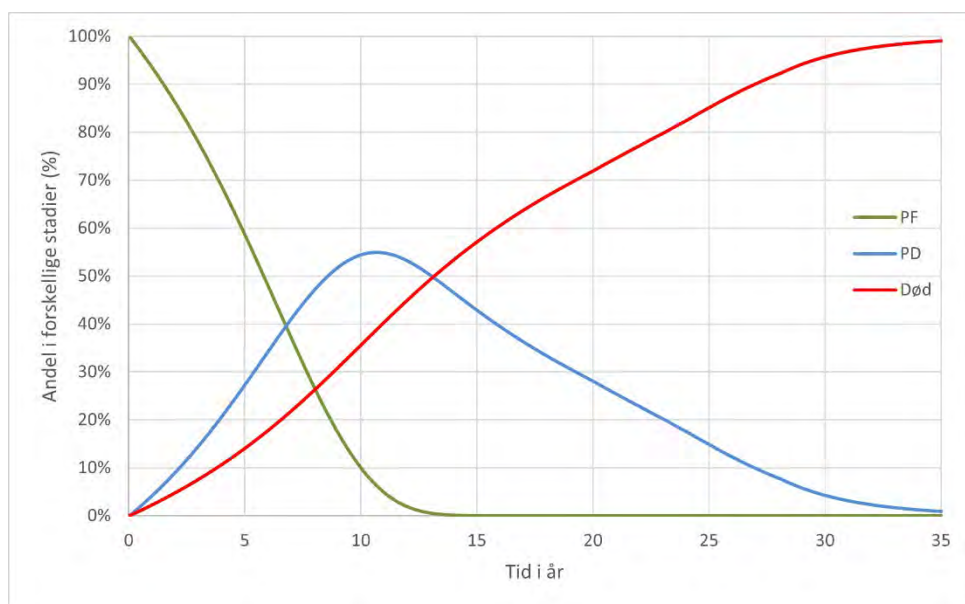
For chlorambucil + obinutuzumab vurderer fagudvalget, at ansøgers valg af den log-normale funktion ikke er repræsentativ for dansk klinisk praksis. Fagudvalget vurderer, at Gompertz-funktionen i højere grad er repræsentativ dansk klinisk praksis. Derfor ændrer Medicinrådet valget af ekstrapolering for TP1 for chlorambucil + obinutuzumab til Gompertz i Medicinrådets hovedanalyse. Medicinrådet præsenterer to følsomhedsanalyser, hvor hhv. Weibull-funktionen og den log-normale anvendes til ekstrapolering for TP1. De er mere optimistiske valg af ekstrapoleringer ift. fagudvalgets valg. I Figur 11 præsenteres ekstrapoleringen af TP1 fra ELEVATE-TN-studiet.

For valg af ekstrapolering for TP2, accepterer fagudvalget ansøgers valg. Dog præsenterer Medicinrådet en følsomhedsanalyse, der undersøger alternative valg af ekstrapoleringer, fordi valget har indflydelse på andelen af patienter, der dør, inden de progredierer, hvilket har betydning for patientens tid i modellen. Derfor præsenterer Medicinrådet to følsomhedsanalyser med hhv. den generaliserede gamma-funktion og Weibull, som begge er mere optimistiske valg end den eksponentielle funktion. I Figur 12 præsenteres ekstrapoleringen af TP2 fra ELEVATE-TN-studiet. I Figur 3 præsenteres patienternes forløb i modellen for behandling med chlorambucil + obinutuzumab, baseret på de valgte ekstrapoleringer for hver transitionssandsynlighed.

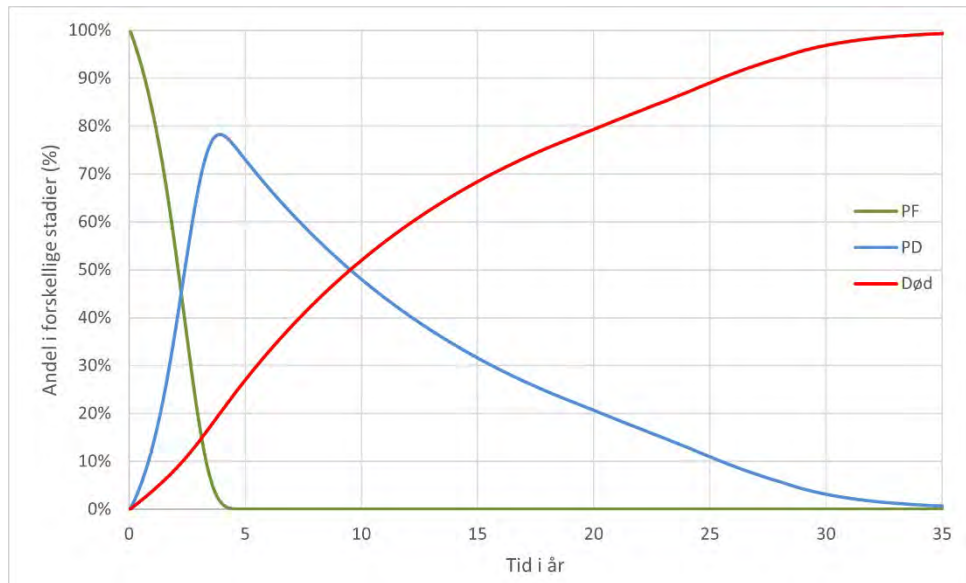




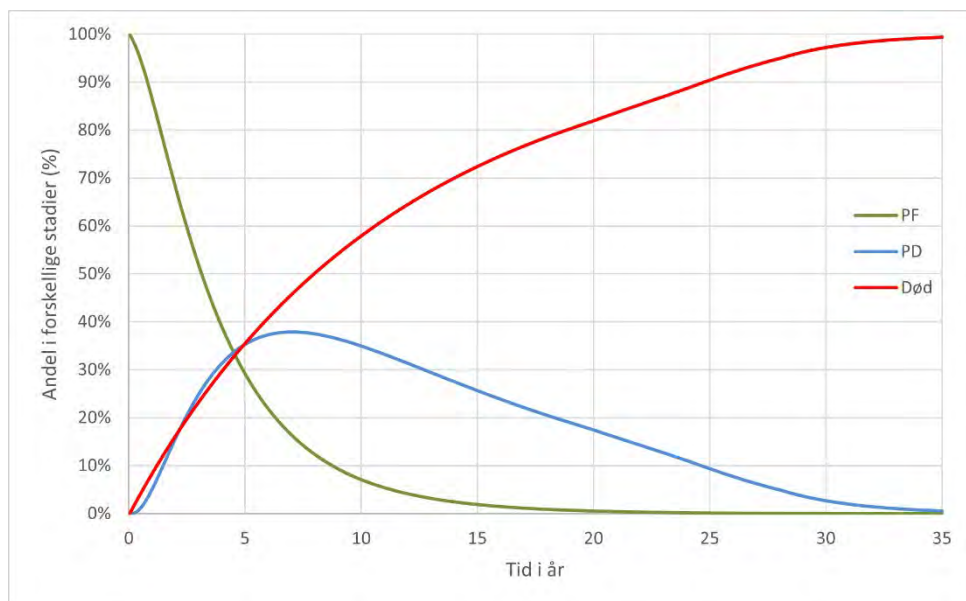
For bendamustin + rituximab vurderer fagudvalget, at ansøgers valg af ekstrapolering for TP1 er underestimeret og vurderer i stedet, at den log-normale funktion er mere klinisk repræsentativ. Derfor ændrer Medicinrådet valget af ekstrapolering for TP1 til den log-normale i Medicinrådets hovedanalyse. Medicinrådet præsenterer to følsomhedsanalyser, der undersøger variation i HR fundet i MAIC-analysen, pga. usikkerheder forbundet med umodent data for acalabrutinib + obinutuzumab armen fra ELEVATE-TN-studiet. Derfor præsenterer Medicinrådet to følsomhedsanalyser, hvor HR justeres  $\pm 20\%$ . I Figur 13 præsenteres ekstrapoleringen af TP1 fra ELEVATE-TN-studiet og i Figur 14 præsenteres ekstrapoleringen af TP2 fra ELEVATE-TN-studiet for acalabrutinib monoterapi, hvor HR fra MAIC-analysen på 2,63 anvendes. I Figur 4 præsenteres patienternes forløb i modellen for behandling med bendamustin + rituximab, baseret på de valgte ekstrapoleringer for hver transitionssandsynlighed.



**Figur 2. Oversigt over Medicinrådets estimat for tiden i de forskellige stadier for acalabrutinib monoterapi**



**Figur 3. Oversigt over Medicinrådets estimat for tiden i de forskellige stadier for chlorambucil + obinutuzumab**



**Figur 4. Oversigt over Medicinrådets estimat for tiden i de forskellige stadier for bendamustin + rituximab**

#### **For sammenligning mellem acalabrutinib + obinutuzumab, chlorambucil + obinutuzumab og bendamustin + rituximab**

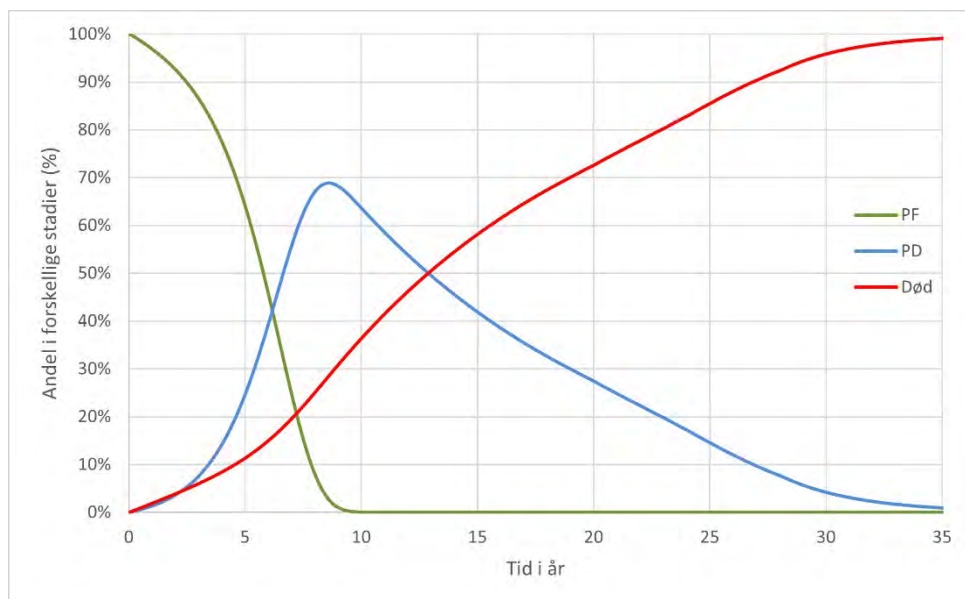
For sammenligning mellem acalabrutinib + obinutuzumab, chlorambucil + obinutuzumab og bendamustin + rituximab vurderer fagudvalget, at ansøgers valg af ekstrapoleringer for TP1 ikke er repræsentativ for dansk klinisk praksis. For acalabrutinib + obinutuzumab vurderer fagudvalget, at Gompertz-funktionen i højere grad er klinisk repræsentativ, hvorfor Medicinrådet ændrer valget af ekstrapolering for TP1 til Gompertz i Medicinrådets hovedanalyse. Medicinrådet præsenterer to følsomhedsanalyser med hhv. den log-logistiske og Weibull-funktionen, som begge er mere optimistiske valg en Gompertz. I Figur 15 præsenteres ekstrapoleringen af TP1 fra ELEVATE-TN-studiet.



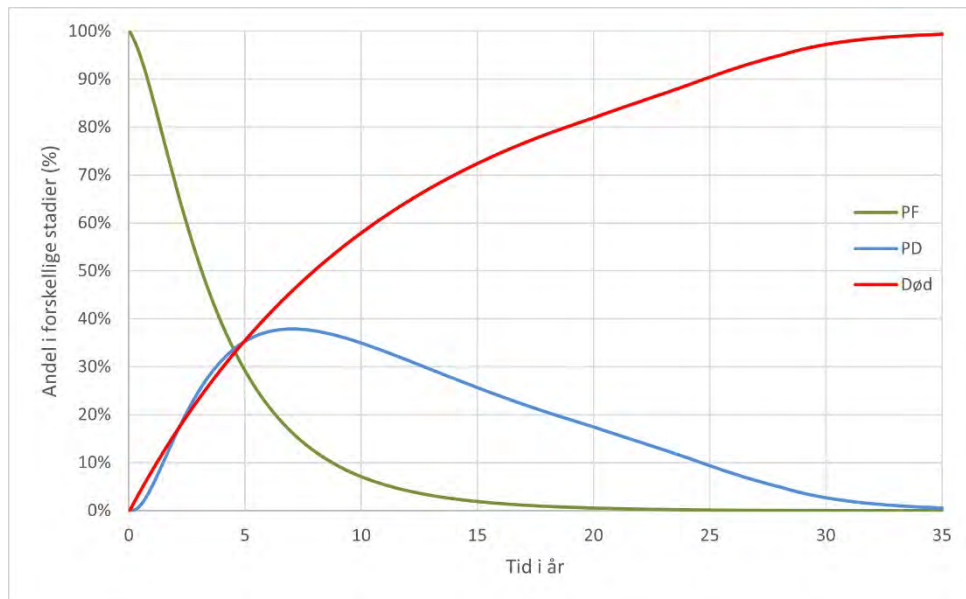
For valg af ekstrapolering for TP2 accepterer fagudvalget ansøgers valg. Dog præsenterer Medicinrådet en følsomhedsanalyse, der undersøger alternative valg af ekstrapoleringer, da valget har indflydelse på andelen af patienter, der dør, inden de progredierer, hvilket har stor betydning for patientens tid i modellen. Derfor præsenterer Medicinrådet to følsomhedsanalyser med hhv. den log-logistiske funktion og Weibull-funktionen, som begge er mere optimistiske valg en den eksponentielle. I Figur 16 præsenteres ekstrapoleringen af TP1 fra ELEVATE-TN-studiet. I Figur 5 præsenteres patienternes forløb i modellen for behandling med acalabrutinib + obinutuzumab, baseret på de valgte ekstrapoleringer for hver transitionssandsynlighed.

For chlorambucil + obinutuzumab henviser Medicinrådet til afsnittet på side 13, hvor fagudvalgets vurdering af chlorambucil + obinutuzumab er beskrevet. Valget af ekstrapolering for hver transitionssandsynlighed er angivet i afsnittet og Figur 3 angiver patienternes forløb i modellen for behandling med chlorambucil + obinutuzumab.

For bendamustin + rituximab vurderer fagudvalget, at ansøgers valg af ekstrapolering for TP1 er underestimeret og vurderer i stedet, at den log-normale funktion er mere klinisk repræsentativ. Derfor ændrer Medicinrådet valget af ekstrapolering for TP1 til den log-normale i Medicinrådets hovedanalyse. Medicinrådet præsenterer to følsomhedsanalyser, der undersøger variation i HR fundet i MAIC-analysen, pga. usikkerheder forbundet med umodent data for acalabrutinib + obinutuzumab armen fra ELEVATE-TN-studiet. Derfor præsenterer Medicinrådet to følsomhedsanalyser, hvor HR justeres  $\pm 20\%$ . I Figur 17 præsenteres ekstrapoleringen af TP1 fra ELEVATE-TN-studiet og i Figur 18 præsenteres ekstrapoleringen af TP2 fra ELEVATE-TN-studiet for acalabrutinib + obinutuzumab, hvor HR fra MAIC-analysen på 4,76 anvendes. I Figur 6 præsenteres patienternes forløb i modellen for behandling med bendamustin + rituximab, baseret på de valgte ekstrapoleringer for hver transitionssandsynlighed.



**Figur 5. Oversigt over Medicinrådets estimat for tiden i de forskellige stadier for Acalabrutinib + obinutuzumab**

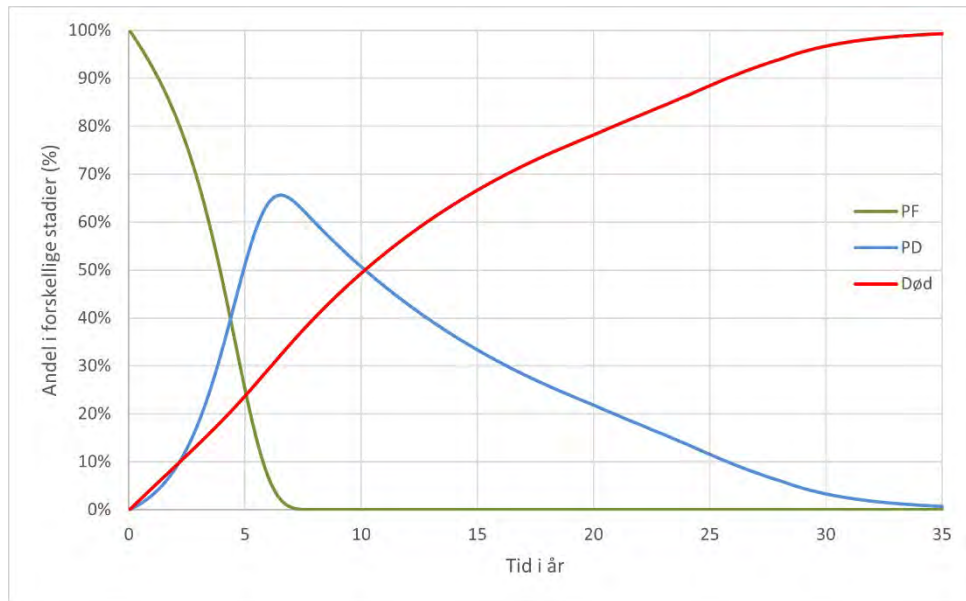


**Figur 6. Oversigt over Medicinrådets estimat for tiden i de forskellige stadier for bendamustin + rituximab**

#### Patienter med deletion17p/p53-mutation

For sammenligning mellem acalabrutinib +/- obinutuzumab og ibrutinib accepterer Medicinrådet ansøgers antagelse vedr. ens effekt, fordi fagudvalget konkluderer jf. vurderingsrapporten at PFS- samt OS-data ikke indikerer forskelle mellem behandlingerne. Fagudvalget vurderer, at ansøgers valg af ekstrapoleringer for TP1 er acceptable, men vurderer, at den log-logistiske og Weibull-funktionen virker rimelige ift. klinisk plausibilitet i dansk klinisk praksis. Derfor præsenterer Medicinrådet to følsomhedsanalyser med hhv. den log-logistiske og Weibull-funktionen i for at undersøge betydningen af valget af ekstrapolering for TP1. De er begge mere optimistiske valg end Gompertz-funktionen. I Figur 19 præsenteres ekstrapoleringen af TP1 fra ELEVATE-TN-studiet.

For valg af ekstrapolering for TP2, der accepterer fagudvalget ansøgers valg. Dog præsenterer Medicinrådet en følsomhedsanalyse, der undersøger alternative valg af ekstrapoleringer, da valget har indflydelse på andelen af patienter, der dør, inden de progredierer, hvilket har betydning for patientens tid i modellen. Derfor præsenterer Medicinrådet to følsomhedsanalyser med hhv. den log-logistiske funktion og Weibull, som begge er mere optimistiske valg en den eksponentielle. I Figur 20 præsenteres ekstrapoleringen af TP2 fra ELEVATE-TN-studiet. I Figur 7 præsenteres patienternes forløb i modellen for behandling med acalabrutinib +/- obinutuzumab og ibrutinib, baseret på de valgte ekstrapoleringer for hver transitionssandsynlighed.



**Figur 7. Oversigt over ansøgers estimat for tiden i de forskellige stadier for poolede data for acalabrutinib monoterapi og acalabrutinib + obinutuzumab**

Estimaterne for den gennemsnitlige tid i stadiet PF, gennemsnitlige tid i stadiet PS og den gennemsnitlige overlevelse i modellen er præsenteret i Tabel 1 sammen med den gennemsnitlige behandlingsvarighed for intervention og komparator.

**Tabel 1. Gennemsnitlig tid i behandling, gennemsnitlig tid i stadiet PF, gennemsnitlig tid i stadiet PS og den gennemsnitlige overlevelse**

Behandling	Mutation	Behandlingsvarighed [år]	PFS [år]	PS [år]	OS [år]
Acalabrutinib	u. del17p/p53	5,8	5,8	8,6	14,4
	m. del17p/p53	■	3,7	8,5	12,2
Acalabrutinib + Obinutuzumab	u. del17p/p53:	5,4	5,4	9,0	14,4
	m. del17p/p53:	■	3,7	8,5	12,2
Chlorambucil + Obinutuzumab	u. del17p/p53:	0,6	2,0	9,7	11,7
Bendamustin + Rituximab	Hazard Ratio: 4,76	0,5	4,1	6,3	10,5



Behandling	Mutation	Behandlingsvarighed [år]	PFS [år]	PS [år]	OS [år]
Ibrutinib	m. del17p/p53:	■	3,7	8,5	12,2

Medicinerådet accepterer ansøgers antagelser, men ændrer valget af ekstrapolering for TP1 for chlorambucil + obinutuzumab, bendamustin + rituximab, acalabrutinib + obinutuzumab. Ydermere udarbejder Medicinerådet følsomhedsanalyser, der undersøger alternative valg af ekstrapoleringer for TP1, TP2 og TP3.

#### 4.1.1 Analyseperspektiv

I overensstemmelse med Medicinerådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 30 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

##### Medicinerådets vurdering af ansøgers analyseperspektiv

Medicinerådet accepterer ansøgers valgte tidshorisont. Tidshorisonten er valgt, da ansøger argumenterer, at den gennemsnitlige behandlingslængde (af både 1., 2. linjebehandling) ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med acalabrutinib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem acalabrutinib og komparatorer set over en tidshorisont på 30 år.

Medicinerådet accepterer ansøgers valg vedr. analyseperspektiv.

## 4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af acalabrutinib +/- obinutuzumab sammenlignet med dets komparatorer. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, efterfølgende behandling og patientomkostninger.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne akkumuleres for hver cyklus, patienten befinder sig i et givent stadie.

##### Patienter uden deletion17p/p53-mutation

Medicinerådet accepterer ansøgers valg vedr. inkludering af lægemiddelomkostninger, hospitalsomkostninger, efterfølgende behandling og patientomkostninger.

##### Patienter med deletion17p/p53-mutation

Medicinerådet ekskluderer omkostninger til monitorering og efterfølgende behandling i Medicinerådets hovedanalyse, fordi der ikke vil være forskel mellem acalabrutinib +/- obinutuzumab og ibrutinib.



#### 4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren*, estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive lægemidlers produktresuméer (SPC'er).

- Acalabrutinib administreres oralt to gange dagligt af 100 mg.
- Ibrutinib administreres oralt en gang dagligt af 420 mg.
- Chlorambucil administreres oralt en gang hver anden uge i 6 cykler af 0,5 mg/kg.
- Obinutuzumab administreres intravenøst (i.v.) én gang hver cyklus i 6 cykler. 100 mg på dag 1, efterfulgt af 900 mg på dag 2. Herefter 1.000 mg på dag 8 og 15 i første 28 dages cyklus. Herefter gives 1.000 mg på dag 1 i de efterfølgende 5 cykler.
- Rituximab administreres i.v. én gang hver cyklus i 6 cykler. 375 mg/m<sup>2</sup> på dag 1 i første cyklus og 500 mg/m<sup>2</sup> på dag 1 i de efterfølgende 5 cykler.
- Bendamustin administreres i.v. to gange i hver cyklus i 6 cykler. 90 mg/m<sup>2</sup> på dag 1 og dag 2 i hver cyklus.

For lægemidler doseret efter kropsoverfladeareal (BSA) og kropsvægt anvender ansøger estimater fra ELEVATE-TN-studiet på 1,90 m<sup>2</sup> og 78,9 kg.

Ansøger har ikke inkluderet spild i deres hovedanalyse.

#### Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger

Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 2.

**Tabel 2. Anvendte lægemiddelpriser, SAIP (september, 2021)**

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Acalabrutinib	100 mg	60 stk.	■	Amgros
Bendamustin	100 mg/m <sup>2</sup>	5 x 25 mg	■	Amgros
Chlorambucil	2 mg	25 stk.	■	Amgros
Obinutuzumab	1000 mg/ml	1 stk.	■	Amgros
Ibrutinib	420 mg	28 stk.	■	Amgros
Rituximab	500 mg/m <sup>2</sup>	1 stk.	■	Amgros

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.



#### 4.2.2 Hospitalsomkostninger

Til beregning af hospitalsomkostningerne har ansøger inkluderet omkostninger forbundet med lægemiddeladministration, monitorering og bivirkninger.

##### Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger for behandling med lægemidler, der administreres i.v. (obinutuzumab, bendamustin og rituximab) i form af DRG-taksten 17MA98, MDC17 1-dagsgruppe, pat. mindst 7 år. Ansøger antager ingen administrationsomkostninger forbundet med lægemidler, der administreres per oralt, da patienten får udleveret lægemidlerne ifm. monitoreringsbesøg.

##### Medicinerådets vurdering af ansøgers antagelser vedr. administrationsomkostninger

Medicinerådet accepterer ansøgers tilgang til estimering af administrationsomkostninger, men opdaterer ansøgers anvendte DRG 2021-takster til DRG 2022-takster. Anvendte enhedsomkostninger kan ses i Tabel 3.

**Tabel 3. Omkostninger til lægemiddeladministration**

	Enhedsomkostning [DKK]	Kilde
Ambulant besøg - konsultation	3.225	DRG-2022: 17MA98

*Medicinerådet accepterer ansøgers tilgang vedr. administrationsomkostninger, men opdaterer ansøgers anvendte DRG-takst til DRG-2022.*

##### Monitoreringsomkostning

Ansøger har inkluderet monitoreringsomkostninger i form af 2021 DRG-takster, omkostninger til Rigshospitalets Labportal og omkostninger til Laboratoriemedicinsk vejledning (LVM) for Region Sjælland.

Ansøger antager, at patienter, behandlet i overensstemmelse med dansk klinisk praksis, vil blive monitoreret én gang hver tredje måned uafhængig af behandlingsform. Patienterne vil modtage én CT-scanning, én blodtransfusion, transfusion af blodplader, knoglemarvsprøve, biopsi, fuld blodprøve og får målt lymfocytaltal, kreatin-niveau og urinsyre. Ydermere antager ansøger, at patienter forud for i.v.-administration får målt lymfocytaltal og kreatin-niveau og får taget en fuld blodprøve ved et ambulant besøg.

##### Medicinerådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Fagudvalget vurderer, at måling af lymfocytaltal, kreatin-niveau og urinsyre normalvis indgår i en blodprøvetagning, hvorfor Medicinerådet vælger at ekskludere disse omkostninger. Idet ansøger anvender DRG-takster til at estimere omkostninger til monitorering, vælger Medicinerådet at ekskludere omkostninger til blodprøver samt test forud for i.v.-administration, da de vil være inkluderet i DRG-taksten anvendt som enhedsomkostning for et ambulant besøg i forbindelse med administration. Denne ændring vurderes at have minimal betydning for analysens resultat.

Fagudvalget accepterer ansøgers antagelse vedr. ambulant monitorering én gang hver tredje måned, men vurderer, at patienterne hverken får foretaget CT-scanning,





knoglemarvsprøve, blodtransfusion, transfusion af blodplader eller biopsi regelmæssigt ifm. monitorering. Derfor vælger Medicinrådet at ekskludere omkostningerne til alle disse elementer, men beholder omkostningen vedr. ambulant besøg hver tredje måned. Denne ændring vurderes at have mindre betydning for analysens resultat. Medicinrådet vælger at opdatere ansøgers anvendte DRG-2021-takster til DRG-2022-takster for ambulant besøg.

Jf. afsnit 4.2 vælger Medicinrådet at ekskludere monitoreringsomkostninger for patienter med deletion17p/p53-mutation, fordi formålet med analysen er at estimere de inkrementelle omkostninger pr. patient ved behandling med acalabrutinib +/- obinutuzumab og ibrutinib, og da data er poolede for både acalabrutinib +/- obinutuzumab og ibrutinib, der vil omkostninger til monitorering være ens.

**Table 4. Enhedsomkostninger til estimering af ressourceforbruget forbundet med monitorering**

	Enhedsomkostning [DKK]	Kilde
Ambulant besøg	3.225	DRG-2022: 17MA98

*Medicinrådet ekskluderer omkostninger til måling af lymfocytal, kreatin-niveau og urinsyre samt CT-scanning, knoglemarvsprøve, blodtransfusion, transfusion af blodplader og biopsi. Medicinrådet opdaterer anvendte DRG-takster og ekskluderer omkostninger til monitorering for patienter med deletion17p/p53-mutation.*

#### Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger. De benytter frekvenser for uønskede hændelser (AE) af grad 3-4 med en forekomst på mindst 2 %. Enhedsomkostningerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på 2021 DRG-takster, hvor AE enten behandles ambulant eller via indlæggelse.

Ansøger anvender bivirkningsfrekvenser for de fem forskellige behandlingsregimer, der stammer fra hvert af deres studier. For acalabrutinib monoterapi +/- obinutuzumab og chlorambucil + obinutuzumab anvender ansøger bivirkningsfrekvenser fra ELEVATE-TN-studiet. For ibrutinib anvender ansøger bivirkningsfrekvenser fra RESONATE-studiet. For bendamustin + rituximab anvender ansøger bivirkningsfrekvenser fra Woyach et al. [4]. Ansøger anvender en fordeling mellem indlæggelse og ambulant behandling for de rapporterede bivirkninger.

#### Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Fagudvalget vurderer, at lavt antal blodplader, leukopeni og trombocytopeni dækker over det samme, hvorfor Medicinrådet vælger at ekskludere lavt antal blodplader og leukopeni, se anvendte bivirkningsfrekvenser i Tabel 46. Denne ændring vurderes at have minimal betydning for analysens resultat. Fagudvalget vurderer, at fordelingen mellem indlæggelse og ambulant behandling for anæmi bør være 5 % for indlæggelse og 95 % for ambulant behandling. Derfor ændrer Medicinrådet fordelingen mellem indlæggelse og ambulant behandling for anæmi, se Tabel 47, hvor fordeling mellem indlæggelse og ambulant behandling fremgår.



*Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger og ekskluderer bivirkningsfrekvensen samt omkostningen for lavt antal blodplader og leukopeni.*

#### **4.2.3 Efterfølgende behandling**

Ansøger inkluderer omkostninger til efterfølgende behandling, da OS forventes at afspejle både effekten af 1. linjebehandling, men også effekten af de efterfølgende behandlinger. Ansøger antager, at patienter, som progredierer, vil modtage én af nedenstående behandlinger:

- Acalabrutinib administreres oralt to gange dagligt af 100 mg.
- Ibrutinib administreres oralt en gang dagligt af 420 mg.
- Venetoclax + rituximab: Venetoclax administreres oralt en gang dagligt af 400 mg en gang dagligt i kombination med rituximab, der administreres i.v. én gang hver cyklus i 6 cykler. 375 mg/m<sup>2</sup> på dag 1 i første cyklus og 500 mg/m<sup>2</sup> på dag 1 i de efterfølgende 5 cykler.

Ansøger antager, at patienter, der progredierer efter 1. linjebehandling, modtager forskellige regimer af efterfølgende behandling (2. linjebehandling), hvorfor ansøger har præsenteret en fordeling over efterfølgende behandling.

Ansøger antager, at behandling med venetoclax er forbundet med øget risiko for udvikling af tumorlysesyndrom (TLS), jf. lægemidlers SPC. Derfor opstartes behandling med venetoclax med en dosis på 20 mg dagligt og derefter gradvist stigende til 400 mg dagligt i uge fem af behandlingen. Ansøger antager i forbindelse med den gradvise dosisforøgelse en engangsmonitoreringsomkostning forbundet med behandlingen pga. en højere monitoreringsfrekvens. Ansøger antager, at patienter vil monitoreres ambulant én gang ugentligt i de fem uger. Ansøger anvender 2021 DRG-taksten 10MA98, MDC10 1-dagsgruppe, pat. mindst 7 år, der er særlig for monitorering af risiko for udvikling af tumorlysesyndrom.

Ansøger antager, at den gennemsnitlige behandlingsvarighed for efterfølgende behandling for patienter, der vil modtage acalabrutinib og ibrutinib, er lig PFS for ibrutinib og acalabrutinib fra ELEVATE-RR-studiet, da behandlingerne gives indtil progression. Derfor antages den gennemsnitlige behandlingsvarighed for acalabrutinib og ibrutinib at være ca. 2,9 år. Ansøger baserer behandlingsvarigheden for patienter, der modtager venetoclax + rituximab, på oplysninger fra venetoclax SPC. Patienter opstartes i behandling med venetoclax med en dosis på 20 mg dagligt og gradvist stigende til 400 mg dagligt i uge fem af behandlingen for derefter at forsætte behandlingen 2 år frem.

#### **Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling**

Medicinrådet vælger at ekskludere acalabrutinib som behandlingsalternativ for efterfølgende behandling, fordi acalabrutinib ikke er godkendt til behandling i dansk klinisk praksis, derfor er det ikke en mulig behandling ved efterfølgende behandling. Medicinrådet præsenterer nedenfor lægemiddelpriser for de lægemidler, der indgår i efterfølgende behandling, som ikke tidligere er blevet præsenteret, se Tabel 5.



**Tabel 5. Anvendte lægemiddelpriser for efterfølgende behandling, SAIP (marts 2022)**

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Venetoclax	100 mg	112 stk.	■	Amgros

Fagudvalget vurderer, at ansøgers anvendte fordeling over efterfølgende behandling ikke repræsenterer dansk klinisk praksis, hvorfor Medicinrådet ændrer fordelingen. For sammenligning mellem acalabrutinib +/- obinutuzumab med chlorambucil + obinutuzumab og bendamustin + rituximab fremgår fagudvalgets estimering af fordelingen for efterfølgende behandling i Tabel 6.

Jf. afsnit 4.2 ekskluderer Medicinrådet omkostninger til efterfølgende behandling for patienter med deletion17p/p53-mutation, fordi formålet med analysen er at estimere de inkrementelle omkostninger pr. patient ved behandling med acalabrutinib +/- obinutuzumab og ibrutinib, og da data er poolede for både acalabrutinib +/- obinutuzumab og ibrutinib, der vil omkostninger til efterfølgende behandling være ens.

**Tabel 6. Fordeling af patienter, der modtager efterfølgende behandling for patienter uden deletion17p/p53-mutation**

	Ibrutinib	Venetoclax + rituximab
Acalabrutinib +/- obinutuzumab	0 %	100 %
Chlorambucil + obinutuzumab	30 %	70 %
Bendamustin + rituximab	30 %	70 %

Fagudvalget vurderer, at ansøgers estimer for behandlingsvarigheden for både ibrutinib og venetoclax + rituximab virker klinisk plausible, hvorfor Medicinrådet accepterer ansøgers antagelse om behandlingsvarighed.

**Tabel 7. Den gennemsnitlige behandlingsvarighed for efterfølgende behandling for tidligere ubehandlede kronisk lymfatisk leukæmi-patienter med og uden deletion17p/p53-mutation**

	Gennemsnitlig behandlingsvarighed [år]
Ibrutinib	2,9
Venetoclax + Rituximab	2

*Medicinrådet accepterer ansøgers antagelser, men ekskluderer acalabrutinib som behandlingsalternativ i efterfølgende behandling. Samtidig ændrer Medicinrådet fordelingen mellem behandlingsalternativerne i efterfølgende behandling og ekskluderer efterfølgende behandling for patienter med deletion17p/p53-mutation.*



#### 4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. *Medicinrådets værdisætning af enhedsomkostninger*. Ansøger antager, at patienten har en transporttid på 30 minutter hver vej.

Ansøger antager forskellige varigheder i forbindelse med monitorering, hvor en CT-scanning varer 15 minutter, blodpladetransfusion varer 40 minutter, blodtransfusion varer 180 minutter, knoglemarvsprøve og biopsi varer 30 minutter samlet, mens blodprøvetagning, kreatin-niveau-, lymfocyt-, urinsyremåling varer 5 minutter hver. Ansøger præsenterer patienttiden forbundet med lægemiddeladministration for hvert lægemiddel. Forud for i.v.-administration får patienten udført en lymfocyt-, kreatin-niveau-måling og en fuld blodprøve, hvilket ansøger antager varer 20 minutter.

Ansøger antager ligeledes en gangs monitoreringsomkostninger forbundet med opstart af venetoclax + rituximab behandling én gang ugentligt over 5 uger. Ansøger antager, at testen forbundet med monitorering af TLS varer 20 minutter. Ansøger har valgt at ekskludere patientomkostninger til bivirkningsbehandling og patientomkostninger forbundet med administration og monitorering af efterfølgende behandling.

#### Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger

Medicinrådet vælger at ekskludere patienttid forbundet med CT-scanning, blodpladetransfusion, transfusion af blod, knoglemarvsprøve og biopsi, fordi patienten ikke får det regelmæssigt ifm. monitorering hver 3. måned. Medicinrådet vælger at opdatere omkostningen for patienttid til 181 DKK pr. time og transportomkostninger på 140 DKK pr. besøg, jf. *Medicinrådets værdisætning af enhedsomkostninger*.

Medicinrådet accepterer ansøgers antagelser forbundet med den estimerede patienttid, se Tabel 8. Denne ændring vurderes at have lille betydning for analysens resultat.

**Tabel 8. Estimat af effektiv patienttid til monitorering**

	Patienttid [minutter]
Blodprøve, kreatin-niveautest, lymfocyttest, urinsyretest	5
Ventetid	25
Transport	30
Profylaktisk TLS-monitorering	20

Medicinrådet accepterer ansøgers tilgang til estimering af patientomkostninger. I Tabel 9 er estimeret for patienternes ressourceforbrug vist.



**Tabel 9. Estimerede patientomkostninger pr. cyklus (28 dage)**

	Acalabrutinib	Acalabrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Bendamustin + rituximab	Ibrutinib
Patienttid, besøg [timer]	0,43	6,04	6,04	4,08	0,43
Patienttid, transport [antal gange]	0,15	1,5	1,5	1	0,15

*Medicinerådet accepterer ansøgers antagelser, men opdaterer timeomkostning og transportomkostning, ekskluderer patientomkostninger til CT-scanning, blodpladetransfusion, transfusion af blod, knoglemarvsprøve og biopsi.*

### 4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en lang række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Ansøger har udarbejdet de samme typer følsomhedsanalyser for hvert klinisk spørgsmål.

#### **Medicinerådets vurdering af ansøgers valg af følsomhedsanalyser**

Medicinerådet vælger ikke at præsentere ansøgers følsomhedsanalyser. I stedet vælger Medicinerådet at præsentere egne følsomhedsanalyser, se Tabel 10.

For mere uddybende information omkring følsomhedsanalyser vedr. ekstrapoleringer, se afsnit 4.1.2.

**Tabel 10. Følsomhedsanalyser og beskrivelse**

Følsomhedsanalyse	Beskrivelse
<b>Patienter uden deletion17p/p53-mutation – acalabrutinib monoterapi</b>	
Ekstrapolering af TP1 – generaliseret gamma	Data for TP1 ekstrapoleres via generaliseret gammafunktionen i stedet for Gompertz
Ekstrapolering af TP2 – log-logistisk	Data for TP2 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
Ekstrapolering af TP2 – Weibull	Data for TP2 ekstrapoleres via Weibull funktionen i stedet for den eksponentielle
<b>Patienter uden deletion17p/p53-mutation – acalabrutinib + obinutuzumab</b>	



Følsomhedsanalyse	Beskrivelse
Ekstrapolering af TP1 – Weibull	Data for TP1 ekstrapoleres via Weibull funktionen i stedet for Gompertz
Ekstrapolering af TP1 – log-logistisk	Data for TP1 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
Ekstrapolering af TP2 – log-logistisk	Data for TP2 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
Ekstrapolering af TP2 – Weibull	Data for TP2 ekstrapoleres via Weibull funktionen i stedet for den eksponentielle
<b>Patienter uden deletion17p/p53-mutation – chlorambucil + obinutuzumab</b>	
Ekstrapolering af TP1 – generaliseret gamma	Data for TP1 ekstrapoleres via generaliseret gammafunktionen i stedet for Gompertz
Ekstrapolering af TP2 – log-logistisk	Data for TP2 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
Ekstrapolering af TP2 – Weibull	Data for TP2 ekstrapoleres via Weibull funktionen i stedet for den eksponentielle
<b>Patienter uden deletion17p/p53-mutation – bendamustin + rituximab</b>	
Ekstrapolering af TP1 – generaliseret gamma	Data for TP1 ekstrapoleres via generaliseret gammafunktionen i stedet for Gompertz
Hazard Ratio +20%	Ændrer hazard ration +20 % fra MAIC-analysen
Hazard Ratio -20%	Ændrer hazard ration -20 % fra MAIC-analysen
<b>Patienter med deletion17p/p53-mutation – acalabrutinib monoterapi og ibrutinib</b>	
Ekstrapolering af TP1 – Weibull	Data for TP1 ekstrapoleres via Weibull funktionen i stedet for den eksponentielle
Ekstrapolering af TP1 – log-logistisk	Data for TP1 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
Ekstrapolering af TP2 – Weibull	Data for TP1 ekstrapoleres via Weibull funktionen i stedet for den eksponentielle
Ekstrapolering af TP2 – log-logistisk	Data for TP1 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
<b>Patienter med deletion17p/p53-mutation – acalabrutinib + obinutuzumab og ibrutinib</b>	
Ekstrapolering af TP1 – Weibull	Data for TP1 ekstrapoleres via Weibull-funktionen i stedet for den eksponentielle



Følsomhedsanalyse	Beskrivelse
Ekstrapolering af TP1 – log-logistisk	Data for TP1 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
Ekstrapolering af TP2 – Weibull	Data for TP1 ekstrapoleres via Weibull-funktionen i stedet for den eksponentielle
Ekstrapolering af TP2 – log-logistisk	Data for TP1 ekstrapoleres via den log-logistiske funktion i stedet for den eksponentielle
<b>Patienter med og uden deletion17p/p53-mutation alle behandlingsalternativerne</b>	
Ekstrapolering af TP3 – log-logistisk	Data for TP1 ekstrapoleres ved anvendelse af Log-logistiske funktion i stedet for den eksponentielle
Ekstrapolering af TP3 – Gompertz	Data for TP1 ekstrapoleres ved anvendelse af Gompertz-funktionen i stedet for den eksponentielle

*Medicinerådet vælger ikke at præsentere ansøgers følsomhedsanalyser, men præsenterer egne følsomhedsanalyser, der undersøger valget af ekstrapoleringer.*

#### 4.4 Opsummering af basisantagelser

I Tabel 11 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinerådets hovedanalyse.

**Tabel 11. Basisantagelser for ansøgers og Medicinerådets hovedanalyse**

Basisantagelser	Ansøger	Medicinerådet
<b>Klinisk Spørgsmål 1</b>		
<b>Patienter uden deletion17p/p53-mutation</b>		
Tidshorisont	30 år	30 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemedielomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger	Lægemedielomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger
Behandlingslinje	1. linjebehandling	1. linjebehandling
<b>Behandlingslængde:</b>		



Basisantagelser	Ansøger	Medicinrådet
Acalabrutinib	5,8 år	5,8 år
Chlorambucil + obinutuzumab	0,6 år	0,6 år
Bendamustin + rituximab	0,5 år	0,5 år
<b>Parametriske funktioner for TP1</b>		
Acalabrutinib	Gompertz	Gompertz
Chlorambucil + obinutuzumab	Log-normal	Gompertz
Bendamustin + rituximab	Gompertz	Log-normal
<b>Parametriske funktioner for TP2</b>		
Acalabrutinib	Eksponentiel	Eksponentiel
Chlorambucil + obinutuzumab	Eksponentiel	Eksponentiel
Bendamustin + rituximab	Eksponentiel	Eksponentiel
<b>Parametriske funktioner for TP3</b>		
Acalabrutinib	Eksponentiel	Eksponentiel
Chlorambucil + obinutuzumab	Eksponentiel	Eksponentiel
Bendamustin + rituximab	Eksponentiel	Eksponentiel
Inkludering af spild	Nej	Nej
<b>Klinisk Spørgsmål 2</b>		
<b>Patienter uden deletion17p/p53-mutation</b>		
Tidshorisont	30 år	30 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemedielomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger	Lægemedielomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger
Behandlingslinje	1. linjebehandling	1. linjebehandling
<b>Behandlingslængde:</b>		
Acalabrutinib + obinutuzumab	9,1 år	5,4 år
Chlorambucil + obinutuzumab	0,6 år	0,6 år
Bendamustin + rituximab	0,5 år	0,5 år
<b>Parametriske funktioner for TP1</b>		





Basisantagelser	Ansøger	Medicinrådet
Acalabrutinib + obinutuzumab	Weibull	Gompertz
Chlorambucil + obinutuzumab	Log-normal	Gompertz
Bendamustin + rituximab	Weibull	Log-normal
<b>Parametriske funktioner for TP2</b>		
Acalabrutinib + obinutuzumab	Eksponentiel	Eksponentiel
Chlorambucil + obinutuzumab	Eksponentiel	Eksponentiel
Bendamustin + rituximab	Eksponentiel	Eksponentiel
<b>Parametriske funktioner for TP3</b>		
Acalabrutinib + obinutuzumab	Eksponentiel	Eksponentiel
Chlorambucil + obinutuzumab	Eksponentiel	Eksponentiel
Bendamustin + rituximab	Eksponentiel	Eksponentiel
Inkludering af spild	Nej	Nej
<b>Klinisk Spørgsmål 3</b>		
<b>Patienter med deletion17p/p53-mutation</b>		
Tidshorisont	30 år	30 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemedlommkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger	Lægemedlommkostninger Hospitalsomkostninger
Behandlingslinje	1. linjebehandling	1. linjebehandling
Behandlingslængde:		
Acalabrutinib	7,0 år	3,7 år
Ibrutinib	7,0 år	3,7 år
<b>Parametriske funktioner for TP1</b>		
Acalabrutinib	Log-normal	Gompertz
Ibrutinib	Log-normal	Gompertz
<b>Parametriske funktioner for TP2</b>		
Acalabrutinib	Eksponentiel	Eksponentiel
Ibrutinib	Eksponentiel	Eksponentiel



Basisantagelser	Ansøger	Medicinrådet
<b>Parametriske funktioner for TP3</b>		
Acalabrutinib	Eksponentiel	Eksponentiel
Ibrutinib	Eksponentiel	Eksponentiel
Inkludering af spild	Nej	Nej
<b>Klinisk Spørgsmål 4</b>		
<b>Patienter med deletion17p/p53-mutation</b>		
Tidshorisont	30 år	30 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemedielomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger	Lægemedielomkostninger Hospitalsomkostninger Patientomkostninger
Behandlingslinje	1. linjebehandling	1. linjebehandling
<b>Behandlingslængde:</b>		
Acalabrutinib + obinutuzumab	7,0 år	3,7 år
Ibrutinib	7,0 år	3,7 år
<b>Parametriske funktioner for TP1</b>		
Acalabrutinib + obinutuzumab	Log-normal	Gompertz
Ibrutinib	Log-normal	Gompertz
<b>Parametriske funktioner for TP2</b>		
Acalabrutinib + obinutuzumab	Eksponentiel	Eksponentiel
Ibrutinib	Eksponentiel	Eksponentiel
<b>Parametriske funktioner for TP3</b>		
Acalabrutinib + obinutuzumab	Eksponentiel	Eksponentiel
Ibrutinib	Eksponentiel	Eksponentiel
Inkludering af spild	Nej	Nej



## 5. Resultater

### 5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 11.

**For sammenligning mellem acalabrutinib monoterapi og chlorambucil + obinutuzumab**

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [REDACTED] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet med acalabrutinib

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 2.340.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 12.

**Tabel 12. Resultatet af Medicinrådets hovedanalyse ved sammenligning med chlorambucil + obinutuzumab, DKK, diskonterede tal**

	Acalabrutinib	Chlorambucil + obinutuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[REDACTED]	[REDACTED]	[REDACTED]
Hospitalsomkostninger	147.962	162.590	-14.628
Efterfølgende behandling	[REDACTED]	[REDACTED]	[REDACTED]
Patientomkostninger	8.707	13.617	-4.909
<b>Totale omkostninger</b>	[REDACTED]	[REDACTED]	[REDACTED]

**For sammenligning mellem acalabrutinib monoterapi og bendamustin + rituximab**

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [REDACTED] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet med acalabrutinib.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 2.600.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 13.



**Tabel 13. Resultatet af Medicinrådets hovedanalyse ved sammenligning med bendamustin + rituximab, DKK, diskonterede tal**

	Acalabrutinib	Bendamustin + rituximab	Inkrementelle omkostninger
Lægemiddelomkostninger	████████	██████	████████
Hospitalsomkostninger	147.962	159.386	-11.424
Efterfølgende behandling	████████	████████	████████
Patientomkostninger	8.707	10.858	-2.150
<b>Totale omkostninger</b>	████████	████████	████████

**For sammenligning mellem acalabrutinib + obinutuzumab og chlorambucil + obinutuzumab**

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ████████ DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet med acalabrutinib + obinutuzumab.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 2.500.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 14.

**Tabel 14. Resultatet af Medicinrådets hovedanalyse ved sammenligning med chlorambucil + obinutuzumab, DKK, diskonterede tal**

	Acalabrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	████████	████████	████████
Hospitalsomkostninger	188.453	162.590	25.863
Efterfølgende behandling	████████	████████	████████
Patientomkostninger	15.257	13.617	1.641
<b>Totale omkostninger</b>	████████	████████	████████

**For sammenligning mellem acalabrutinib + obinutuzumab og bendamustin + rituximab**

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ████████ DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet med acalabrutinib + obinutuzumab.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 2.900.000 DKK.



Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 15.

**Tabel 15. Resultatet af Medicinrådets hovedanalyse ved sammenligning med bendamustin + rituximab, DKK, diskonterede tal**

	Acalabrutinib + obinutuzumab	Bendamustin + rituximab	Inkrementelle omkostninger
Lægemiddelomkostninger	████████	██████	████████
Hospitalsomkostninger	188.453	159.386	29.066
Efterfølgende behandling	████████	████████	████████
Patientomkostninger	15.257	10.858	4.400
<b>Totale omkostninger</b>	████████	████████	████████

For sammenligning mellem acalabrutinib monoterapi og ibrutinib

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. ████████ DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient -2.215 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 16.

**Tabel 16. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ibrutinib, DKK, diskonterede tal**

	Acalabrutinib	Ibrutinib	Inkrementelle omkostninger
Lægemiddelomkostninger	████████	████████	████████
Hospitalsomkostninger	7.355	13.780	-6.425
<b>Totale omkostninger</b>	████████	████████	████████

For sammenligning mellem acalabrutinib + obinutuzumab og ibrutinib

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ████████ DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 245.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 17.



**Tabel 17. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ibrutinib, DKK, diskonterede tal**

	Acalabrutinib + obinutuzumab	Ibrutinib	Inkrementelle omkostninger
Lægemiddelomkostninger	████████	████████	████████
Hospitalsomkostninger	46.949	13.780	33.169
Patientomkostninger	13.961	7.509	6.452
<b>Totale omkostninger</b>	████████	████████	████████

### 5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i tabellen nedenfor:

- For sammenligningen mellem acalabrutinib monoterapi og chlorambucil + obinutuzumab, se Tabel 48.
- For sammenligningen mellem acalabrutinib monoterapi og bendamustin + rituximab, se Tabel 49.
- For sammenligningen mellem acalabrutinib + obinutuzumab og chlorambucil obinutuzumab, se Tabel 50
- For sammenligningen mellem acalabrutinib + obinutuzumab og bendamustin + rituximab, se Tabel 51
- For sammenligningen mellem acalabrutinib monoterapi og ibrutinib, se Tabel 52
- For sammenligningen mellem acalabrutinib + obinutuzumab og ibrutinib, se Tabel 53.

## 6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at acalabrutinib monoterapi og acalabrutinib + obinutuzumab vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Acalabrutinib bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Acalabrutinib bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.



## 6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at der er 151 patienter om året med behandlingsbehov i 1. linje, hvoraf 90 % ikke har deletion17p/p53-mutation, mens de resterende 10 % har deletion17p/p53-mutation. Dermed antager ansøger, at der er 136 patienter årligt, som ikke har deletion17p/p53-mutation, og 15 patienter årligt, som har deletion17p/p53-mutation. Ansøger antager yderligere, at 20 % af patienterne uden deletion17p/p53-mutation vil blive behandlet med FCR, hvorfor de ikke vil komme i betragtning til behandlingen med acalabrutinib +/- obinutuzumab. Dermed antager ansøger, at der er 109 patienter uden deletion17p/p53-mutation årligt, som vil kandidere til behandlingen.

Ansøger antager, at:

### Patienter uden deletion17p/p53-mutation

- Der er 109 patienter uden deletion17p/p53-mutation, som er kandidater til behandling med acalabrutinib monoterapi, hvoraf ansøger antager, at acalabrutinib vil have et stigende markedsoptag fra 30 % i år 1 til 80 % i år 5.
- Der er 109 patienter uden deletion17p/p53-mutation, som er kandidater til behandling med acalabrutinib + obinutuzumab, hvoraf ansøger antager, at acalabrutinib vil have et stigende markedsoptag fra 30 % i år 1 til 80 % i år 5.

### Patienter med deletion17p/p53-mutation

- Der er 15 patienter med deletion17p/p53-mutation, som er kandidater til behandling med acalabrutinib monoterapi, hvoraf ansøger antager, at acalabrutinib vil have et stigende markedsoptag fra 20 % i år 1 til 40 % i år 5.
- Der er 15 patienter uden deletion17p/p53-mutation, som er kandidater til behandling med acalabrutinib + obinutuzumab, hvoraf ansøger antager, at acalabrutinib vil have et stigende markedsoptag fra 20 % i år 1 til 40 % i år 5.

Ansøger har for patienter med deletion17p/p53-mutation valgt at inddrage en supplerende komparator, venetoclax + obinutuzumab, i deres budgetkonsekvensanalyse. Ansøger sandsynliggør en sammenligning mellem acalabrutinib, ibrutinib og venetoclax + obinutuzumab via en MAIC-analyse, og finder en sammenlignelig effekt henover behandlingsalternativerne. Medicinrådet anbefalede i november 2020 venetoclax + obinutuzumab til netop denne population. Ansøger antager, at venetoclax + obinutuzumab vil have et stigende markedsoptag fra 30 % i år 1 til 55 % i år 5.

### Scenarieanalyse

Ansøger præsenterer en scenarieanalyse i deres budgetkonsekvenser, hvor både acalabrutinib monoterapi og acalabrutinib + obinutuzumab anbefales til patienter med og uden deletion17p/p53-mutation. Ansøger antager, at:

- Der er 109 patienter uden deletion17p/p53-mutation, som er kandidater til behandling med acalabrutinib +/- obinutuzumab, hvoraf ansøger antager, at acalabrutinib monoterapi vil have et stigende markedsoptag fra 20 % i år 1 til 45 % i



år 5, mens acalabrutinib + obinutuzumab vil have et stigende markedsoptag fra 10 % i år 1 til 35 % i år 5.

- Der er 15 patienter med deletion17p/p53-mutation, som er kandidater til behandling med acalabrutinib +/- obinutuzumab, hvoraf ansøger antager, at acalabrutinib monoterapi vil have et stigende markedsoptag fra 10 % i år 1 til 25 % i år 5, mens acalabrutinib + obinutuzumab vil have et stigende markedsoptag fra 10 % i år 1 til 15 % i år 5.

#### Medicinerådets vurdering af ansøgers budgetkonsekvensanalyse

Fagudvalget er blevet konsulteret i forhold til patientantal, hvis acalabrutinib +/- obinutuzumab anbefales som mulig standardbehandling, og hvis ikke acalabrutinib +/- obinutuzumab anbefales. Jf. *Medicinerådets protokol for acalabrutinib +/- obinutuzumab* har fagudvalget angivet, at der er 135 patienter, der ikke har deletion17p/p53-mutation, som vil være kandidater til behandling med acalabrutinib +/- obinutuzumab. Derfor ændrer Medicinerådet patientantallet i Medicinerådets budgetkonsekvensanalyse. For patienter med deletion17p/p53-mutation accepterer fagudvalget ansøgers antagelser, at der er 15 patienter, der har deletion17p/p53-mutation, som vil være kandidater til behandling med acalabrutinib +/- obinutuzumab.

#### Patienter uden deletion17p/p53-mutation

Fagudvalget finder ansøgers estimat for markedsoptag rimelige, men vurderer, at hvis acalabrutinib +/- obinutuzumab anbefales, vil det udkonkurrere komparatoren chlorambucil + obinutuzumab, der i år 5 ikke vil have noget markedsoptag, hvorfor fagudvalget vurderer, at i år 5 vil markedsfordelingen være 90 % til acalabrutinib +/- obinutuzumab og 10 % til bendamustin + rituximab. Medicinerådet vælger at ændre markedsfordelingen i budgetkonsekvensanalysen.

**Tablet 18. Medicinerådets estimat af antal nye patienter pr. år for patienter uden deletion17p/p53-mutation for sammenligningen mellem acalabrutinib monoterapi, chlorambucil + obinutuzumab og bendamustin + rituximab**

	År 1	År 2	År 3	År 4	År 5
<b>Anbefales</b>					
Acalabrutinib	54	68	81	95	122
Chlorambucil + obinutuzumab	41	34	27	20	0
Bendamustin + rituximab	40	33	26	20	13
<b>Anbefales ikke</b>					
Acalabrutinib	0	0	0	0	0
Chlorambucil + obinutuzumab	40	40	40	40	40





	År 1	År 2	År 3	År 4	År 5
Bendamustin + rituximab	95	95	95	95	95

**Tabel 19. Medicinrådets estimat af antal nye patienter pr. år for patienter uden deletion17p/p53-mutation for sammenligningen mellem acalabrutinib + obinutuzumab, chlorambucil + obinutuzumab og bendamustin + rituximab**

	År 1	År 2	År 3	År 4	År 5
<b>Anbefales</b>					
Acalabrutinib + obinutuzumab	54	68	81	95	122
Bendamustin + rituximab	41	34	27	20	0
Chlorambucil + obinutuzumab	40	33	26	20	13
<b>Anbefales ikke</b>					
Acalabrutinib + obinutuzumab	0	0	0	0	0
Bendamustin + rituximab	40	40	40	40	40
Chlorambucil + obinutuzumab	95	95	95	95	95

#### Patienter med deletion17p/p53-mutation

Fagudvalget er blevet konsulteret i forhold til patientantal, hvis acalabrutinib +/- obinutuzumab anbefales som mulig standardbehandling, og hvis ikke acalabrutinib +/- obinutuzumab anbefales. Fagudvalget finder ansøgers antagelser rimelige, at der er 15 patienter pr. år, som kandidater til behandling med acalabrutinib +/- obinutuzumab.

Fagudvalget vurderer, at man på nuværende tidspunkt anvender venetoclax + obinutuzumab i dansk klinisk praksis. Fagudvalget forventer yderligere, at markedsoptaget for venetoclax + obinutuzumab stiger hen over de kommende år. Men da Medicinrådet ikke har vurderet den kliniske værdi af venetoclax + obinutuzumab overfor acalabrutinib +/- obinutuzumab, der er det ikke muligt at inkludere venetoclax + obinutuzumab i budgetkonsekvensanalysen. Derfor vælger Medicinrådet at ekskludere markedsandelen for venetoclax + obinutuzumab, men fordi ansøger har sandsynliggjort en sammenligning via en MAIC-analyse præsenterer Medicinrådet en følsomhedsanalyse, hvor venetoclax + obinutuzumab indgår i



budgetkonsekvensanalysen. Fagudvalget vurderer samtidig, at en anbefaling af acalabrutinib +/- obinutuzumab ikke vil ændre på markedsandelen for venetoclax + obinutuzumab. På grund af usikkerhederne forbundet med dette vælger Medicinrådet at præsentere to følsomhedsanalyser, hvor en anbefaling af acalabrutinib +/- obinutuzumab vil nedjustere markedsandelen for venetoclax + obinutuzumab med hhv. 10 % og 20 % til fordel for acalabrutinib +/- obinutuzumab.

**Table 20. Medicinrådets estimat af antal nye patienter pr. år for patienter med deletion17p/p53-mutation for sammenligningen mellem acalabrutinib og ibrutinib**

	År 1	År 2	År 3	År 4	År 5
<b>Anbefales</b>					
Acalabrutinib	3	5	6	6	6
Ibrutinib	8	5	2	1	1
<b>Anbefales ikke</b>					
Acalabrutinib	0	0	0	0	0
Ibrutinib	9	6	5	5	5

**Table 21. Medicinrådets estimat af antal nye patienter pr. år for patienter med deletion17p/p53-mutation for sammenligningen mellem acalabrutinib + obinutuzumab og ibrutinib**

	År 1	År 2	År 3	År 4	År 5
<b>Anbefales</b>					
Acalabrutinib + obinutuzumab	3	5	6	6	6
Ibrutinib	8	5	2	1	1
<b>Anbefales ikke</b>					
Acalabrutinib + obinutuzumab	0	0	0	0	0
Ibrutinib	9	6	5	5	5

### Scenarieanalyse

Fagudvalget vurderer, at ansøgers scenarieanalyse, hvor en samlet markedsfordeling hen over begge behandlingsmuligheder, acalabrutinib +/- obinutuzumab, for patienter med og uden deletion17p/p53-mutation vil være klinisk meningsfuldt, såfremt Medicinrådet vælger at anbefale begge behandlingsmuligheder. Derfor vælger Medicinrådet at præsentere to følsomhedsanalyser, der belyser markedsøptaget for hhv. patienter med



og uden deletion17p/p53-mutation, men vælger at ændre i ansøgers patientantal til 135 for patienter uden deletion17p/p53-mutation.

*Medicinerådet ændrer patientantallet til 135 for patienter uden deletion17p/p53-mutation patienter pr. år og accepterer ansøgers patientantal for patienter med deletion17p/p53-mutation patienter pr. år. Medicinerådet ændrer markedsoplagsfordelingen for patienter med og uden deletion17p/p53-mutation. Medicinerådet vælger at ekskludere markedsandelen for venetoclax + obinutuzumab for deletion17p/p53-mutation, men pga. usikkerhed præsenterer to følsomhedsanalyser. Ydermere vælger Medicinerådet at præsenterer ansøgers scenarieanalyse, hvor begge behandlingsalternativer anbefales.*

## 6.2 Medicinerådets budgetkonsekvensanalyse

Medicinerådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- For sammenligning mellem acalabrutinib monoterapi, chlorambucil + obinutuzumab og bendamustin + rituximab: 150 patienter
- For sammenligning mellem acalabrutinib + obinutuzumab, chlorambucil + obinutuzumab og bendamustin + rituximab: 150 patienter
- For sammenligning mellem acalabrutinib og ibrutinib: 15 patienter
- For sammenligning mellem acalabrutinib + obinutuzumab og ibrutinib: 15 patienter

### Patienter uden deletion17p/p53-mutation

#### **For sammenligning mellem acalabrutinib, chlorambucil + obinutuzumab og bendamustin + rituximab**

Medicinerådet estimerer, at anvendelse af acalabrutinib monoterapi vil resultere i budgetkonsekvenser på ca. [REDACTED] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 22.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 149 mio. DKK i år 5.

#### **For sammenligning mellem acalabrutinib + obinutuzumab, chlorambucil + obinutuzumab og bendamustin + rituximab**

Medicinerådet estimerer, at anvendelse af acalabrutinib monoterapi vil resultere i budgetkonsekvenser på ca. [REDACTED] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 23.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 190 mio. DKK i år 5.

### Patienter med deletion17p/p53-mutation

#### **For sammenligning mellem acalabrutinib monoterapi og ibrutinib**

Medicinerådet estimerer, at anvendelse af acalabrutinib monoterapi vil resultere i budgetkonsekvenser på ca. [REDACTED] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 24.



Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 5 mio DKK i år 5.

**For sammenligning mellem acalabrutinib + obinutuzumab og ibrutinib**

Medicinerådet estimerer, at anvendelse af acalabrutinib + obinutuzumab vil resultere i budgetkonsekvenser på ca. [REDACTED] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 25.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 6 mio. DKK i år 5.

**Tabel 22. Medicinerådets analyse af totale budgetkonsekvenser for sammenligning mellem acalabrutinib monoterapi, chlorambucil + obinutuzumab og bendamustin + rituximab, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Anbefales ikke	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Totale budgetkonsekvenser</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**Tabel 23. Medicinerådets analyse af totale budgetkonsekvenser for sammenligning mellem acalabrutinib + obinutuzumab, chlorambucil + obinutuzumab og bendamustin + rituximab, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Anbefales ikke	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Totale budgetkonsekvenser</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**Tabel 24. Medicinerådets analyse af totale budgetkonsekvenser for sammenligning mellem acalabrutinib monoterapi og ibrutinib, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Anbefales ikke	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Totale budgetkonsekvenser</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



**Tabel 25. Medicinrådets analyse af totale budgetkonsekvenser for sammenligning mellem acalabrutinib + obinutuzumab og ibrutinib, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

### 6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

#### Patienter med deletion17p/p53-mutation

##### For sammenligning mellem acalabrutinib monoterapi og ibrutinib

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor acalabrutinib monoterapi opnår 10 % yderligere markedsoptag fra venetoclax + obinutuzumab, der vil omkostningerne i år 5 være ca. ■■■■■, se Tabel 26.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor acalabrutinib monoterapi opnår 20 % yderligere markedsoptag fra venetoclax + obinutuzumab, der vil omkostningerne i år 5 være ca. ■■■■■, se Tabel 27.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor venetoclax + obinutuzumab indgår som komparator i, der vil omkostningerne i år 5 være ca. ■■■■■, se Tabel 28

##### For sammenligning mellem acalabrutinib + obinutuzumab og ibrutinib

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor acalabrutinib + obinutuzumab opnår 10 % yderligere markedsoptag fra venetoclax + obinutuzumab, der vil omkostningerne i år 5 være ca. ■■■■■, se Tabel 29.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor acalabrutinib + obinutuzumab opnår 20 % yderligere markedsoptag fra venetoclax + obinutuzumab, der vil omkostningerne i år 5 være ca. ■■■■■, se Tabel 30.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor venetoclax + obinutuzumab indgår som komparator i, der vil omkostningerne i år 5 være ca. ■■■■■, se Tabel 31.

##### Scenarieanalyse

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor både acalabrutinib +/- obinutuzumab vil være en tilgængelig behandling for patienter uden deletion17p/p53-mutation, der vil omkostningerne i år 5 være ca. ■■■■■, se Tabel 32.



Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor både acalabrutinib +/- obinutuzumab vil være en tilgængelig behandling for patienter med deletion17p/p53-mutation, der vil omkostningerne i år 5 være ca. [redacted] se Tabel 33.

**Tabel 26. Medicinrådets analyse af totale budgetkonsekvenser, hvor acalabrutinib monoterapi opnår 10 % yderligere markedsoptag, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

**Tabel 27. Medicinrådets analyse af totale budgetkonsekvenser, hvor acalabrutinib monoterapi opnår 20 % yderligere markedsoptag, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

**Tabel 28. Medicinrådets analyse af totale budgetkonsekvenser, hvor venetoclax + obinutuzumab indgår som komparator, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

**Tabel 29. Medicinrådets analyse af totale budgetkonsekvenser, hvor acalabrutinib + obinutuzumab opnår 10 % yderligere markedsoptag, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■



**Tabel 30. Medicinrådets analyse af totale budgetkonsekvenser, hvor acalabrutinib + obinutuzumab opnår 20 % yderligere markedsoptag, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

**Tabel 31. Medicinrådets analyse af totale budgetkonsekvenser, hvor venetoclax + obinutuzumab indgår som komparator, mio. DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

**Tabel 32. Medicinrådets analyse af totale budgetkonsekvenser hvor både acalabrutinib +/- obinutuzumab er tilgængelig for patienter uden deletion17p/p53-mutation, mio DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

**Tabel 33. Medicinrådets analyse af totale budgetkonsekvenser hvor både acalabrutinib +/- obinutuzumab er tilgængelig for patienter med deletion17p/p53-mutation, mio DKK, ikke-diskonterede tal**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■



## 7. Diskussion

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostninger for acalabrutinib +/- obinutuzumab.

Analyserne i Medicinrådets vurdering af acalabrutinib +/- obinutuzumab er baseret på *data cut* med en median opfølgning på 28 måneder, hvor data anskues at være umodent. Efterfølgende er der publiceret data fra et senere *data cut* med ca. fire års opfølgning (46,9 måneder) [8], hvor median PFS for acalabrutinib +/- obinutuzumab ikke var nået, mens den mediane PFS for chlorambucil + obinutuzumab var 27,8 måneder. PFS-raten ved måned 48 var 78 % for acalabrutinib monoterapi og 87 % for acalabrutinib + obinutuzumab for patienter uden deletion17p/p53-mutation. Og PFS-raten ved måned 48 var 76 % for acalabrutinib monoterapi og 75 % for acalabrutinib + obinutuzumab for patienter med deletion17p/p53-mutation. Disse nye data er ikke blevet inkluderet i den sundhedsøkonomiske model, men underbygger, at valget af ekstrapolering for TP1 for acalabrutinib +/- obinutuzumab er det mest klinisk plausible valg af ekstrapolering for dansk klinisk praksis. Det nye data giver ikke nogen yderligere informationer omkring data for TP2, hvorfor det ikke giver anledning til ændringer eller opdateringer vedr. TP2.

Fagudvalget vurderer i vurderingsrapporten, afsnit 5.2.2, at data for median PFS er umodne, hvorfor valget af ekstrapoleringer for TP1 bør tolkes med stor forsigtighed for sammenligningen mellem acalabrutinib +/- obinutuzumab og komparatorerne, fordi det har stor indflydelse på, hvor lang tid patienten befinder sig i modellens stadie, PFS, hvor patienten akkumulerer omkostninger til behandling med acalabrutinib +/- obinutuzumab. Medicinrådet præsenterer følsomhedsanalyser, der undersøger alternative valg af ekstrapolering for at undersøge omfanget af usikkerheden på de inkrementelle omkostninger. Dette uddybes nedenfor for hver sammenligning:

### *Acalabrutinib monoterapi vs. chlorambucil + obinutuzumab*

I Medicinrådets hovedanalyse anvendes Gompertz-funktionen til ekstrapolering af TP1 for acalabrutinib monoterapi sammenlignet med chlorambucil + obinutuzumab, der bliver de inkrementelle omkostninger [REDACTED]. Ved anvendelse af den generaliseret gammafunktion for acalabrutinib monoterapi bliver de inkrementelle omkostninger [REDACTED]. Det resulterer fortsat i betydelige inkrementelle omkostninger især fordi patienterne behandles længere tid med acalabrutinib monoterapi.

### *Acalabrutinib monoterapi vs. bendamustin + rituximab*

I Medicinrådets hovedanalyse anvendes Gompertz-funktionen til ekstrapolering af TP1 for acalabrutinib monoterapi sammenlignet med bendamustin + rituximab, der bliver de inkrementelle omkostninger [REDACTED]. Ved anvendelse af den generaliseret gammafunktion for acalabrutinib monoterapi bliver de inkrementelle omkostninger [REDACTED]. Det resulterer fortsat i betydelige inkrementelle omkostninger især fordi patienterne behandles længere tid med acalabrutinib monoterapi.





#### *Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab*

I Medicinrådets hovedanalyse anvendes Gompertz-funktionen til ekstrapolering af TP1 for acalabrutinib + obinutuzumab sammenlignet med chlorambucil + obinutuzumab, der bliver de inkrementelle omkostninger [REDACTED]. Ved anvendelse af Weibull-funktionen for acalabrutinib + obinutuzumab bliver de inkrementelle omkostninger [REDACTED] mens ved anvendelse af den log-logistiske funktion for acalabrutinib + obinutuzumab bliver de inkrementelle omkostninger [REDACTED]. Det resulterer fortsat i betydelige inkrementelle omkostninger især fordi patienterne behandles længere tid med acalabrutinib + obinutuzumab.

#### *Acalabrutinib + obinutuzumab vs. bendamustin + rituximab*

I Medicinrådets hovedanalyse anvendes Gompertz-funktionen til ekstrapolering af TP1 for acalabrutinib + obinutuzumab sammenlignet med bendamustin + rituximab, der bliver de inkrementelle omkostninger [REDACTED]. Ved anvendelse af Weibull-funktionen for acalabrutinib + obinutuzumab bliver de inkrementelle omkostninger [REDACTED] mens ved anvendelse af den log-logistiske funktion for acalabrutinib + obinutuzumab bliver de inkrementelle omkostninger [REDACTED]. Det resulterer fortsat i betydelige inkrementelle omkostninger især fordi patienterne behandles længere tid med acalabrutinib + obinutuzumab.

#### *Acalabrutinib monoterapi vs. ibrutinib*

I Medicinrådets hovedanalyse anvendes Gompertz-funktionen til ekstrapolering af TP1 for acalabrutinib monoterapi sammenlignet med ibrutinib, der bliver de inkrementelle omkostninger [REDACTED]. Ved anvendelse af den Weibull-funktionen for begge behandlinger bliver de inkrementelle omkostninger [REDACTED] mens ved anvendelse af den log-logistiske funktion for begge behandlinger bliver de inkrementelle omkostninger [REDACTED]. Patienterne behandles længere tid med både acalabrutinib og ibrutinib, fordi de behandles indtil progression.

#### *Acalabrutinib + obinutuzumab vs. ibrutinib*

I Medicinrådets hovedanalyse anvendes Gompertz-funktionen til ekstrapolering af TP1 for acalabrutinib + obinutuzumab sammenlignet med ibrutinib, der bliver de inkrementelle omkostninger [REDACTED]. Ved anvendelse af Weibull-funktionen for begge behandlinger bliver de inkrementelle omkostninger [REDACTED] mens ved anvendelse af den log-logistiske funktion for begge behandlinger bliver de inkrementelle omkostninger [REDACTED]. Patienterne behandles længere tid med både acalabrutinib og ibrutinib, fordi de behandles indtil progression, men det resulterer fortsat i betydelige inkrementelle omkostninger.

På baggrund af umodne data fra ELEVATE-TN-studiet, der skal valget af ekstrapoleringer for TP2 tolkes med stor forsigtighed for sammenligningen mellem acalabrutinib +/- obinutuzumab og komparatorerne, fordi TP2 informerer omkring andelen af patienter, der dør, inden de progredierer i modellen. Dette har mindre indflydelse på de inkrementelle omkostninger, fordi de i høj grad drives af lægemiddelomkostninger for acalabrutinib +/- obinutuzumab ifm. behandling i PF-stadiet, og da andelen af patienter



der går direkte fra helbredsstadiet PF til død er små, har det mindre betydning på de inkrementelle omkostninger.

Ansøger vælger at poole data for acalabrutinib +/- obinutuzumab for patienter med del(17p)/p53 mutation fra ELEVATE-TN-studiet, men da andelen af patienter med denne mutation ikke er særlig stor i ELEVATE-TN, kan der forekomme usikkerhed omkring styrken af PFS og OS-kurverne præsenteret. Dette skaber større usikkerhed omkring valget af ekstrapoleringer, hvorfor Medicinrådet vælger at præsentere forskellige følsomhedsanalyser, der undersøger betydningen af valget af en anden ekstrapolering.



## 8. Referencer

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## 9. Versionslog

### Versionslog

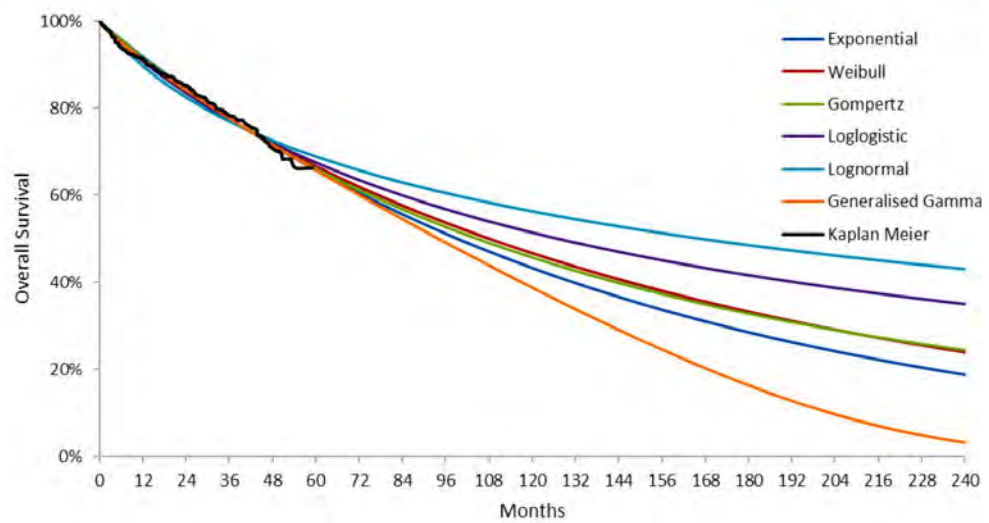
Version	Dato	Ændring
1.0	15. juni 2022	Godkendt af Medicinrådet.



# 10. Bilag

## 10.1 Ekstrapoleringer

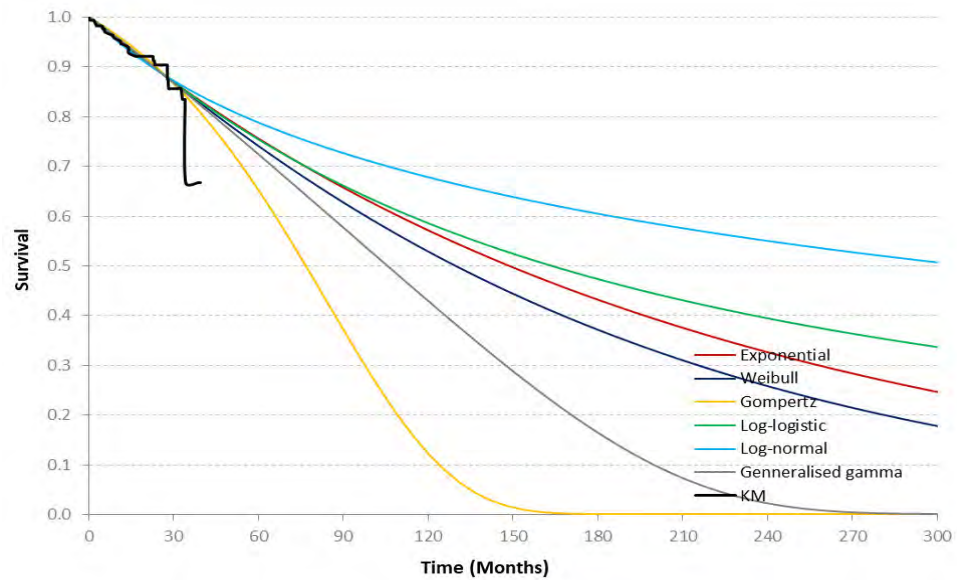
Nedenfor præsenteres ekstrapoleringer for intervention og komparatorerne. Fordi ekstrapoleringen for TP3 fra ELEVATE-RR-studiet omtales først i afrapporteringen, bliver den præsenteret først, samt fordi den også anvendes på alle behandlingerne.



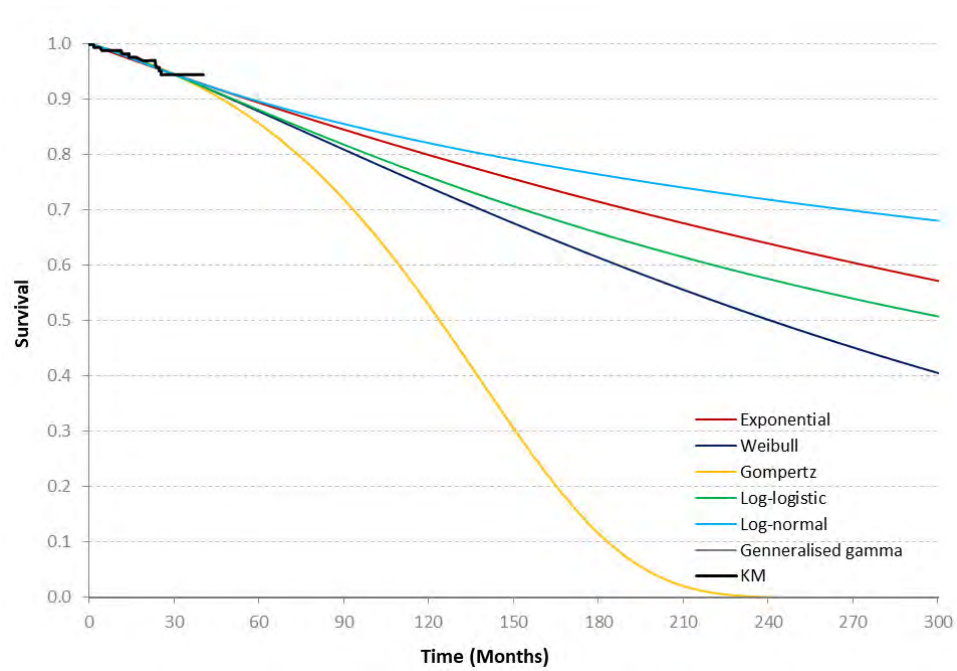
Figur 8. TP3 fra ELEVATE-RR for alle behandlingsalternativer



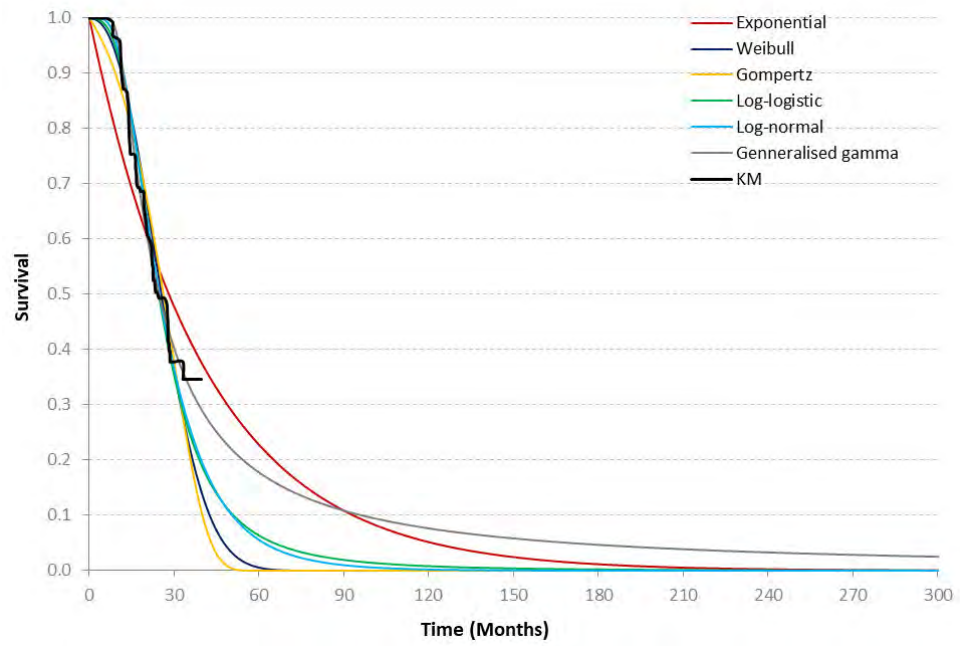
Patienter uden deletion17p/p53-mutation



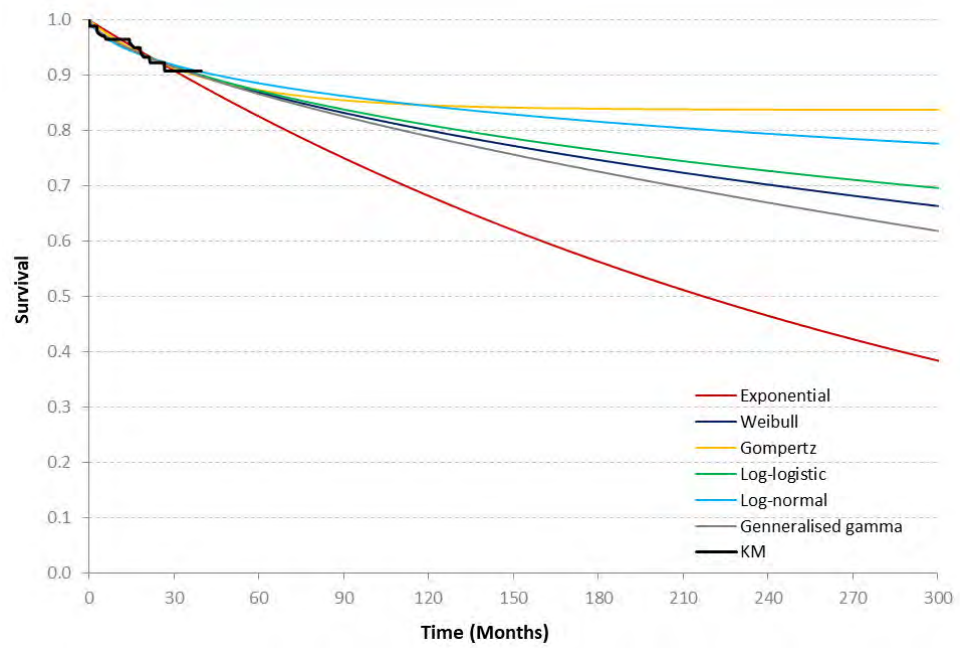
Figur 9. TP1 fra ELEVATE-TN for acalabrutinib monoterapi



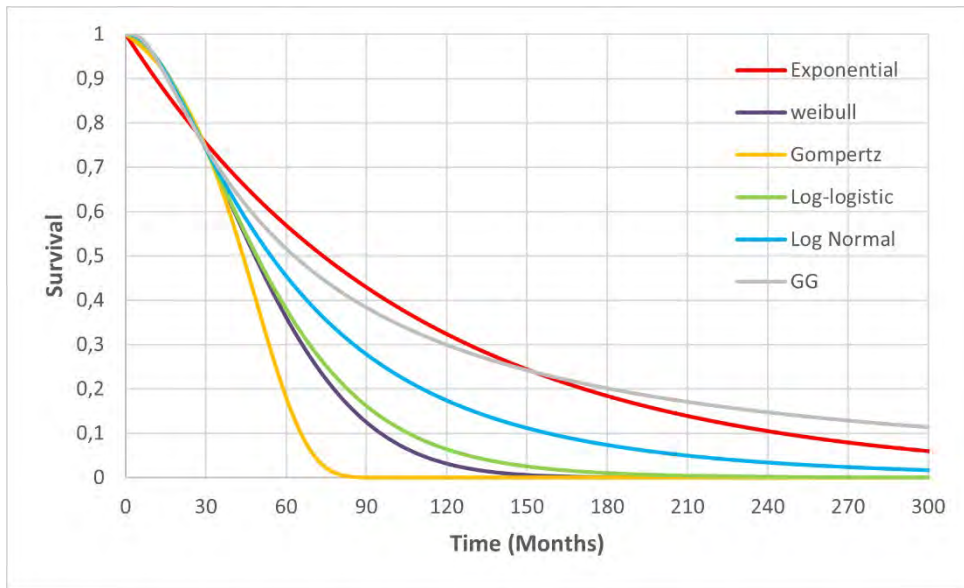
Figur 10. TP2 fra ELEVATE-TN for acalabrutinib monoterapi



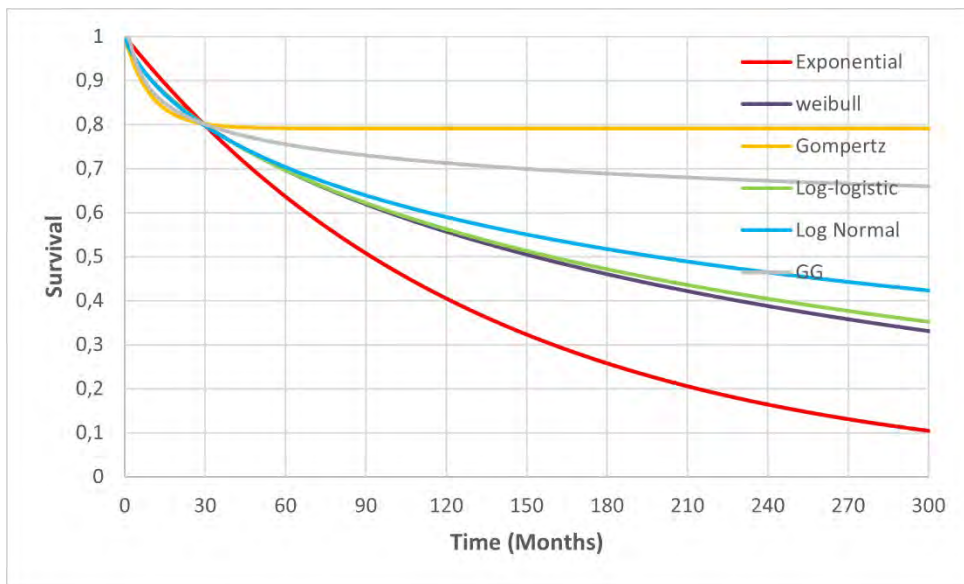
Figur 11. TP1 fra ELEVATE-TN for chlorambucil + obinutuzumab



Figur 12. TP2 fra ELEVATE-TN for chlorambucil + obinutuzumab

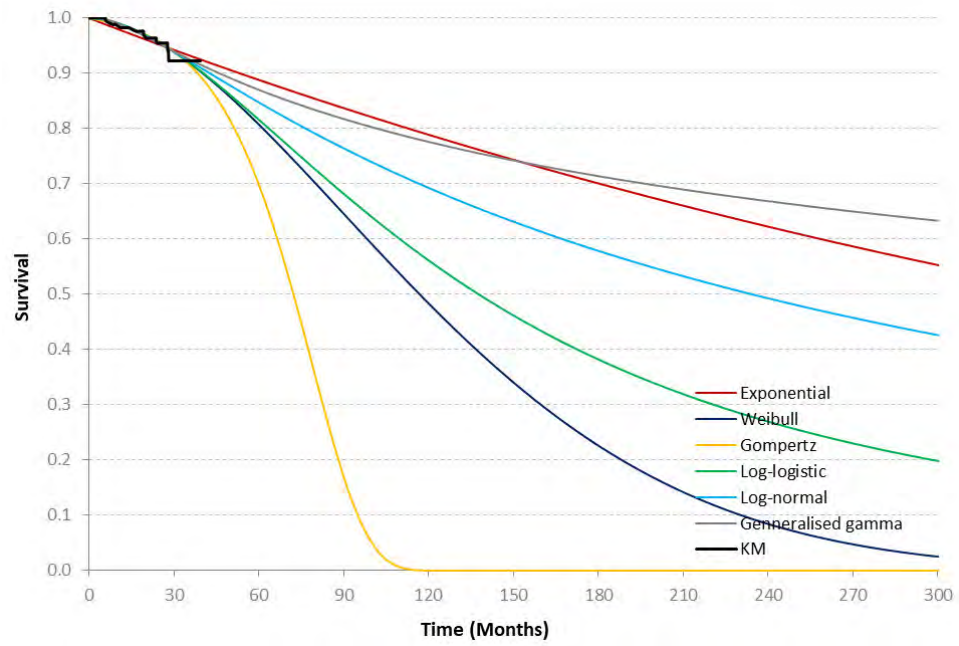


**Figur 13. TP1 fra ELEVATE-TN fra acalabrutinib monoterapi med Hazard Ratio på 2,63 fra MAIC for bendamustin + rituximab**

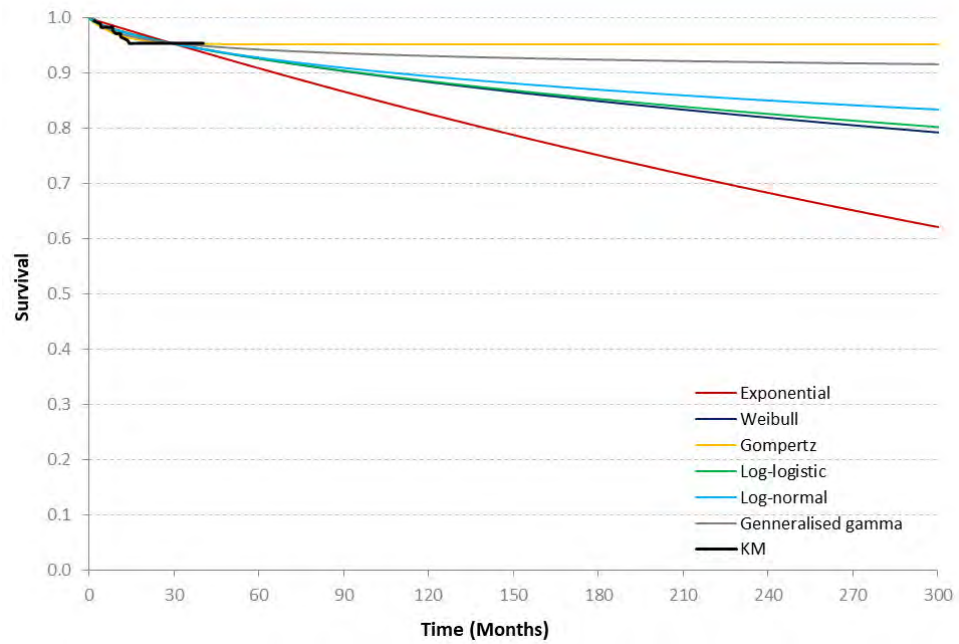


**Figur 14. TP2 fra ELEVATE-TN fra acalabrutinib monoterapi med Hazard Ratio på 2,63 fra MAIC for bendamustin + rituximab**

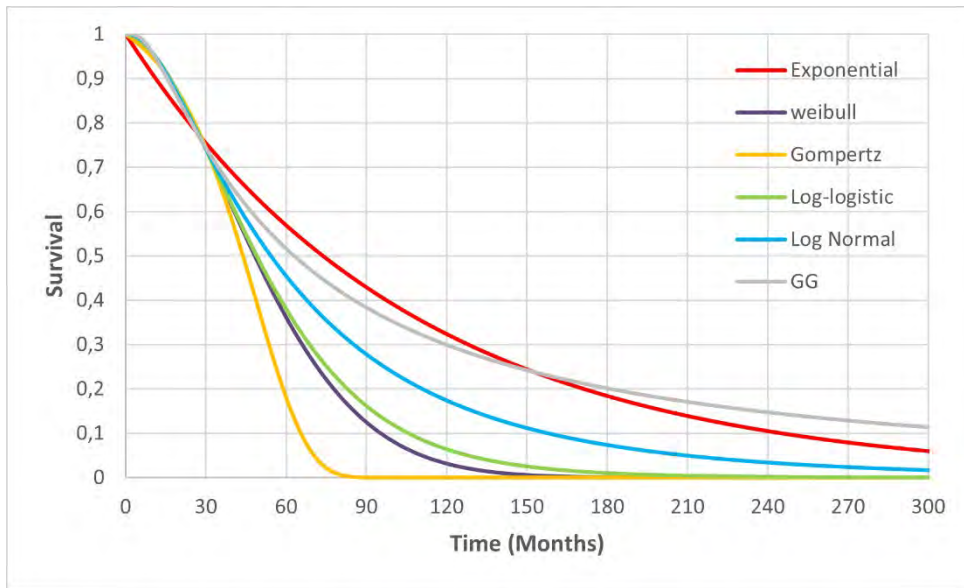




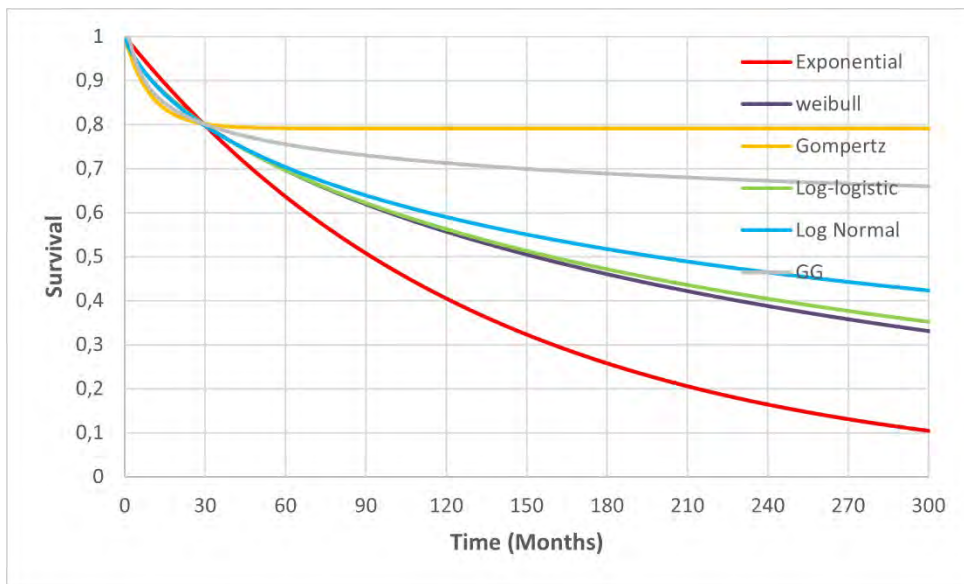
Figur 15. TP1 fra ELEVATE-TN for acalabrutinib + obinutuzumab



Figur 16. TP2 fra ELEVATE-TN for acalabrutinib + obinutuzumab



**Figur 17. TP1 fra ELEVATE-TN fra acalabrutinib + obinutuzumab med Hazard Ratio på 4,76 fra MAIC for bendamustin + rituximab**

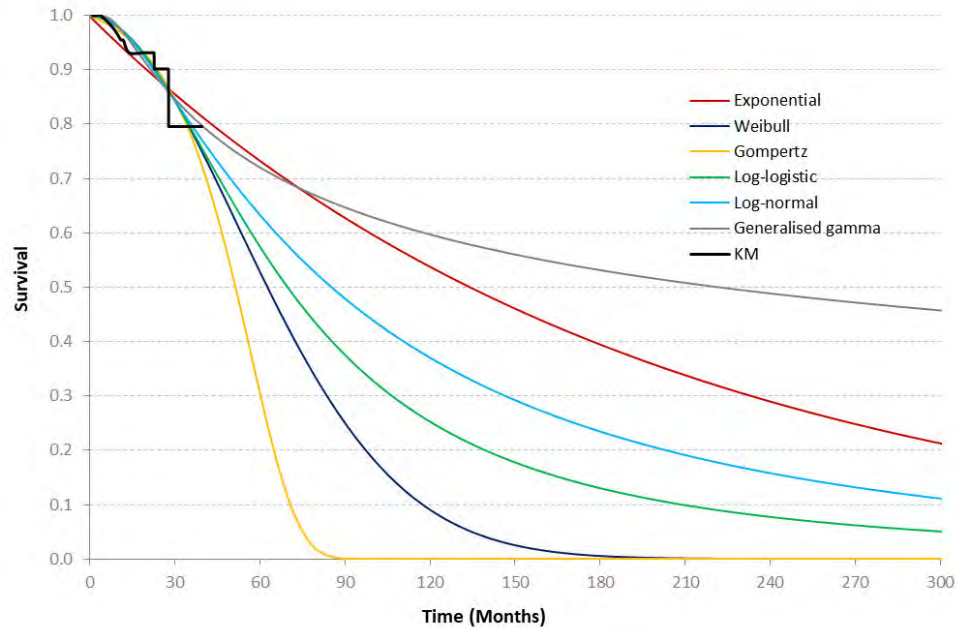


**Figur 18. TP2 fra ELEVATE-TN fra acalabrutinib + obinutuzumab med Hazard Ratio på 4,76 fra MAIC for bendamustin + rituximab**

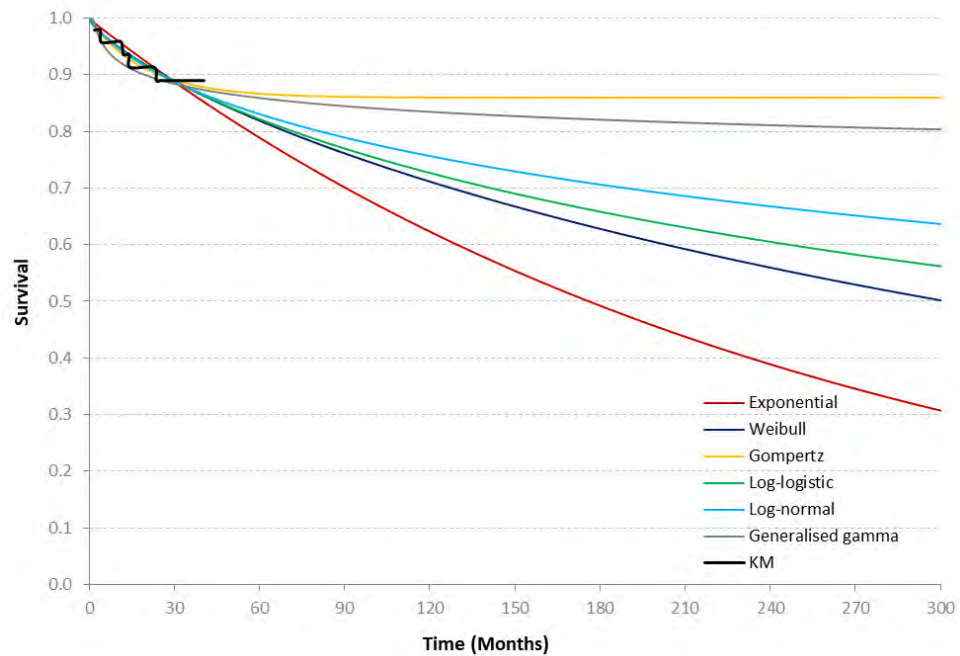


## Patienter med deletion17p/p53-mutation

### TP1 for acalabrutinib og ibrutinib



Figur 19. TP1 fra ELEVATE-TN for acalabrutinib +/- obinutuzumab og ibrutinib



Figur 20. TP2 fra ELEVATE-TN for acalabrutinib +/- obinutuzumab og ibrutinib



## 10.2 Resultatet af ansøgers hovedanalyse

### Patienter uden deletion17p/p53-mutation

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient for sammenligning med acalabrutinib og chlorambucil + obinutuzumab [REDACTED] DKK og for sammenligning med acalabrutinib og bendamustin + rituximab [REDACTED] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 34 og Tabel 35.

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient for sammenligning med acalabrutinib + obinutuzumab og chlorambucil + obinutuzumab [REDACTED] DKK og for sammenligning med acalabrutinib + obinutuzumab og bendamustin + rituximab [REDACTED] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 34 og Tabel 35.

### Patienter med deletion17p/p53-mutation

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient for sammenligning med acalabrutinib og ibrutinib [REDACTED] DKK og for sammenligning med acalabrutinib + obinutuzumab og venetoclax + obinutuzumab [REDACTED] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 36 og Tabel 37 .

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient for sammenligning med acalabrutinib og ibrutinib [REDACTED] DKK og for sammenligning med acalabrutinib + obinutuzumab og venetoclax + obinutuzumab [REDACTED] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 38 og Tabel 39.

**Tabel 34. Resultatet af ansøgers hovedanalyse ved sammenligning med chlorambucil + obinutuzumab, DKK, diskonterede tal**

	Acalabrutinib	Chlorambucil + obinutuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[REDACTED]	[REDACTED]	[REDACTED]
Hospitalsomkostninger	1.343.590	1.170.713	172.877
Efterfølgende behandling	[REDACTED]	[REDACTED]	[REDACTED]
Patientomkostninger	49.644	50.298	-655
<b>Totale omkostninger</b>	[REDACTED]	[REDACTED]	[REDACTED]

**Tabel 35. Resultatet af ansøgers hovedanalyse ved sammenligning med bendamustin + rituximab, DKK, diskonterede tal**

	Acalabrutinib	Bendamustin + rituximab	Inkrementelle omkostninger
Lægemiddelomkostninger	[REDACTED]	[REDACTED]	[REDACTED]



	Acalabrutinib	Bendamustin + rituximab	Inkrementelle omkostninger
Hospitalsomkostninger	1.343.590	1.063.223	280.367
Efterfølgende behandling	██████	██████	██████
Patientomkostninger	49.644	45.011	4.633
<b>Totale omkostninger</b>	██████	██████	██████

**Tabel 36. Resultatet af ansøgers hovedanalyse ved sammenligning med chlorambucil + obinutuzumab, DKK, diskonterede tal**

	Acalabrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	██████	██████	██████
Hospitalsomkostninger	1.516.504	1.170.713	345.791
Efterfølgende behandling	██████	██████	██████
Patientomkostninger	63.101	50.298	12.803
<b>Totale omkostninger</b>	██████	██████	██████

**Tabel 37. Resultatet af ansøgers hovedanalyse ved sammenligning med bendamustin + rituximab, DKK, diskonterede tal**

	Acalabrutinib + obinutuzumab	Bendamustin + rituximab	Inkrementelle omkostninger
Lægemiddelomkostninger	██████	██████	██████
Hospitalsomkostninger	1.516.504	1.060.731	455.773
Efterfølgende behandling	██████	██████	██████
Patientomkostninger	63.101	44.961	18.140
<b>Totale omkostninger</b>	██████	██████	██████

**Tabel 38. Resultatet af ansøgers hovedanalyse ved sammenligning med ibrutinib, DKK, diskonterede tal**

	Acalabrutinib	Ibrutinib	Inkrementelle omkostninger
Lægemiddelomkostninger	██████	██████	██████



	Acalabrutinib	Ibrutinib	Inkrementelle omkostninger
Hospitalsomkostninger	1.229.947	1.235.845	-5.897
Efterfølgende behandling	█	█	█
Patientomkostninger	45.423	45.423	0
<b>Totale omkostninger</b>	<b>█</b>	<b>█</b>	<b>█</b>

**Table 39. Resultatet af ansøgers hovedanalyse ved sammenligning med ibrutinib, DKK, diskonterede tal**

	Acalabrutinib	Venetoclax + obinutuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	█	█	█
Hospitalsomkostninger	1.229.947	56.651	1.173.296
Efterfølgende behandling	█	█	█
Patientomkostninger	45.423	55.589	-10.166
<b>Totale omkostninger</b>	<b>█</b>	<b>█</b>	<b>█</b>

**Table 40. Resultatet af ansøgers hovedanalyse ved sammenligning med ibrutinib, DKK, diskonterede tal**

	Acalabrutinib + obinutuzumab	Ibrutinib	Inkrementelle omkostninger
Lægemiddelomkostninger	█	█	█
Hospitalsomkostninger	1.269.840	1.235.845	33.995
Efterfølgende behandling	█	█	█
Patientomkostninger	53.895	45.423	8.472
<b>Totale omkostninger</b>	<b>█</b>	<b>█</b>	<b>█</b>

**Table 41. Resultatet af ansøgers hovedanalyse ved sammenligning med venetoclax + obinutuzumab, DKK, diskonterede tal**

	Acalabrutinib + obinutuzumab	Venetoclax + obinutuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	█	█	█



	Acalabrutinib + obinutuzumab	Venetoclax + obinutuzumab	Inkrementelle omkostninger
Hospitalsomkostninger	1.269.840	56.651	1.213.189
Efterfølgende behandling	■	■	■
Patientomkostninger	53.895	55.589	-1.693
<b>Totale omkostninger</b>	■	■	■

#### Resultatet af ansøgers budgetkonsekvensanalyse

##### Patienter uden deletion17p/p53-mutation

Ansøger estimerer, at anvendelse af acalabrutinib monoterapi vil resultere i budgetkonsekvenser på ca. ■ DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 42.

Ansøger estimerer, at anvendelse af acalabrutinib + obinutuzumab vil resultere i budgetkonsekvenser på ca. ■ DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 43.

**Tabel 42. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal: Acalabrutinib monoterapi**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■

**Tabel 43. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal: Acalabrutinib + obinutuzumab**

	År 1	År 2	År 3	År 4	År 5
Anbefales	■	■	■	■	■
Anbefales ikke	■	■	■	■	■
<b>Totale budgetkonsekvenser</b>	■	■	■	■	■



### Patienter med deletion17p/p53-mutation

Ansøger estimerer, at anvendelse af acalabrutinib monoterapi vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 44

Ansøger estimerer, at anvendelse af acalabrutinib + obinutuzumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 45.

**Tabel 44. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal: Acalabrutinib monoterapi**

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>Totale budgetkonsekvenser</b>	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**Tabel 45. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal: Acalabrutinib + obinutuzumab**

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>Totale budgetkonsekvenser</b>	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]





### 10.3 Ansøgere anvendte bivirkningsfrekvenser for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi

**Tablet 46. Rapporterede bivirkningsfrekvenser ved behandling med acalabrutinib og komparatorer for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med og uden deletion17p/p53-mutation**

	Acalabrutinib	Acalabrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Ibrutinib	Bendamustin + Rituximab
Abdominale smerter	0 %	0 %	0 %	2,96 %	0 %
ALT- / AST-stigning	0,56 %	2,81 %	1,78 %	0 %	0 %
Anæmi	6,70 %	5,62 %	7,10 %	5,93 %	11,93 %
Atrieflimren	0 %	0,60 %	0 %	4,00 %	0 %
Blødning	1,70 %	1,70 %	0 %	6,00 %	0 %
Febril neutropeni	1,12 %	1,69 %	5,33 %	2,22 %	7,39 %
Hyperglykæmi	0 %	0 %	0 %	0 %	0 %
Hypotension	2,25 %	2,81 %	2,96 %	4,44 %	10,80 %
Hypertension	0,56 %	4,49 %	1,78 %	3,70 %	0 %
Infektion	14,00 %	20,8 %	8,30 %	25,00 %	8,52 %
Infusionsrelaterede reaktioner	0 %	2,25 %	5,33 %	0 %	0 %
Neutropeni	9,50 %	29,78 %	41,42 %	10,37 %	0 %
Nedsat neutrofilital	0 %	1,12 %	2,96 %	0 %	37,50 %
Udslæt	0,56 %	0,56 %	0 %	2,96 %	0 %
Trombocytopeni	2,79 %	8,43 %	11,83 %	2,22 %	0 %
Tumorlysesyndrom	0 %	1,12 %	7,69 %	0 %	0 %
<b>Kilde (studie)</b>	<b>ELEVATE-TN [1]</b>	<b>ELEVATE-TN [1]</b>	<b>ELEVATE-TN [1]</b>	<b>RESONATE [3]</b>	<b>Woyach et al. [2]</b>

[1]: ELEVATE-TN, [2]: Woyach et al. 2018, [3]: Barr et al. 2018.



## 10.4 Ansøgers anvendte fordeling af bivirkningsbehandling og estimering af bivirkningsomkostning for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi

**Tabel 47. Fordeling af bivirkningsbehandling og estimering af bivirkningsomkostning for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med og uden deletion17p/p53-mutation**

	Indlæggelse		Ambulant	
	Frekvens	DRG-takst	Frekvens	DRG-takst
Abdominale smerter / Diarré	70 %	06MA11	30 %	06MA98
ALT- / AST-stigning	0 %	-	-	-
Anæmi	5 %	16MA10	95 %	16MA98
Atrieflimren	100 %	05MA07	0 %	-
Blødning	0 %	-	100 %	16MA98
Febril neutropeni	100 %	16MA03	0 %	-
Hyperglykæmi	0 %	-	100 %	10MA98
Hypotension	100 %	05MA15	0 %	-
Hypertension	100 %	05MA11	0 %	-
Infektion	100 %	18MA08	0 %	-
Infusionsrelaterede reaktioner	0 %	-	100 %	18MA98
Neutropeni	10 %	16MA03	90 %	16MA98
Nedsat neutrofilital	10 %	16MA03	90 %	16MA98
Udslæt	0 %	-	100 %	70AK02
Trombocytopeni	10 %	16MA09	90 %	16MA98
Tumorlysesyndrom	100 %	10MA06	0 %	-



## 10.5 Resultatet af Medicinrådets følsomhedsanalyser

**Table 48. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen for sammenligningen mellem acalabrutinib monoterapi og chlorambucil + obinutuzumab, DKK**

Scenarie	Inkrementelle omkostninger
<b>Resultatet af hovedanalysen: acalabrutinib monoterapi sammenlignet med chlorambucil + obinutuzumab</b>	████████
Anvender den generaliserede gamma-funktion for TP1 for acalabrutinib monoterapi	████████
Anvender den log-logistiske funktion for TP2 for acalabrutinib monoterapi	████████
Anvender Weibull-funktionen for TP2 for acalabrutinib monoterapi	████████
Anvender den log-logistiske funktion for TP3 for acalabrutinib monoterapi	████████
Anvender Gompertz-funktionen for TP3 for acalabrutinib monoterapi	████████
Anvender Weibull-funktionen for TP1 for chlorambucil + obinutuzumab	████████
Anvender den log-normale funktion for TP1 for chlorambucil + obinutuzumab	████████
Anvender den generaliserede gamma-funktion for TP2 for chlorambucil + obinutuzumab	████████
Anvender Weibull-funktionen for TP2 for chlorambucil + obinutuzumab	████████
Anvender den log-logistiske funktion for TP3 for chlorambucil + obinutuzumab	████████
Anvender Gompertz-funktionen for TP3 for chlorambucil + obinutuzumab	████████



**Table 49. Result of the Council of Medicine's sensitivity analysis compared with the main analysis for the comparison between acalabrutinib monotherapy and bendamustin + rituximab, DKK**

Scenario	Incremental costs
<b>Result of the main analysis: acalabrutinib monotherapy compared with bendamustin + rituximab</b>	████████
Uses the generalized gamma function for TP1 for acalabrutinib monotherapy	████████
Uses the log-logistic function for TP2 for acalabrutinib monotherapy	████████
Uses the Weibull function for TP2 for acalabrutinib monotherapy	████████
Uses the log-logistic function for TP3 for acalabrutinib monotherapy	████████
Uses the Gompertz function for TP3 for acalabrutinib monotherapy	████████
Changes hazard ratio +20% from MAIC analysis for bendamustin + rituximab	████████
Changes hazard ratio -20% from MAIC analysis for bendamustin + rituximab	████████
Uses the log-logistic function for TP3 for bendamustin + rituximab	████████
Uses the Gompertz function for TP3 for bendamustin + rituximab	████████

**Table 50. Result of the Council of Medicine's sensitivity analysis compared with the main analysis for the comparison between acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab, DKK**

Scenario	Incremental costs
<b>Result of the main analysis: acalabrutinib + obinutuzumab compared with chlorambucil + obinutuzumab</b>	████████
Uses the Weibull function for TP1 for acalabrutinib + obinutuzumab	████████
Uses the log-logistic function for TP1 for acalabrutinib + obinutuzumab	████████
Uses the Weibull function for TP2 for acalabrutinib + obinutuzumab	████████



Scenarie	Inkrementelle omkostninger
Anvender den log-logistiske funktion for TP2 for acalabrutinib + obinutuzumab	████████
Anvender den log-logistiske funktion for TP3 for acalabrutinib + obinutuzumab	████████
Anvender Gompertz-funktionen for TP3 for acalabrutinib + obinutuzumab	████████
Anvender Weibull-funktionen for TP1 for chlorambucil + obinutuzumab	████████
Anvender den log-normale funktion for TP1 for chlorambucil + obinutuzumab	████████
Anvender den generaliserede gamma-funktion for TP2 for chlorambucil + obinutuzumab	████████
Anvender Weibull-funktionen for TP2 for chlorambucil + obinutuzumab	████████
Anvender den log-logistiske funktion for TP3 for chlorambucil + obinutuzumab	████████
Anvender Gompertz-funktionen for TP3 for chlorambucil + obinutuzumab	████████

**Tabel 51. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen for sammenligningen mellem acalabrutinib + obinutuzumab og bendamustin + rixtuximab, DKK**

Scenarie	Inkrementelle omkostninger
<b>Resultatet af hovedanalysen: acalabrutinib + obinutuzumab sammenlignet med bendamustin + rituximab</b>	████████
Anvender Weibull-funktionen for TP1 for acalabrutinib + obinutuzumab	████████
Anvender den log-logistiske funktion for TP1 for acalabrutinib + obinutuzumab	████████
Anvender Weibull-funktionen for TP2 for acalabrutinib + obinutuzumab	████████
Anvender den log-logistiske funktion for TP2 for acalabrutinib + obinutuzumab	████████
Anvender den log-logistiske funktion for TP3 for acalabrutinib + obinutuzumab	████████



Scenarie	Inkrementelle omkostninger
Anvender Gompertz-funktionen for TP3 for acalabrutinib + obinutuzumab	████████
Ændrer hazard ration +20 % fra MAIC-analysen for bendamustin + rituximab	████████
Ændrer hazard ration -20 % fra MAIC-analysen for bendamustin + rituximab	████████
Anvender den log-logistiske funktion for TP3 for bendamustin + rituximab	████████
Anvender Gompertz-funktionen for TP3 for bendamustin + rituximab	████████

**Tabel 52. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen for sammenligningen mellem acalabrutinib monoterapi og ibrutinib, DKK**

Scenarie	Inkrementelle omkostninger
<b>Resultatet af hovedanalysen: acalabrutinib monoterapi sammenlignet med ibrutinib</b>	████████
Anvender Weibull-funktionen for TP1 for acalabrutinib monoterapi og ibrutinib	████████
Anvender den log-logistiske funktion for TP1 for acalabrutinib monoterapi og ibrutinib	████████
Anvender Weibull-funktionen for TP2 for acalabrutinib monoterapi og ibrutinib	████████
Anvender den log-logistiske funktion for TP2 for acalabrutinib monoterapi og ibrutinib	████████
Anvender den log-logistiske funktion for TP3 for acalabrutinib monoterapi og ibrutinib	████████
Anvender Gompertz-funktionen for TP3 for acalabrutinib monoterapi og ibrutinib	████████



**Table 53. Result of the Medicinrådets sensitivity analysis compared with the main analysis for the comparison between acalabrutinib + obinutuzumab and ibrutinib, DKK**

Scenario	Incremental costs
Result of the main analysis: acalabrutinib + obinutuzumab compared with ibrutinib	██████
Uses Weibull function for TP1 for acalabrutinib + obinutuzumab and ibrutinib	██████
Uses the log-logistic function for TP1 for acalabrutinib + obinutuzumab and ibrutinib	██████
Uses Weibull function for TP2 for acalabrutinib + obinutuzumab and ibrutinib	██████
Uses the log-logistic function for TP2 for acalabrutinib + obinutuzumab and ibrutinib	██████
Uses the log-logistic function for TP3 for acalabrutinib + obinutuzumab and ibrutinib	██████
Uses Gompertz function for TP3 for acalabrutinib + obinutuzumab and ibrutinib	██████

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01.06.2022  
MGK/SNI

## Forhandlingsnotat



Dato for behandling i Medicinrådet	15.06.2022
Leverandør	AstraZeneca
Lægemiddel	Calquence (acalabrutinib)
Ansøgt indikation	Acalabrutinib som monoterapi og acalabrutinib i kombination med obinutuzumab til behandling af kronisk lymfatisk leukæmi (CLL)

## Forhandlingsresultat

Amgros har opnået følgende pris på Calquence (acalabrutinib):

Tabel 1: Priser på Calquence (acalabrutinib):

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	SAIP (DKK)	Rabatprocent ift. AIP
Calquence (acalabrutinib):	100mg/200mg dagligt	60 stk. hårde kapsler	44.093,59	████████	██████



## Informationer fra forhandlingen



## Konkurrencesituationen

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
<b>Acalabrutinib</b>	100 mg 2 x dagligt	60 stk. x 100 mg	████████	12	████████
<b>Komparator - klinisk spørgsmål 1 og 2</b>					
Obinutuzumab	8.000 mg (fordelt over 6 cykler)	1 stk. x 1000 mg	████████	8	████████
Chlorambucil	6 cykler af 0,5 mg/kg	25 stk. x 2 mg	████████	5	████████
<b>Obinutuzumab + chlorambucil</b>	-	-	-	-	████████
<b>Komparator - klinisk spørgsmål 1 og 2</b>					
Bendamustin	6 cykler af 90 mg/m <sup>2</sup> på dag 1 og 2 i hver cyklus	5 x 25 mg	████████	16	████████
Rituximab	6 cykler af 375 mg/m <sup>2</sup> på dag 1 i første cyklus og 500 mg/m <sup>2</sup> på dag 1 i de efterfølgende 5 cykler	1 stk. x 500 mg	████████	11	████████
<b>Bendamustin + rituximab</b>	-	-	-	-	████████
<b>Komparator - klinisk spørgsmål 3, 4 og 5</b>					
<b>Ibrutinib</b>	420 mg 1 x dagligt	28 stk. x 420 mg	████████	13	████████

\*Gns vægt: 78,9 kg, \*\*BSA: 1,9 m<sup>2</sup>

## Status fra andre lande

**Norge:** Under vurdering

**Sverige:** Anbefalet med begrænsning<sup>1</sup>

**England:** Anbefalet<sup>2</sup>

## Konklusion

Det er Amgros vurdering, at det ikke er muligt at opnå lavere pris på Calquence (acalabrutinib) på nuværende tidspunkt.



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<sup>1</sup> [Calquence ingår i högkostnadsskyddet med begränsning - Tandvårds- och läkemedelsförmånsverket TLV](#)

<sup>2</sup> [1 Recommendations | Acalabrutinib for treating chronic lymphocytic leukaemia | Guidance | NICE](#)

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## Calquence (acalabrutinib) for the treatment of CLL

29. april 2022

AstraZeneca thanks the Danish Medicines Council (DMC) for their comprehensive review of the submitted clinical and economic documentation for the use of Calquence in various lines of CLL. Below you find our comments related to the clinical and health economic documents submitted to us following the April meeting in DMC. We have divided the response into a clinical and economic part.

### Clinical

In both the 1<sup>st</sup> line and RR part of the document DMC refer to missing CI's for the absolute values. We have now updated the table with the requested information, and we apologize for the missing values. It does overall not show a different pattern compared to the relative values that have already been used in the assessment.

**Table 1.** Updated efficacy data from ELEVATE-RR

Trial name:		ELEVATE RR Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2021 NTC: NCT02477696									
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	
				Difference	95% CI	P value	Hazard/Odds/RR	95% CI	P value		
IRC-assessed PFS	acalabrutinib	268	Median: 38.4 m (33.0; 38.6) 36 months: 51.4% (44.7; 57.8)	36m PFS: -2.4%	-11.7; 6.9	0.6116*	HR: 1.00	0.79; 1.27	N/A	A Cox proportional hazards model was used for the primary analysis of non-inferiority. KM curve was used to estimate the distribution of PFS and a stratified Cox proportional hazards model was used to estimate the HR.  95% CI based on normal approximation with use of Wilson's score. P-value estimated based on Cochran-Mantel-Haenszel test stratified by 17p deletion status and number of prior therapies (1-3 vs. ≥4)  A stratified Cox proportional hazards model was used to estimate the HR  Unstratified analysis and naive estimation of difference and RR	
	ibrutinib	265	Median: 38.4 m (33.0; 41.6) 36 months: 53.8% (47.0; 60.1)								
Investigator-assessed PFS	acalabrutinib	268	Median: 46.9 m (42.4; NE) 36 months: 66.4% (60.1; 71.9)	36m PFS: 6.1%	-2.5; 14.7	0.1642*	HR 0.90	0.69; 1.16	N/A		
	ibrutinib	265	Median: 44.1 m (41.5; NE) 36 months: 60.3% (53.7; 66.2)								
IRC-assessed ORR	acalabrutinib	268	81.0% (75.8; 85.2)	4.0%	-2.9; 10.9	0.2503	RR: 1.05	0.96; 1.15	0.2581*		
	ibrutinib	265	77.0% (71.5; 81.6)								
OS	acalabrutinib	268	36 months: 80.7% (75.2; 85.0)	4.9%	-2.4; 12.2	0.1856*	HR: 0.82	0.59; 1.15	0.2517		
	ibrutinib	265	36 months: 75.8% (70.0; 80.7)								
TEAEs leading to discontinuation	acalabrutinib	266	n = 39 (14.7%)	-6.6%	-13.2; -0.1	0.0463*	RR: 0.69	0.47; 1.00	0.0490*		
	ibrutinib	263	n = 56 (21.3%)								
Grade ≥3 TEAEs	acalabrutinib	266	n = 183 (68.8%)	-6.1%	-13.8; 1.5	0.1174*	RR: 0.92	0.83; 1.02	0.1191*		
	ibrutinib	263	n = 197 (74.9%)								
Grade ≥3 SAEs	acalabrutinib	266	n = 126 (47.4%)	-5.1%	-13.6; 3.4	0.2399*	RR: 0.90	0.76; 1.07	0.2412*		
	ibrutinib	263	n = 138 (52.5%)								

\* Nominal p-value (not adjusted for stratification factors or protocol specified)

## Economic evaluation and documents

We believe that many of the assumptions and changes adopted by DMC are fair, and that the scenarios presented are a reasonable attempt to quantify any residual uncertainty in the data. However, there remain a number of aspects to which AstraZeneca wish to question the methodological quality of the approach adopted by the DMC in both the reports of the previously untreated and previously treated patients. In addition, a number of probable typing errors have been identified. These are covered at the end of this document.

The aspects of the report in previously untreated patients on which AstraZeneca wish to challenge the approach adopted by DMC are:

1. The parametric model fit for time to progression for acalabrutinib + obinutuzumab in the assessment of previously untreated patients without 17p deletion or TP53 mutation
2. The approach for modelling time to event outcomes for bendamustine + rituximab (BR) in the assessment of previously untreated patients without 17p deletion or TP53 mutation
3. The data source for estimating time on treatment for acalabrutinib and ibrutinib and the parametric function selected in the assessment of relapsed/refractory patients
4. The methods for the estimating patient numbers in the budget impact assessments

### Ad 1) Parametric model fit for time to progression for acalabrutinib + obinutuzumab in 1L CLL

In their assessment, DMC has opted to change the functional form of the time to progression curve for acalabrutinib + obinutuzumab from the Weibull distribution to the Gompertz, based on feedback from the expert committee. Whilst the feedback and validation from the expert committee is appreciated, we believe the results obtained when using the Gompertz distribution lack face validity. As can be seen from Table 11 (p.29) of DMC's report, this approach leads to a duration of treatment of 5.4 years for acalabrutinib + obinutuzumab. This compares to the preferred extrapolation for acalabrutinib monotherapy where the duration of treatment is 5.8 years. Despite the favourable economic result of this extrapolation choice, it seems implausible that time on treatment with the combination therapy would be shorter than with the monotherapy, given that even with the four year follow-up of ELEVATE-TN PFS was greater for acalabrutinib + obinutuzumab (48 month PFS 87%) than for acalabrutinib monotherapy (48 months PFS 78%).<sup>1</sup> It seems unlikely that the hazard of progression in the acalabrutinib + obinutuzumab arm would be significantly higher than in the monotherapy arm beyond trial follow-up given that at this time point patients are on the same therapy. The Weibull distribution for acalabrutinib + obinutuzumab provides the shortest duration of treatment that is longer than the monotherapy. An alternative option is to assume that the hazard of disease progression in the acalabrutinib + obinutuzumab arm is equal to that of the acalabrutinib monotherapy arm after the end of trial follow-up (~39 months in the included data). A quick post hoc estimation of this result in an average time on treatment of 6.4 years for patients treated with acalabrutinib + obinutuzumab.

### Ad 2) Modelling time to event outcomes for bendamustine + rituximab in 1L CLL

In the submitted documentation, time to progression and time to death (pre-progression) for BR were always modelled relative to acalabrutinib + obinutuzumab using the hazard ratio (HR) reported, regardless of whether acalabrutinib or acalabrutinib + obinutuzumab was considered the intervention of interest. The choice whether to model BR relative to acalabrutinib + obinutuzumab was made somewhat arbitrarily, but it was assumed that given acalabrutinib + obinutuzumab contains a component of the regimen that is of finite

duration, the underlying hazard of disease progression for patients treated with BR (also a finite regimen) may be better reflected by a regimen containing a finite component rather than solely something continued until progression. Whilst we do not disagree with the choice to model time to event data for BR based on the acalabrutinib monotherapy curves, it does seem somewhat counterintuitive to assume that survival outcomes (and therefore costs) with BR would differ depending on the regimen it is compared to in clinical practice. Whilst the impact on first line treatment costs is minimal (both approaches ~6 months), as can be seen from Figures 4 and 6 generated by DMC in their report, occupancy of the post-progression health state changes considerably (peaking at 45% in one case or 38% in another) and therefore subsequent treatment costs may be influenced. We would therefore advocate that a single survival curve for BR is used for all comparisons. This functionality is readily available in the model already provided to DMC.

In addition, on page 13 of the report, it is noted by DMC that the expert committee considered the choice of extrapolation for time to progression underestimates the effect of BR and that generalised gamma distribution would be more representative of clinical practice, and therefore the DMC changed the choice of extrapolation accordingly. However, above on the same page it is noted that the Gompertz distribution was considered plausible for acalabrutinib (with the generalised gamma as a scenario). Should this be interpreted as BR being modelled to have 2.63-times the hazard of progression of “acalabrutinib” if it were to be modelled using the generalised gamma distribution, but acalabrutinib itself should be modelled using the Gompertz? If this is the case, the approach taken by DMC appears assume that the proportional hazards assumption between acalabrutinib and BR is violated, but the solution to handling this is somewhat unique. The guidelines for extrapolation from the DMC, based on the NICE DSU Technical Support Document 14, recommend fitting individual models based on the patient-level data or piecewise or other more flexible models for indirect comparisons.<sup>2</sup> Given that the shape of the relative hazards of between acalabrutinib and BR have not been formally assessed, whilst the face validity of the results has been assessed by the expert committee, the technical validity of this more “flexible” approach has not.

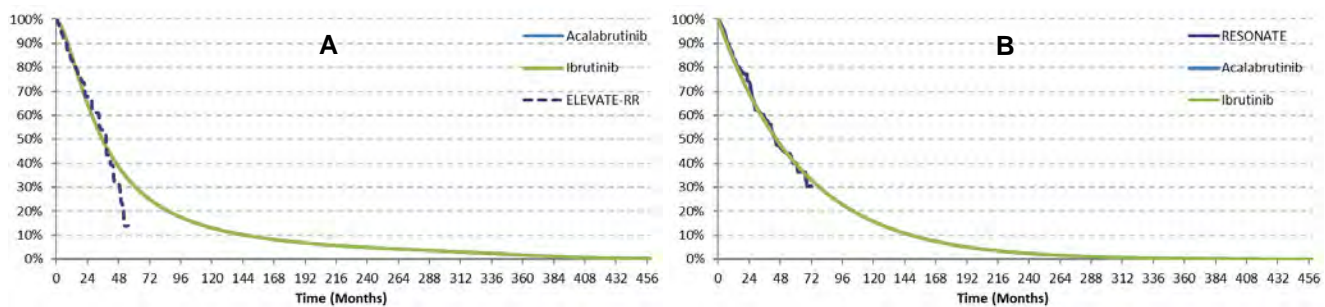
**Ad 3) The data source for estimating time on treatment for acalabrutinib and ibrutinib and the parametric function selected in R/R CLL**

On page 8 of the report for previously treated patients, it is stated by DMC that the expert committee thought that the chosen functional form in the submission underestimates PFS for acalabrutinib and ibrutinib that might be expected in clinical practice. This is due to patients in ELEVATE-RR having a worse prognosis than patients in Danish clinical practice.

AstraZeneca has maintained throughout the appraisal process that data from the RESONATE trial of ibrutinib or the ASCEND trial of acalabrutinib would be a better data source for extrapolating time on treatment. This is because patients recruited in these trials have likely to have a more similar prognosis to the average Danish patient, given the baseline characteristics. Upon request from the DMC secretariat, the model was updated to extrapolate time on treatment based on data from the ELEVATE-RR trial (submitted in November 2021), which included only patients with 17p deletion or 11q deletion. This trial provides evidence that acalabrutinib and ibrutinib are similar in efficacy in these patients, but the previously submitted matching-adjusted indirect comparison also provides additional evidence to suggest the therapies are similar in efficacy in the “average” relapsed or refractory patient. Therefore, if the question is to derive an estimate of the time on treatment with ibrutinib or acalabrutinib in Danish clinical practice the most appropriate source should be used.

Extrapolation of the RESONATE data, as originally submitted, data gave an estimated time on treatment of 5.4 years, similar to the preferred parametric extrapolation of the ELEVATE-RR from the expert committee using the log-logistic distribution of 5.1 years. Whilst the result of the approach leads to equal results regardless, we believe that accepting the approach taken by DMC would set a negative precedent for accepting poor methodological practice on behalf of manufacturers or DMC. The DMC guidelines for extrapolation state that the function must be adapted acceptably to the observed effect data from the study and be clinically and biologically plausible and that functions that fail to meet either of these criteria are likely not appropriate for use.<sup>2</sup> As can be seen the figure below, the log-logistic function provides a poor fit to the trial data. Therefore, using trial data not representative of Danish patients on which a poor fitting curve is applied should not be used to estimate time on treatment: two wrongs do not make a right. Good statistical and methodological practice should be followed by both manufacturers and the Medicines Council in assessments to allow for both parties to efficiently collaborate in ensuring Danish patients get fair and efficient access to effective therapies.

**Figure 1.** Kaplan-Meier curve of the pooled IRC-assessed progression-free survival from ELEVATE-RR and the log-logistic parametric extrapolation of this as preferred by the expert committee (A) and the KM curve of progression-free survival from RESONATE and the exponential parametric extrapolation as originally submitted (B)



#### Ad 4) Methods for estimating patients numbers in the budget impact assessment

With regards to estimates of the patient counts for patients without del(17p)/TP53mut, the DMC claim on page 37 of their report that in the DMC protocol for acalabrutinib ± obinutuzumab, the expert committee stated that there are 135 patients who do not have del(17p)/TP53mut who would be candidates for treatment with acalabrutinib ± obinutuzumab. This is factually inaccurate as the protocol actually states that there are 135 patients who do not have del(17p)/TP53mut who would be candidates for treatment with chemotherapy in combination with an anti-CD20 antibody. This reflects the population of patients who could be treated with FCR, BR or chlorambucil + anti-CD20. As no efficacy data has yet been presented assessing the efficacy of acalabrutinib for “fit” patients eligible for FCR, and an economic assessment compared to FCR has not been presented, these patients have been excluded from the budget impact assessment. Based on the source referenced in the DMC protocol from which the patient counts were derived, 20% (45/225) of first line patients without del(17p)/TP53mut would be candidates for FCR.<sup>3</sup> AstraZeneca has therefore assumed that 20% of the 135 patients without del(17p)/TP53mut as reported in the protocol would not be considered candidates for acalabrutinib in clinical practice at this time. As a result, having fewer patients on treatment switching from chemoimmunotherapy to an acalabrutinib-based therapy should result in a lower budget impact than reported by the DMC for patients without del(17p)/TP53mut.

In addition, AstraZeneca would like to strongly object to the methods of the budget impact assessment for patients with del(17p)/TP53mut or relapsed/refractory patients as adopted by the DMC as this is a gross violation of good methodological practice and the assessment guidelines from the DMC.

In tables 20 and 21 (p.39) of their report for previously untreated patients and table 7 (p.14) of the report for previously treated patients, the Medicines Council show the patient counts for acalabrutinib ± obinutuzumab and ibrutinib. These values show that were acalabrutinib not to receive a DMC recommendation, the number of patients on ibrutinib (i.e., total BTKi patients) would decrease from 9 to 5 in first line or 26 to 6 in second line over the coming 5 years. If acalabrutinib is to be recommended, the total number of BTKi patients is assumed to change from 11 in the first year to 7 in the fifth year in first line and 26 to 16 in second line. This means that the number of BTKi patients increased by between 2 and 16 per year (across both line) as a result of the recommendations (see table below). This therefore indirectly means that if one is estimating the budget impact (i.e., the increase in health expenditure as the result of the recommendation, including displacement of other products), then these new BTKi patients are assumed to be receiving no treatment if acalabrutinib was not recommended. As noted by DMC, and in the submission from AstraZeneca, this is not the case. These patients are in fact thought to be treated with venetoclax + anti-CD20 antibody. In prior correspondence with DMC it was requested that AstraZeneca’s application includes venetoclax + obinutuzumab/rituximab as a comparator in the economic analyses and accordingly this was provided, despite not being included as a clinical comparator (also accepted by DMC). DMC has opted to exclude venetoclax from the assessment as no clinical comparison was provided. Therefore, the analysis presented by DMC in the report is not in fact the “budget impact” of the recommendation *per se*, but rather the “additional expenditure on BTKi” as a result of the recommendation. This latter analysis fails to account for the reduction in costs due to other therapies as displaced by acalabrutinib. This appears to be in contravention of the guidelines for assessing the budget impact, which state that the costs of currently financed medicines which shall be displaced should be deducted (original Danish: “*fradrag for omkostninger til eksisterende lægemidler, der finansieres af regionerne, som vil blive erstattet af det nye lægemiddel, hvis lægemidlet anbefales til indikationen*”).<sup>4</sup> AstraZeneca therefore request that good methodological practice is followed, in line with DMC guidelines, to correctly estimate the budget impact.

**Table 2.** Patient counts reported in the Medicine Council’s budget impact assessment of acalabrutinib for patients with 17p deletion and/or TP53 mutation

	Year 1	Year 2	Year 3	Year 4	Year 5
<i>Acalabrutinib is recommended for patients with del(17p)/TP53mut</i>					
Acalabrutinib	3	5	6	6	6
Ibrutinib	8	5	2	1	1
Total	11	10	8	7	7
<i>Acalabrutinib is not recommended for patients with del(17p)/TP53mut</i>					
Ibrutinib	9	6	5	5	5
No Treatment	2	4	3	2	2
Total	11	10	8	7	7
<i>Acalabrutinib is recommended for patients with relapsed/refractory CLL</i>					
Acalabrutinib	6	10	13	13	13

	Year 1	Year 2	Year 3	Year 4	Year 5
Ibrutinib	20	13	6	3	3
Total	26	23	19	16	16
<i>Acalabrutinib is not recommended for patients with relapsed/refractory CLL</i>					
Ibrutinib	26	13	6	6	6
No Treatment	0	10	13	10	10
Total	26	23	19	16	16

We hope DMC will incorporate our comment and we look forward to finalizing the assessment of Calquence.

Kind Regards



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Market Access Head  
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Health Economist  
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### Smaller changes/mistakes

#### Clinical document:

- **Page 46-paragraph 4**, acalabrutinib monoterapi should be changed to acalabrutinib + obinutuzumab (please see highlighted section)
  - "Fagudvalget vurderer, at acalabrutinib + obinutuzumab samlet set har en stor merværdi vedr. PFS, fordi hazard ratioen for subgruppen uden del(17p)/p53-mutation viser en markant forskel på behandlingerne til fordel for [redacted] (HR = 0,10 (95% CI: 0,05-0,18))"
- **Page 52-last paragraph**, acalabrutinib monoterapi should be changed to acalabrutinib + obinutuzumab. (please see highlighted section)
  - "Fagudvalget vurderer, at acalabrutinib + obinutuzumab samlet set har en stor merværdi vedr. PFS, fordi hazard ratioen for PFS viser en signifikant forskel til fordel for [redacted] "stor



merværdi”. PFS-raterne, som dog er behæftet med usikkerhed, indikerer også, at acalabrutinib er et bedre behandlingsalternativ.”

Economic document:

- Previous untreated report page 40: claims that the patient numbers for the budget impact assessment for patients without del(17p)/TP53mut are 150, but on the previous pages the Medicines Council has stated that this was 135 (and AstraZeneca believes this should in fact be ~108 – see above).
- Previously treated report page 6: on lines 4 and 5 of section 4.1 it states that patients included ELEVATE-RR has del(17p)/TP53mut when in fact this was del(17p) or del(11q).

## References:

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- <sup>1</sup> Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia*. 2022;36:1171-75.
- <sup>2</sup> Medicinrådet. Anvendelse af forløbsdata i sundhedsøkonomiske analyser (Version 1.1). Copenhagen: Medicinrådet; 2020 [cited 2022 Apr 27]. Available from: [https://medicinraadet.dk/media/ickpupwo/anvendelse\\_af\\_forl%C3%B8bsdata\\_i\\_sundheds%C3%B8konomiske\\_analyser-vers-\\_1-1\\_adlegacy.pdf](https://medicinraadet.dk/media/ickpupwo/anvendelse_af_forl%C3%B8bsdata_i_sundheds%C3%B8konomiske_analyser-vers-_1-1_adlegacy.pdf)
- <sup>3</sup> RADS. Behandlingsvejledning for kronisk lymfatisk leukæmi (CLL). Copenhagen: Rådet for Anvendelse af Dyr Sygehusmedicin; 2016 [cited 2022 Apr 27]. Available from: <https://rads.dk/media/4242/behandlingsvejledning-for-kronisk-lymfatisk-leukaemi.pdf>
- <sup>4</sup> Medicinrådet. Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren (Version 1.8). Copenhagen: Medicinrådet; 2020 [cited 2022 Apr 27]. Available from: [https://medicinraadet.dk/media/pqkfj2oj/metodevejledning\\_for\\_omkostningsanalyser\\_af\\_nye\\_l%C3%A6gemidler\\_og\\_indikationer\\_i\\_hospitalssektoren-vers-\\_1-8\\_februar\\_adlegacy.pdf](https://medicinraadet.dk/media/pqkfj2oj/metodevejledning_for_omkostningsanalyser_af_nye_l%C3%A6gemidler_og_indikationer_i_hospitalssektoren-vers-_1-8_februar_adlegacy.pdf)

# Medicinrådets vurdering vedrørende acalabrutinib som monoterapi og acalabrutinib i kombination med obinutuzumab til behandling af kronisk lymfatisk leukæmi



## Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

## Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

### Dokumentoplysninger

<b>Godkendelsesdato</b>	20. april 2022
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<b>Versionsnummer</b>	1.0
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# 1. Medicinrådets konklusion

## Klinisk spørgsmål 1

### *Acalabrutinib monoterapi vs. chlorambucil + obinutuzumab*

Medicinrådet vurderer, at behandling med acalabrutinib monoterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion(17p)/p53-mutation giver en moderat merværdi sammenlignet med chlorambucil + obinutuzumab. I vurderingen er der lagt vægt på stor forskel i progressionsfri overlevelse mellem de to behandlinger. Data for overlevelse er endnu umodent, men viser en tendens til forbedret overlevelse ved acalabrutinib monoterapi. Der lægges i vurderingen også vægt på, at acalabrutinib monoterapi har en favorabel bivirkningsprofil sammenlignet med chlorambucil + obinutuzumab.

### *Acalabrutinib monoterapi vs. bendamustin + rituximab*

Medicinrådet vurderer, at behandling med acalabrutinib monoterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion(17p)/p53-mutation giver en moderat merværdi sammenlignet med bendamustin + rituximab. I vurderingen er der lagt vægt på stor forskel i progressionsfri overlevelse mellem de to behandlinger. Data for overlevelse er endnu umodent, men viser en tendens til forbedret overlevelse ved acalabrutinib monoterapi. Samtidig er acalabrutinib monoterapi et bedre tolereret lægemiddel end bendamustin + rituximab. Acalabrutinib medfører færre grad  $\geq 3$  uønskede hændelser og færre klinisk betydende hæmatologiske bivirkninger, som kan medføre øget infektionsrisiko.

## Klinisk spørgsmål 2

### *Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab*

Medicinrådet vurderer, at behandling med acalabrutinib i kombination med obinutuzumab sammenlignet med chlorambucil + obinutuzumab for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion(17p)/p53-mutation giver en lille merværdi. I vurderingen er der lagt vægt på stor forskel i progressionsfri overlevelse mellem de to behandlinger. Data for overlevelse er endnu umodent, men viser en tendens til forbedret overlevelse ved acalabrutinib + obinutuzumab. De to behandlingsalternativer vurderes at have sammenlignelige bivirkningsprofiler.

### *Acalabrutinib + obinutuzumab vs. bendamustin + rituximab*

Medicinrådet vurderer, at behandling med acalabrutinib i kombination med obinutuzumab sammenlignet med bendamustin + rituximab for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion(17p)/p53-mutation giver en lille merværdi. I vurderingen er der lagt vægt på stor forskel i progressionsfri overlevelse mellem de to behandlinger. Data for overlevelse er endnu umodent, men viser en tendens til forbedret overlevelse ved acalabrutinib + obinutuzumab. De to behandlingsalternativer vurderes at have sammenlignelige bivirkningsprofiler.



### Klinisk spørgsmål 3

#### *Acalabrutinib monoterapi vs. ibrutinib*

Medicinrådet vurderer, at den samlede værdi af behandling med acalabrutinib monoterapi sammenlignet med ibrutinib for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion(17p)/p53-mutation ikke kan kategoriseres efter Medicinrådets metoder på baggrund af det nuværende datagrundlag. Medicinrådet vurderer, at bivirkningsprofilen for acalabrutinib monoterapi er sammenlignelig med ibrutinib. Data for progressionsfri overlevelse viser, at de to behandlinger er omtrent ligeværdige, mens data for overlevelse er umodent.

### Klinisk spørgsmål 4

#### *Acalabrutinib + obinutuzumab vs. ibrutinib*

Medicinrådet vurderer, at den samlede værdi af behandling med acalabrutinib + obinutuzumab sammenlignet med ibrutinib for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion(17p)/p53-mutation ikke kan kategoriseres efter Medicinrådets metoder på baggrund af det nuværende datagrundlag. Medicinrådet vurderer, at bivirkningsprofilen for acalabrutinib + obinutuzumab er sammenlignelig med ibrutinib. Data for progressionsfri overlevelse viser, at de to behandlinger er omtrent ligeværdige, mens data for overlevelse er umodent.

### Klinisk spørgsmål 5

#### *Acalabrutinib monoterapi vs. ibrutinib*

Medicinrådet vurderer, at den samlede værdi af behandling med acalabrutinib monoterapi sammenlignet med ibrutinib til patienter med kronisk lymfatisk leukæmi, som tidligere har modtaget en behandling, ikke kan kategoriseres efter Medicinrådets metoder på baggrund af det nuværende datagrundlag. Medicinrådet vurderer, at bivirkningsprofilen for acalabrutinib monoterapi er sammenlignelig med ibrutinib. Data for progressionsfri overlevelse viser, at de to behandlinger er omtrent ligeværdige, mens data for overlevelse er umodent.





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### MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

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### MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET), I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.



## 2. Begreber og forkortelser

<b>BTK:</b>	Brutons tyrosinkinase
<b>CI:</b>	Konfidensinterval
<b>CIRS:</b>	<i>Cumulative illness scale</i>
<b>CLL:</b>	Kronisk lymfatisk leukæmi
<b>CLL-IPI:</b>	<i>International Prognostic Index for Chronic Lymphocytic Leukemia</i>
<b>DLG:</b>	Dansk Lymfom Gruppe
<b>EMA:</b>	Det Europæiske Lægemiddelagentur ( <i>European Medicines Agency</i> )
<b>EPAR:</b>	<i>European Public Assessment Report</i>
<b>FISH:</b>	<i>Fluorescent in-situ hybridization</i>
<b>GHS:</b>	<i>Global Health Score</i>
<b>GRADE:</b>	System til at vurdere evidens ( <i>Grading of Recommendations, Assessment, Development and Evaluation</i> )
<b>HR:</b>	<i>Hazard ratio</i>
<b>IGHV:</b>	<i>Immunoglobulin heavy-chain variable region</i>
<b>ITT:</b>	<i>Intention-to-treat</i>
<b>iwCLL:</b>	<i>International Workshop on Chronic Lymphocytic Leukemia</i>
<b>OR:</b>	<i>Odds ratio</i>
<b>PICO:</b>	Population, intervention, komparator og effektmål ( <i>Population, Intervention, Comparison and Outcome</i> )
<b>PP:</b>	<i>Per Protocol</i>
<b>RCT:</b>	Randomiseret kontrolleret studie ( <i>Randomised Controlled Trial</i> )
<b>RR:</b>	Relativ risiko
<b>SLL</b>	Småcellet Lymfocytært Lymfom
<b>SMD:</b>	<i>Standardized Mean Difference</i>



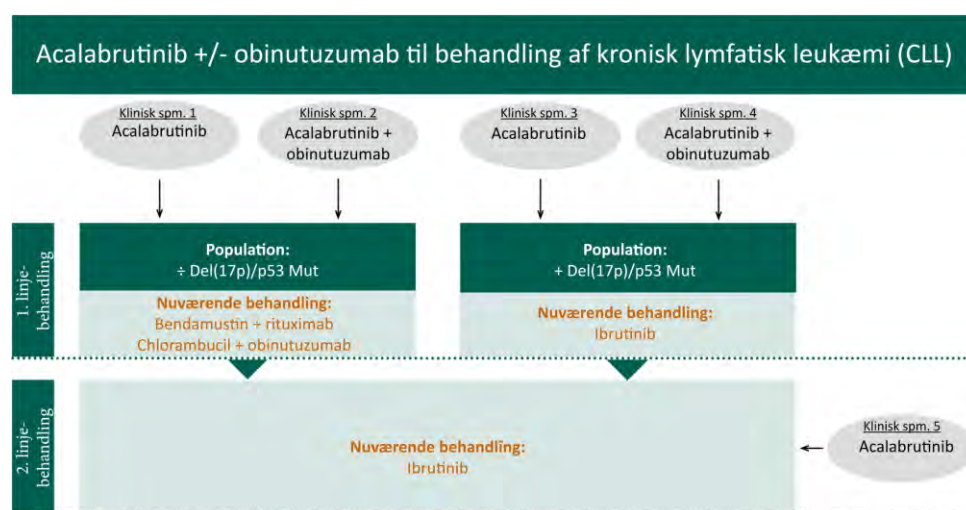
### 3. Introduktion

Formålet med Medicinrådets vurdering af acalabrutinib er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling. Acalabrutinib vurderes som: a) monoterapi til patienter med kronisk lymfatisk leukæmi (1. linje), b) kombinationsbehandling med obinutuzumab til behandling af patienter med tidligere ubehandlet kronisk lymfatisk leukæmi (1. linje) og c) monoterapi til behandling af patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én tidligere behandling (2. linje eller mere).

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca. Medicinrådet modtog ansøgningen den 30. april 2021.

De kliniske spørgsmål er:

- 1) *Hvilken værdi har acalabrutinib som monoterapi sammenlignet med kemoimmunterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion 17p/p53-mutation?*
- 2) *Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med kemoimmunterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion 17p/p53-mutation?*
- 3) *Hvilken værdi har acalabrutinib som monoterapi sammenlignet med dansk standardbehandling (ibrutinib) hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion 17p/p53-mutation?*
- 4) *Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med dansk standardbehandling (ibrutinib) hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion 17p/p53-mutation?*
- 5) *Hvilken værdi har acalabrutinib som monoterapi sammenlignet med dansk standardbehandling til 2. linjebehandling af patienter med kronisk lymfatisk leukæmi?*



Figur 1. Oversigt over klinisk spørgsmål 1-5 i vurderingen. Bemærk, at der for klinisk spørgsmål 1 og 2 er to komparatorer.



### 3.1 Kronisk lymfatisk leukæmi

Kronisk lymfatisk leukæmi (CLL) er en kræftsygdom i blodet, som opstår i kroppens B-celler og påvirker cellernes regulering af celledeling og celledød. Det fører til en ophobning af B-celler i bl.a. knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket. Det hyppigste symptom på CLL er træthed, og oftest opdages sygdommen tilfældigt. Øvrige diskrete symptomer omfatter typisk hævede lymfeknuder, forstørret milt, blodmangel, uforklarlig feber, vægttab og øget risiko for infektion.

Kronisk lymfatisk leukæmi er den mest almindelige blodkræft i de vestlige lande og udgør ca. 30 % af samtlige tilfælde af leukæmi [1]. Incidensen i Danmark er ca. 6-7 pr. 100.000 indbyggere pr. år, og der registreres ca. 450-500 nye tilfælde om året [2]. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark [3]. Medianalderen ved diagnosetidspunktet er 70 år, og dobbelt så mange mænd som kvinder får diagnosen [1,2].

Da CLL ofte er asymptomatisk ved diagnosetidspunktet, opdages det typisk tilfældigt efter en blodprøve. Diagnosen stilles ved konstatering af vedvarende unormale niveauer af B-celler (lymfocytose), defineret som > 5 mia. monoklonale B-celler pr. liter blod over tre måneder eller derover. På diagnosetidspunktet foretages en vurdering af sygdomsstadie (baseret på sygdomsudbredelse, stadiemdeling jf. Binet-systemet) og sygdommens aggressivitet (risikoprofil på baggrund af kromosomforandringer (cytogenetiske abnormaliteter) og eventuel mutation i et gen, der koder for en specifik immunreceptor (*immunoglobulin heavy-chain variable region (IGHV)*)).

Kronisk lymfatisk leukæmi har ofte et mildt (indolent) forløb, hvor patienter med tidlige stadier og langsomt progredierende sygdom følges ved årlige kontroller eller afsluttes til egen læge. Medianoverlevelse fra diagnosetidspunktet varierer fra ca. 4 år til over 12 år afhængigt af sygdomsstadie og risikoprofil. Både sygdomsstadie, patientens symptomer og risikoprofil har indflydelse på igangsættelse og valg af behandling, ligesom faktorerne har betydning for patienternes prognose, hvilket er afspejlet i det internationale prognostiske indeks for CLL (*CLL-International Prognostic Index (IPI)*) [4].

Tilstedeværelse af del17p/p53-mutation er forbundet med en væsentligt dårligere prognose og har betydning for den behandling, der tilbydes, idet patienter med del17p/p53-mutation ikke behandles med kemoimmunterapi. Af andre kromosomforandringer med betydning for prognosen er del11q og trisomi 12, som er forbundet med en dårlig prognose, og del13q, som er forbundet med en bedre prognose. Umuteret IGHV-status er associeret med forringet prognose og signifikant kortere overlevelse sammenlignet med muteret IGHV-status uanset stadiet af sygdommen [5,6].



## 3.2 Acalabrutinib som monoterapi og i kombination med obinutuzumab

Acalabrutinib hæmmer enzymet Brutons tyrosinkinase (BTK), som er vigtig for deling og vækst af de abnorme B-celler i CLL [7,8].

Lægemidlerne administreres som følger i serier af 28 dage:

- Acalabrutinib som monoterapi:  
p.o. 100 mg 2 x dagligt (hver 12. time) indtil sygdomsprogression eller uacceptabel toksicitet
- Acalabrutinib i kombination med obinutuzumab:  
acalabrutinib p.o. 100 mg 2 x dagligt (hver 12. time) indtil sygdomsprogression eller uacceptabel toksicitet, og  
obinutuzumab i.v. 100 mg på dag 1 og 900 mg på dag 2 og 1.000 mg på dag 8 og 15 i 2. serie, herefter i.v. 1.000 mg på dag 1 i serie 3-7.

Acalabrutinib som monoterapi har markedsføringstilladelse til 1. og 2. linjebehandling, mens acalabrutinib i kombination med obinutuzumab har markedsføringstilladelse til 1. linjebehandling. Markedsføringstilladelsen blev givet den 5. november 2020.

## 3.3 Nuværende behandling

Behandlingen af CLL varetages af de hæmatologiske afdelinger. På diagnosetidspunktet skelnes mellem behandlingskrævende og ikke-behandlingskrævende sygdom. Ikke-behandlingskrævende sygdom følges med *watch and wait* (observation), indtil sygdommen bliver behandlingskrævende ifølge kriterier defineret af *International Workshop on Chronic Lymphocytic Leukemia (iwCLL)*.

Ved behandlingskrævende sygdom afhænger behandlingsstrategien af patientspecifikke faktorer (performancestatus, komorbiditet (*cumulative illness rating scale* (CIRS)), alder, præferencer), sygdoms karakteristika (tumorbyrde, stadie, risikoprofil (karakteriseret ved *fluorescent in-situ hybridization* [FISH]), IGHV-mutationsstatus) og behandlingsmuligheder.

I behandlingsøjemed opdeles patientpopulationen efter, om de har deletion 17p/p53-mutation eller ej og efter performancestatus, alder og komorbiditeter. Om patienterne har deletion 17p/p53-mutation eller ej er afgørende for, hvilken behandling de kan tilbydes i 1. linje. Patienter *uden* deletion 17p/p53-mutation bliver behandlet med cytostatika i form af enten chlorambucil, fludarabin og cyklofosamid eller bendamustin i kombination med et anti-CD20-antistof. Patienter *med* deletion 17p/p53-mutation er ikke følsomme for behandling med cytostatika og behandles i stedet med ibrutinib eller venetoclax i kombination med obinutuzumab. Hvis de to behandlinger ikke tolereres af patienten, kan i stedet anvendes idelalisib i kombination med rituximab. Idelalisib anvendes sjældent i Danmark.



For patienter *uden* deletion 17p/p53-mutation afgøres valget af cytostatika og anti-CD20-antistof ud fra patientens alder, performancestatus og komorbiditet [9]. Fludarabin og cyklofosfamid i kombination med rituximab anvendes typisk til yngre patienter med god performancestatus, bendamustin og rituximab til ældre patienter med god performancestatus (eller de yngre patienter med dårlig performancestatus), og chlorambucil + et CD20-antistof til patienter med dårlig performancestatus. Traditionelt har man anvendt cytostatika i 1. linje, når det var muligt, fordi de medicinske behandlingsmuligheder har været få, og fordi højere alder og deletion 17p/p53-mutation senere i sygdomsforløbet kan udelukke behandling med cytostatika. Dog har nye targeterede behandlinger vist sig at være mere effektive og have en bedre bivirkningsprofil, hvorfor brugen af kemoimmunterapi er faldende.

Patienter med umuteret sygdom har en dårligere prognose end patienter med muteret IGHV-status, men i nuværende dansk klinisk praksis skelnes der i behandlingsøjemed ikke imellem, om patienterne har IGHV-mutation eller ej. Studier viser, at en opdeling af patienterne ud fra IGHV-status er relevant for effekten af nogle behandlinger, og fagudvalget forventer, at denne praksis på sigt vil blive aktuel i dansk klinisk praksis [10–12]. Denne ændring i behandlingspraksis er reflekteret i den seneste retningslinje for CLL fra DLG, hvor tidligere ubehandlede patienter uden IGHV-mutation og uden deletion 17p/p53-mutation anbefales at behandles med enten ibrutinib eller venetoclax i kombination med et CD20-antistof (enten rituximab eller obinutuzumab). På nuværende tidspunkt er det dog ikke muligt at behandle efter denne retningslinje, da Medicinrådet ikke har anbefalet venetoclax til patienter uden del17p/p53-mutation.

Ved tilbagefald efter behandling med cytostatika behandles patienterne, uanset deletion 17p/p53-mutation, med enten venetoclax i kombination med rituximab, som er et anti-CD20-antistof, eller ibrutinib [9].

Der er ca. 150 patienter om året med behandlingsbehov i 1. linje [9], hvoraf ca. 90 % (ca. 135 patienter) ikke har deletion 17p/p53-mutation og derfor behandles med cytostatika i kombination med et CD20-antistof [13]. I denne patientgruppe forventer fagudvalget, at 40 % (ca. 55 patienter) har muteret IGHV, og at 60 % (ca. 80 patienter) er umuteret. De resterende 10 % (ca. 15 patienter) med deletion 17p/p53-mutation behandles med ibrutinib eller venetoclax i kombination med obinutuzumab.

Fagudvalget vurderer, at ca. 65-70 patienter om året vil kunne modtage 2. linjebehandling. Fagudvalgets estimering af patientantal i de forskellige grupper er baseret på informationer fra hhv. den landsdækkende LYFO-database, viden om tid til første tilbagefald og forekomsten af deletion 17p/p53-mutation på forskellige tidspunkter i behandlingsforløbet [14–17].



## 4. Metode

Medicinrådets protokol for vurdering vedrørende acalabrutinib beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

## 5. Resultater

### 5.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 32 referencer, som beskriver 20 kliniske studier, der blev fundet relevante for besvarelsen af de kliniske spørgsmål. I Tabel 1 ses en oversigt over de studier og tilhørende publikationer, som Medicinrådet har inddraget i vurderingen:

**Tabel 1. Oversigt over studier og artikler**

Studier (NCT-nummmmer)	Reference
<b>ELEVATE-TN</b> (NCT02475681) A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination With Chlorambucil, Acalabrutinib (ACP-196) in Combination With Obinutuzumab, and Acalabrutinib Monotherapy in Subjects With Previously Untreated CLL	<b>Sharman JP.</b> et al. Acalabrutinib with or without obinutuzumab Sharman JP. et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia: a randomised, controlled, phase 3 trial. <i>Lancet</i> 2020;395:1278-1291.[8] <b>Sharman JP.</b> et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Elevate-TN four-year follow up. <i>J Clin Oncol</i> [internet]. 2021;39(15_suppl):7509–7509. [18]
<b>ELEVATE-RR</b> (NCT02477696) ELEVATE RR Phase 3, randomized, multicenter, open-label, noninferiority study study in previously treated subjects with high risk CLL.	<b>Byrd JC.</b> et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. <i>Journal of Clinical Oncology</i> 2021. [19]
<b>ASCEND</b> (NCT02970318) A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or	<b>Ghia P,</b> et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. <i>J Clin Oncol.</i> May. 2020. [7]



Studier (NCT-nummmer)	Reference
<p>Bendamustine Plus Rituximab in Subjects With R/R Chronic Lymphocytic Leukemia</p>	<p><b>Ghia P</b>, et al. Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final results, Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 8015-8015. [20]</p>
<p><b>RESONATE-2</b> (1: NCT01722487; 2: NCT01724346)</p> <p>1) Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma</p> <p>2) An Open-label Extension Study in Patients 65 Years or Older With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib Versus Chlorambucil)</p>	<p>Jan A <b>Burger</b> , Alessandra Tedeschi, Paul M Barr et al., Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia, NEJM. 2015 Dec 17;373(25):2425-37. [21]</p> <p><b>Barr PM</b> et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: Haematologica 2018;103:1502-1510. [22]</p> <p>Jan A. <b>Burger</b>, Paul M. Barr et al., Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study, Leukemia volume 34, pages787–798(2020). [23]</p>
<p><b>ALLIANCE</b> (NCT01886872)</p> <p>A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients <math>\geq</math> 65 Years of Age) With Chronic Lymphocytic Leukemia (CLL)</p>	<p><b>Woyach JA</b>, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018 Dec 27;379(26):2517-2528. [24]</p>
<p>PCI-32765 for Special Cases of Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (NCT01500733).</p> <p>A Phase II Study of PCI-32765 for Patients With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Need Therapy and Are Older Than 65 or Have a 17p Deletion</p>	<p><b>Ahn IE</b>, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 2018 May 24;131(21):2357-2366. [25]</p> <p><b>Farooqui MZ</b>, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with p53 aberrations: a phase 2, single-arm trial. Lancet Oncol. 2015 Feb;16(2):169-76. [26]</p>
<p><b>RESONATE</b> (NCT01578707)</p> <p>A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic</p>	<p><b>Byrd JC</b> et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia, N Engl J Med 2014; 371:213-223. [27]</p> <p><b>Brown JR</b> et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously</p>





Studier (NCT-nummmmer)	Reference
Lymphocytic Leukemia/Small Lymphocytic Lymphoma.	<p>treated CLL/SLL. Leukemia. 2018;32(1):83-91. [28]</p> <p><b>Byrd JC et al.</b>, Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab, Blood (2019) 133 (19): 2031–2042. [29]</p> <p><b>Munir T et al.</b> Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma, American Journal of Hematology, Volume94, Issue12, December 2019, Pages 1353-1363. [30]</p>
<b>COMPLEMENT1</b> (NCT00748189)	<b>Hillmen P, et al.</b> Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet (London, England). 2015;385(9980):1873-83. [31]
<b>CAM-307</b> (NCT00046683)	<b>Hillmen P, et al.</b> Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2007;25(35):5616-23. [32]
<b>CLL11</b> (NCT01010061)	<b>Goede V, et al.</b> Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. The New England journal of medicine. 2014;370(12):1101-10. [33]
<b>CLL10</b> (NCT00769522)  Phase III Trial of Combined immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Bendamustine and Rituximab (BR) in Patients With Previously Untreated Chronic Lymphocytic Leukaemia.	<p><b>Eichhorst B, et al.</b> First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016. [34]</p> <p><b>Kutsch N, et al.</b> Long Term Follow-up Data and Health-Related Quality of Life in Frontline Therapy of Fit Patients Treated With FCR Versus BR (CLL10 Trial of the GCLLSG). HemaSphere. 2020;4(1):e336. [35]</p>
<b>MaBLE</b> (NCT01056510)  A Randomized Study to Assess the Effect on Response Rate of MabThera (Rituximab) Added to a Standard	<b>Michallet AS, et al</b> Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: Primary analysis of the randomized,



Studier (NCT-nummmer)	Reference
Chemotherapy, Bendamustine or Chlorambucil, in Patients With Chronic Lymphocytic Leukemia.	open-label MaBLE study. Haematologica. 2018;103(4):698–706. [36]
<p><b>iLLUMINATE</b> (NCT02264574)</p> <p>A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Subjects With Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.</p>	<p><b>Moreno C.</b> et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia: Lancet Oncol 2019;20:43-56. [11]</p>
<p><b>HELIOS</b> (NCT01611090)</p> <p>Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination With Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.</p>	<p><b>Chanan-Khan A,</b> et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. The Lancet, VOLUME 17, ISSUE 2, P200-211, FEBRUARY 01, 2016 PRINT, 1-10. [37]</p>
<p><b>CLL14</b> (NCT02242942)</p> <p>A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare The Efficacy and Safety of A Combined Regimen of Obinutuzumab and Venetoclax (GDC-0199/ABT-199) Versus Obinutuzumab and Chlorambucil in Previously Untreated Patients With CLL and Coexisting Medical Conditions.</p>	<p><b>Fischer K.</b> et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med 2019;380:2225-2236. [38]</p>
<p><b>Murano</b> (NCT02005471)</p> <p>A Multicenter, Phase III, Open-Label, Randomized Study in Relapsed/Refractory Patients With Chronic Lymphocytic Leukemia to Evaluate the Benefit of Venetoclax (GDC-0199/ABT-199) Plus Rituximab Compared With Bendamustine Plus Rituximab</p>	<p><b>Seymour JF,</b> et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378(12):1107-1120. [39]</p> <p><b>Kater AP,</b> et al., Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study, Clinical Oncology 37, no. 4 (February 01, 2019) 269-277. [40]</p>



Studier (NCT-nummmmer)	Reference
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia. (NCT01539512)	<b>Furman RR</b> , et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. The New England journal of medicine. 2014;370(11):997-1007. [41]
A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia. (NCT01659021)	<b>Jones JA</b> , et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. The Lancet Haematology. 2017;4(3):e114-e26. [42]
Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia. (NCT01569295)	<b>Zelenetz AD</b> , et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, 16 binutuzum, double-blind, placebo-controlled trial. The Lancet Oncology. 2017;18(3):297-311. [43]

Ansøger har på baggrund af de ovenfor listede studier besvaret de fem kliniske spørgsmål. I besvarelsen indgår to netværksmetaanalyser (NMA), to *matching-adjusted-indirect-comparisons* (MAIC) samt to direkte analyser (ELEVATE-TN og ELEVATE-RR). Derudover inkluderes en række studier, som gennemgås narrativt.

NMA'erne belyser behandling i 1. og 2. linje. Ligeledes belyser MAIC-analyserne også 1. og 2. linje, mens ELEVATE-TN inkluderer en sammenligning af acalabrutinib +/- obinutuzumab over for chlorambucil + obinutuzumab i 1. linje. I ELEVATE-RR sammenlignes acalabrutinib monoterapi med ibrutinib i 2. linje.

I Tabel 2 ses en oversigt over ansøgers analyser, hvad de belyser, studier, som indgår i analyserne, samt de lægemiddelkombinationer, som studierne undersøger.



**Tabel 2. Ansøgers analyser**

	Analyser	Studier	Lægemidler
1. linje	Direkte analyse	ELEVATE-TN	Acalabrutinib +/- obinutuzumab vs. obinutuzumab + chlorambucil
	MAIC	ELEVATE-TN RESONATE-2 iLLUMINATE CLL14 ALLIANCE CLL11	Acalabrutinib +/- obinutuzumab vs. obinutuzumab + chlorambucil Ibrutinib vs. obinutuzumab + chlorambucil Ibrutinib + obinutuzumab vs. obinutuzumab + chlorambucil Venetoclax + obinutuzumab vs. obinutuzumab + chlorambucil Bendamustin + rituximab vs. ibrutinib +/- rituximab Chlorambucil + rituximab vs. obinutuzumab + chlorambucil
	NMA	COMPLEMENT1 RESONATE-2 CAM-307 iLLUMINATE ALLIANCE MaBLE CLL11 ELEVATE-TN CLL14	Ofatumumab + chlorambucil vs. chlorambucil Ibrutinib vs. chlorambucil Alemtuzumab vs. chlorambucil Ibrutinib + obinutuzumab vs. obinutuzumab + chlorambucil Ibrutinib vs. ibrutinib + rituximab vs. bendamustin + rituximab bendamustin + rituximab vs. chlorambucil + rituximab Chlorambucil vs. rituximab + chlorambucil vs. obinutuzumab + chlorambucil Acalabrutinib +/- obinutuzumab vs. obinutuzumab + chlorambucil Venetoclax + obinutuzumab vs. obinutuzumab + chlorambucil
2. linje	Direkte analyse	ELEVATE-RR	Acalabrutinib vs. ibrutinib
	MAIC	ASCEND RESONATE MURANO	Acalabrutinib vs. idelalisib + rituximab vs. bendamustin + rituximab Ibrutinib vs. ofatumumab Venetoclax + rituximab vs. bendamustin + rituximab
	NMA	ASCEND RESONATE MURANO Furman et al. Jones et al. HELIOS Zeneletz et al.	Acalabrutinib vs. idelalisib + rituximab vs. bendamustin + rituximab Ibrutinib vs. ofatumumab Venetoclax + rituximab vs. bendamustin + rituximab Rituximab + idelalisib vs. rituximab Idelalisib + ofatumumab vs. ofatumumab Ibrutinib + bendamustin + rituximab vs. bendamustin + rituximab Idelalisib + bendamustin + rituximab vs. bendamustin + rituximab

For at besvare de kliniske spørgsmål har fagudvalget inddraget de ovenstående analyser.

### Valg af komparator

Ansøger har valgt at anvende ibrutinib som komparator i klinisk spørgsmål 3, 4 og 5, da fagudvalget i Medicinrådets protokol vedr. acalabrutinib [44] gav ansøger mulighed for at vælge komparator ud fra, hvor datagrundlaget er størst. Således er venetoclax + obinutuzumab fravalgt som komparator i 1. linje, og venetoclax + rituximab er fravalgt som komparator i 2. linje. Ansøgers begrundelser for valg af ibrutinib som komparator er, at acalabrutinib og ibrutinib har samme virkningsmekanisme og samme indikation samt anvendes indtil progression. Dernæst er ibrutinib på nuværende tidspunkt hyppigt



anvendt til behandling af patientgruppen i Danmark. Fagudvalget tilslutter sig ansøgers tilgang.

Derudover er kombinationen fludarabin + cyklofosamid + rituximab ikke medtaget som komparator i klinisk spørgsmål 1 og 2. Det skyldes, at den danske patientpopulation, som behandles med fludarabin + cyklofosamid + rituximab, er væsentlig anderledes (yngre og *fit*) end den population, som indgår i ELEVATE-TN-studiet ( $> 65$  år/*cummulative illness rating scale* (CIRS)  $> 6$ ). Acalabrutinib forventes således ikke at blive anvendt til de patienter, der i dansk klinisk praksis kandiderer til fludarabin + cyklofosamid + rituximab.

### Oversigt over kliniske spørgsmål

I Tabel 3 ses en oversigt over de fem kliniske spørgsmål med tilhørende patientpopulationer. De ønskede interventioner (acalabrutinib +/- obinutuzumab) og komparatorer (bendamustin + rituximab/chlorambucil + obinutuzumab/ibrutinib) fremgår også. Bemærk, at der for klinisk spørgsmål 1 og 2 er to komparatorer. Ligeledes fremgår ansøgers analyser for hvert af de kliniske spørgsmål.

**Tabel 3. Oversigt over kliniske spørgsmål og tilhørende analyser**

Klinisk spørgsmål	Population	Intervention	Komparator	Analyser
1	1. linje uden del(17p)/p53- mutation	Acalabrutinib	Obinutuzumab + chlorambucil	Direkte sammenligning (ELEVATE-TN)
			Bendamustin + rituximab	NMA – 1. linje MAIC – 1. linje
2	1. linje uden del(17p)/p53- mutation	Acalabrutinib + obinutuzumab	Obinutuzumab + chlorambucil	Direkte sammenligning (ELEVATE-TN)
			Bendamustin + rituximab	MAIC – 1. linje NMA – 1. linje
3	1. linje med del(17p)/p53- mutation	Acalabrutinib	Ibrutinib	Direkte sammenligning (ELEVATE-RR) MAIC – 1. linje NMA – 1. linje
4		Acalabrutinib + obinutuzumab	Ibrutinib	MAIC – 1. linje NMA – 1. linje
5	2. linje	Acalabrutinib	Ibrutinib	Direkte sammenligning (ELEVATE-RR) MAIC – 2. linje NMA – 2. linje



## 5.2 Klinisk spørgsmål 1

*Hvilken værdi har acalabrutinib som monoterapi sammenlignet med kemoimmunterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion 17p/p53-mutation?*

### 5.2.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i direkte (ELEVATE-TN) og indirekte analyser (MAIC og NMA) til besvarelse af klinisk spørgsmål 1, hvor acalabrutinib monoterapi sammenlignes med hhv. obinutuzumab + chlorambucil og bendamustin + rituximab.

#### **Acalabrutinib monoterapi vs. obinutuzumab + chlorambucil**

##### *Direkte analyser*

**ELEVATE-TN** sammenligner acalabrutinib monoterapi og acalabrutinib i kombination med obinutuzumab direkte med obinutuzumab + chlorambucil.

ELEVATE-TN er et internationalt, multicenter, open-label, randomiseret fase 3-studie, som inkluderede tidligere ubehandlede CLL-patienter over 65 år og patienter mellem 18-65 år med komorbiditet (kreatinin-clearance på 30-69 ml/min. eller CIRS-G > 6).

Patienterne blev randomiseret 1:1:1 til acalabrutinib + obinutuzumab (n=179), acalabrutinib monoterapi (n=179) eller obinutuzumab + chlorambucil (n=177).

Patienterne blev stratificeret på baggrund af del(17p)/p53-mutation, ECOG PS-score (0-1 vs. 2) og geografisk region.

Oral acalabrutinib i dosis af 100 mg blev administreret to gange dagligt indtil sygdomsprogression eller uacceptabel toksicitet. Acalabrutinib i kombination med obinutuzumab blev givet i en cyklus forud for påbegyndelse af behandling med obinutuzumab. I denne gruppe blev intravenøs obinutuzumab givet efter dosisregimet: 100 mg på dag 1, 900 mg på dag 2, 1.000 mg på dag 8 og dag 15 i anden cyklus og 1.000 mg på dag 1 i cyklus 3-7.

I obinutuzumab + chlorambucil-gruppen blev intravenøs obinutuzumab givet efter dosisregimet: 100 mg på dag 1, 900 mg på dag 2, 1.000 mg på dag 8 og dag 15 i første cyklus og 1.000 mg på dag 1 i cyklus 2-6. Oral chlorambucil 0,5 mg/kg blev givet på dag 1 og dag 15 i hver cyklus. Behandlingerne blev administreret i cykler af 28 dage. Hvis patienterne i obinutuzumab + chlorambucil-gruppen oplevede sygdomsprogression, kunne de krydse over til acalabrutinib monoterapi. Udvalgte baselinekarakteristika for populationerne i acalabrutinib monoterapi- og obinutuzumab + chlorambucil-armene kan findes i Tabel 40 i Bilag 2.

*Data cut-off* for interimanalysen var den 8. februar 2019. Dette *cut-off* var baseret på en planlagt analyse efter 24 måneder. Median opfølgningstid var 28,3 måneder [8].

Analyserne i Medicinrådets vurdering af acalabrutinib er baseret på dette *data cut*.

Efterfølgende er der publiceret analyser/resultater fra yderligere et *data cut* med ca. fire



års opfølgning (46,9 måneder). Disse nye data inddrages i rapporten, hvor det vurderes relevant [18].

#### *Indirekte analyser*

##### Matching Adjusted Indirect Comparison (MAIC)

Ansøger har udført en systematisk litteratursøgning og har identificeret fem studier, som vurderes relevante i en sammenligning med ELEVATE-TN-studiet. Studierne er fase 3-randomiserede kliniske forsøg og inkluderer tidligere ubehandlede CLL-patienter samt relevante effektmål og komparatorer. De fem studier er RESONATE-2, iLLUMINATE, CLL14, ALLIANCE og CLL11. Se Bilag 1 for en beskrivelse af studierne og Tabel 4 nedenfor for et overblik over studierne. Oversigt over udvalgte baselinekarakteristika for de relevante populationer inkluderet i MAIC-analysen kan findes i Bilag 2, Tabel 41.

##### Network Meta-Analysis (NMA)

Ansøger har på baggrund af en systematisk litteratursøgning identificeret ni studier, som er inkluderet i en NMA. Studierne er fase 3-randomiserede kliniske forsøg og inkluderer tidligere ubehandlede CLL-patienter samt relevante effektmål og komparatorer. De ni studier er RESONATE-2, ELEVATE-TN, iLLUMINATE, CLL14, ALLIANCE, CLL11, MaBLE, COMPLEMENT1 og CAM-307. Se Bilag 1 for en beskrivelse af studierne og Tabel 4 for et overblik over studierne. Oversigt over udvalgte baselinekarakteristika for de relevante populationer inkluderet i NMA-analysen kan findes i Tabel 42 i Bilag 2.

**Tabel 4. Oversigt over studier anvendt i besvarelsen af klinisk spørgsmål 1-4**

Klinisk forsøg	Lægemidler	Population	Indgår i
ELEVATE-TN NCT02475681	Acalabrutinib + obinutuzumab vs. acalabrutinib vs. obinutuzumab + chlorambucil	Tidligere ubehandlede CLL- patienter ældre end 65 år eller mellem 18-65 år, hvis de led af komorbiditet (kreatinin- clearance på 30-69 ml/min. eller CIRS-G > 6)	Direkte analyse MAIC NMA
RESONATE-2 NCT01722487	Ibrutinib vs. chlorambucil	Tidligere ubehandlede patienter ≥ 65 år med CLL eller småcellet lymfocytært lymfom	MAIC NMA
iLLUMINATE NCT02264574	Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab	Tidligere ubehandlede patienter med CLL eller småcellet lymfocytært lymfom, som var ≥ 65 år eller under, hvis de led af anden sygdom	MAIC NMA
CLL14 NCT02242942	Venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab	Tidligere ubehandlede voksne patienter (≥ 18 år) med CLL og komorbiditet (CIRS > 6 eller kreatinin-clearance på < 70 ml/min.)	MAIC NMA



Klinisk forsøg	Lægemidler	Population	Indgår i
ALLIANCE NCT01886872	Ibrutinib vs. Ibrutinib + rituximab vs. bendamustin + rituximab	Tidligere ubehandlede voksne patienter over 65 år med CLL uanset mutationstype	MAIC NMA
CLL11 NCT01010061	Obinutuzumab + chlorambucil vs. chlorambucil, rituximab + chlorambucil vs. chlorambucil, obinutuzumab + chlorambucil vs. rituximab + chlorambucil	Tidligere ubehandlede voksne patienter ( $\geq 18$ år) med CLL og komorbiditet (CIRS $> 6$ eller kreatinin-clearance på 30-69 ml/min.)	MAIC NMA
MaBLe NCT01056510	Bendamustin + rituximab vs. chlorambucil + rituximab	Tidligere ubehandlede voksne patienter ( $\geq 18$ år) med CLL, hvor fludarabin ikke anbefales	NMA
COMPLEMENT1 NCT00748189	Ofatumumab + chlorambucil vs. chlorambucil	Tidligere ubehandlede voksne patienter ( $\geq 18$ år) med CLL, hvor fludarabin-baseret behandling ikke er mulig	NMA
CAM-307 NCT00046683	Alemtuzumab vs. chlorambucil	Tidligere ubehandlede voksne patienter ( $\geq 18$ år) med CLL	NMA

### Acalabrutinib monoterapi vs. bendamustin + rituximab

#### Indirekte analyser

Der foreligger ikke et direkte sammenlignende studie af acalabrutinib monoterapi og bendamustin + rituximab. Denne del af klinisk spørgsmål 1 belyses derfor ved hjælp af MAIC- og NMA-analyserne, som er præsenteret i Tabel 4, og ved en narrativ sammenligning. Den narrative gennemgang vil anvende data for acalabrutinib monoterapi fra ELEVATE-TN og data for bendamustin + rituximab fra ALLIANCE, CLL10 og MaBLe. Disse studier er kort præsenteret i Tabel 5 og yderligere beskrevet i Bilag 1. En oversigt over udvalgte baselinekarakteristika for de relevante populationer i studierne kan findes i Tabel 43 Bilag 2.





**Tabel 5. Oversigt over studier, der indgår i den narrative sammenligning for klinisk spørgsmål 1-2 (acalabrutinib +/- obinutuzumab vs. bendamustin + rituximab)**

Klinisk forsøg	Lægemidler	Population
ELEVATE-TN NCT02475681	Acalabrutinib + obinutuzumab, acalabrutinib givet som monoterapi eller obinutuzumab + oral chlorambucil	Tidligere ubehandlede CLL-patienter > 65 år eller mellem 18 og 65 år, hvis de led af komorbiditet (kreatinin- clearance på 30-69 ml/min. eller CIRS-G > 6)
ALLIANCE NCT01886872	Ibrutinib vs. Ibrutinib + rituximab vs. bendamustin + rituximab	Tidligere ubehandlede voksne patienter > 65 år med CLL uanset mutationstype
CLL10 NCT00769522	Fludarabin, cyklofosamid og rituximab vs. bendamustin + rituximab	Tidligere ubehandlede patienter i alderen 33-81 år med svær CCL
MaBLE NCT01056510	Bendamustin + rituximab vs. chlorambucil + rituximab	Tidligere ubehandlede voksne patienter ( $\geq 18$ år) med CLL, hvor fludarabin ikke anbefales

### 5.2.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analysemetode for hvert effektmål beskrevet.

Ansøger har udført en direkte sammenligning af acalabrutinib +/- obinutuzumab over for obinutuzumab + chlorambucil til 1. linjebehandling af CLL (ELEVATE-TN). Derudover er der udført en MAIC-analyse, som ligeledes belyser behandlingen i 1. linje. Dertil belyser en NMA også behandlingen i 1. linje.

#### Direkte analyse (ELEVATE-TN)

ELEVATE-TN inkluderer en direkte sammenligning af acalabrutinib +/- obinutuzumab over for obinutuzumab + chlorambucil.

#### Fagudvalgets kommentarer til datagrundlaget for den direkte analyse og analysens anvendelighed

Fagudvalget bemærker, at data for OS i ELEVATE-TN er umodne ved de tilgængelige opfølgningstider med en median opfølgning på hhv. 28 måneder og 46,9 måneder. Dosering og behandlingstid med obinutuzumab + chlorambucil er i overensstemmelse med dansk klinisk praksis. Patienterne i ELEVATE-TN ligner de danske patienter, som er kandidater til bendamustin + rituximab eller obinutuzumab + chlorambucil, og den observerede effekt i studiet forventes at kunne genfindes ved behandling af danske patienter. Det bemærkes, at patienter, som er progredieret ved behandling med obinutuzumab + chlorambucil, har kunnet krydse over til acalabrutinib monoterapi. Ud af 177 patienter i chlorambucil + obinutuzumab-armen modtog 44 patienter acalabrutinib monoterapi efter progression. Da OS-analysen foretages baseret



på den behandling, som patienten oprindeligt blev randomiseret til, kan overkrydsningen påvirke OS-analyserne til fordel for chlorambucil + obinutuzumab.

Data var ikke tilgængeligt for subgruppen uden del(17p)/p53-mutation, men fagudvalget vurderer, at data for ITT-populationen kan anvendes i stedet, da mere end 85 % af patienterne i studiet ikke havde mutationerne. Effektestimaterne forventes kun at blive påvirket i mindre og ikke betydende grad ved inklusion af patienter med del(17p)/p53-mutation. Denne antagelse er også gældende for de øvrige sammenligninger under klinisk spørgsmål 1 og 2, medmindre andet er angivet.

### Indirekte analyser

#### *Matching-adjusted-indirect-comparison*

En MAIC-analyse kan anvendes til en indirekte sammenlignende analyse mellem flere behandlingsalternativer. Ved en MAIC-analyse er det muligt at justere for udvalgte forskelle i baselinekarakteristika mellem studierne patientpopulationer, som forventes at kunne påvirke effekten af interventionen (*effect modifiers*), eller som har prognostisk betydning (*prognostic factors*). Denne metode giver kun mening ved sammenligning af to eller flere lægemidler, når der findes tilgængelige data på individniveau for mindst det ene af lægemidlerne. Dernæst skal der justeres for alle effektmodificerende (og prognostiske) variable, da analysen ellers vil være *biased*.

MAIC-analysen, som ansøger har udført for 1. linjebehandling, belyser OS, PFS og uønskede hændelser. Analysen er *anchored*, idet der findes fælles komparatorer, som kan knytte acalabrutinib +/- obinutuzumab og komparatorerne sammen. Ansøger har identificeret og justeret analysen for følgende effektmodifikatorer og prognostiske faktorer (se Tabel 6).

**Tabel 6. Effektmodifikatorer og prognostiske faktorer i MAIC-analysen**

<b>MAIC – 1. linje: Effektmodifikatorer og prognostiske faktorer, som justeres i analysen</b>
<ul style="list-style-type: none"><li>• Alder &gt; 75</li><li>• Køn</li><li>• <i>Bulky disease</i> (≥ 5 cm)</li><li>• Del(17p)-mutation</li><li>• p53-mutation</li><li>• Del(11q)-mutation</li><li>• Eastern Cooperative Oncology Group Performance Score (ECOG PS)</li><li>• β2 mikroglobulin ved baseline (&gt; 3,5 mg/L)</li><li>• <i>Rai stage</i> eller <i>Binet stage</i></li><li>• Kompleks karyotype</li><li>• <i>Immunoglobulin heavy-chain variable (IGHV) gene mutation status</i></li><li>• CrCl &lt; 60 ml/min. eller &lt; 70 ml/min. eller &lt; 67/min./ml eller 62 ml/min.</li><li>• CIRS-G ≥ 6 eller ≥ 9</li></ul>



### Fagudvalgets kommentarer til datagrundlaget for den indirekte analyse og analysens anvendelighed

Fagudvalget vurderer, at der overordnet set er matchet for de relevante effektmodifikatorer og prognostiske faktorer i ansøgers MAIC for 1. linjebehandling af CLL. Det bemærkes dog, at køn ikke forventes at have betydning for hverken effekt eller prognose, hvorfor der optimalt set ikke bør matches herfor. Det vurderes dog at være af mindre betydning. Derudover vurderes det, at den valgte grænse for alder (> 75) er arbitrær og ikke klinisk relevant. Det kan diskuteres, om det er relevant at matche på alder, da der matches for flere faktorer, som relaterer til komorbiditet, hvilket er det, alder potentielt kan opfange.

Fagudvalget fremhæver del(17p)-mutation, p53-mutation og del(11q) som faktorer med størst betydning for prognose og behandlingseffekt. Disse faktorer er der justeret for i analysen. Tabel 7 viser en oversigt over fagudvalgets betragtninger vedr. faktorer, som har betydning for prognose og/eller behandlingseffekt.

**Tabel 7. Fagudvalgets betragtninger vedr. faktorer, som har betydning for prognose og/eller behandlingseffekt i 1. linje**

Faktorer med betydning for prognose og/eller behandlingseffekt	
Del(17p)	Har betydning for prognose og behandlingseffekt
p53-mutation	Har betydning for prognose og behandlingseffekt
<i>Immunoglobulin heavy-chain variable (IGHV) gene mutation status</i>	Har betydning for prognose og behandlingseffekt
Mindre vigtige faktorer relateret til prognose og komorbiditet	
<i>Bulky disease</i> ( $\geq 5$ cm)	Har betydning for prognose
Alder	Har betydning for valg af behandling og prognose
<i>Eastern Cooperative Oncology Group Performance Score</i> (ECOG PS)	Har betydning for valg af behandling og prognose
<i>Rai stage</i> eller <i>Binet stage</i>	Betydning for valg af behandling og prognose
Kompleks karyotype	Har betydning for prognose
Del(11q)-mutation	Har betydning for prognose
CrCl < 60 ml/min. eller < 70 ml/min. eller < 67/min./ml eller 62 ml/min.	Har betydning for valg af behandling og prognose
CIRS-G $\geq 6$ eller $\geq 9$	Har betydning for valg af behandling og prognose
$\beta 2$ mikroglobulin ved baseline (> 3,5 mg/L)	Har betydning for prognose
Faktorer, som ikke er relevante for prognose eller behandlingseffekt	
Køn	-

I MAIC-analysen anvendes *data cuts*, som er angivet i Tabel 8.



**Tabel 8. Median opfølgningstid for data i MAIC-analysen**

Klinisk forsøg	Lægemidler	Median opfølgningstid (måneder)
ALLIANCE	Ibrutinib vs. ibrutinib + rituximab vs. bendamustin + rituximab	31,3
RESONATE-2	Ibrutinib vs. chlorambucil	29
CLL11	Obinutuzumab + chlorambucil vs. chlorambucil, rituximab + chlorambucil vs. chlorambucil, obinutuzumab + chlorambucil vs. rituximab + chlorambucil	Ikke rapporteret
iLLUMINATE	Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab	31,3
ELEVATE-TN	Acalabrutinib + obinutuzumab vs. acalabrutinib vs. obinutuzumab + chlorambucil	28,5
CLL14	Venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab	28,1

Ved de anvendte *data cuts* var median OS ikke nået i CLL11, CLL14, ELEVATE-TN, iLLUMINATE og RESONATE-2. Median OS blev ikke evalueret i ALLIANCE.

Median PFS blev ikke nået i ALLIANCE (ibrutinib og ibrutinib + rituximab-armene), CLL14, RESONATE-2 (ibrutinib-armen) og iLLUMINATE (ibrutinib + obinutuzumab-armen).

De anvendte *data cuts* i MAIC-analysen vurderes tilstrækkelig ens ud fra et klinisk perspektiv. Dog er OS-data som forventet ikke modent ved denne opfølgningstid (28,1-31,3 måneder). Det bemærkes også, at data for median PFS også er umodent.

Der ses forskelle i lægemiddeldoseringerne i studierne, som indgår i analysen. Af betydning bemærkes, at dosis af chlorambucil i RESONATE-2 øges fra 0,5 mg/kg til maks. 0,8 mg/kg på dag 1 og dag 15 i op til 12 cyklusser, hvis der ikke opstår uacceptabel toksicitet. Dosis er dermed større, og længden af behandling er længere end de øvrige studier, hvilket er i overensstemmelse med dansk klinisk praksis (0,5 mg/kg på dag 1 og 15 i 6 cyklusser). Konsekvensen af dette kan være, at effekten af chlorambucil fremstår bedre sammenlignet med komparator (ibrutinib). Ligeledes gives der 12 i stedet for 6 cyklusser af chlorambucil i CLL14, hvilket også kan have indflydelse på de relative effektestimater til fordel for chlorambucil + obinutuzumab sammenlignet med komparator (venetoclax + obinutuzumab). Det er dog også muligt, at øget dosering/øget behandlingslængde med chlorambucil ikke forbedrer effekten af behandlingen, men blot medfører flere bivirkninger. Det er derfor usikkert, om patienterne har gavn af øget dosis og behandlingslængde af chlorambucil.



Fagudvalget bemærker, at patienter med del(17p) er ekskluderet i RESONATE-2, samt at der også er stor forskel på, hvad der stratificeres for i studierne. Kun tre studier stratificerer for p53-mutationsstatus, hvilket er den væsentligste forskel. Det forventes, at MAIC-metoden kan kompensere for dette (matching).

Overkrydsning mellem studiearme ved progression tillades i fire studier (ELEVATE-TN, iLLUMINATE, CLL11 og ALLIANCE). Herved bliver det sværere at vurdere resultaterne, da både OS- og bivirkningsestimater kan blive påvirket. Der justeres ikke for overkrydsning i studierne og heller ikke i MAIC-analysen.

#### Fagudvalgets samlede vurdering af analysens anvendelighed

Fagudvalgets vurderer, at der er matchet for relevante faktorer, som har indflydelse på prognose og/eller behandlingseffekt. Det betyder, at forskelle i baseline-patientkarakteristika mellem studierne i analysen formentlig ikke får indflydelse på analysens resultater. Der tages forbehold for de usikkerheder, som forskelle i dosering og længde af behandling for chlorambucil, der varierer i studierne, medfører, og hvor det er uklart, om det kan være til fordel for chlorambucil relativt til de respektive komparatorer. Ligeledes er der et væsentligt forbehold vedr. muligheden for overkrydsning i fire af studierne, som kan påvirke de relative effektestimater til fordel for de ringere behandlingsalternativer i studierne og dermed også for MAIC-analysens estimater. Slutteligt er data generelt umodne for OS – og til dels også for PFS. Analysen vurderes overordnet anvendelig, dog med forbehold for de beskrevne usikkerheder.

#### Netværksmetaanalyse

Da der ikke findes en direkte sammenlignende analyse mellem acalabrutinib +/- obinutuzumab over for bendamustin + rituximab og ibrutinib til 1. linjebehandling, har ansøger udført en indirekte sammenlignende analyse i form af en NMA. En NMA kan udføres, når der ikke findes tilgængelige direkte sammenligninger mellem flere behandlingsalternativer. Dog er det en forudsætning, at karakteristika ved studierne, dvs. populationer, interventioner, fælles komparatorer, opfølgning m.m., er tilstrækkelig ens til at gøre analysen metodisk forsvarlig.

I analysen er anvendt *data cuts*, hvor median opfølgningstid så vidt muligt ligner opfølgningstiden for ELEVATE-TN. Se oversigt over opfølgningstider i de anvendte studier i Tabel 9.

**Tabel 9. Median opfølgningstid for data anvendt i netværksmetaanalysen**

Klinisk forsøg	Lægemidler	Median opfølgningstid (måned)
ALLIANCE	Ibrutinib vs. ibrutinib + rituximab vs. bendamustin + rituximab	38
MaBLE	Bendamustin + rituximab vs. chlorambucil + rituximab	~23,4
RESONATE-2	Ibrutinib vs. chlorambucil	29



Klinisk forsøg	Lægemidler	Median opfølgningstid (måneder)
CLL11	Obinutuzumab + chlorambucil vs. chlorambucil, rituximab + chlorambucil vs. chlorambucil, obinutuzumab + chlorambucil vs. rituximab + chlorambucil	30
iLLUMINATE	Ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab	31,3
ELEVATE-TN	Acalabrutinib + obinutuzumab vs. acalabrutinib vs. obinutuzumab + chlorambucil	~29
CLL14	Venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab	28,1
COMPLEMENT1	Ofatumumab + chlorambucil vs. chlorambucil	28,9
CAM-307	Alemtuzumab vs. chlorambucil	Ikke rapporteret

Ved de anvendte *data cuts* var median OS ikke nået i CAM-307, COMPLEMENT1, CLL11, CLL14, ELEVATE-TN, iLLUMINATE og RESONATE-2. I MaBLE blev median OS kun nået for armen behandlet med chlorambucil + rituximab. Median OS blev ikke rapporteret for iLLUMINATE og blev ikke evalueret i ALLIANCE.

Median PFS blev ikke nået i ALLIANCE (ibrutinib og ibrutinib + rituximab-armene), CLL14, RESONATE-2 (ibrutinib-armen) og iLLUMINATE (ibrutinib + obinutuzumab-armen). Der findes ikke information om median PFS for CAM-307.

#### Fagudvalgets kommentarer til datagrundlaget for analysen

De anvendte *data cuts* i NMA'en vurderes tilstrækkeligt ens set ud fra et klinisk perspektiv. Dog er OS-data som forventet ikke modne med denne opfølgningstid, og datagrundlaget for OS-analysen er således meget spinkelt. Det bemærkes også, at data for median PFS er umodent, men dog knap så spinkelt som for OS.

Der ses forskelle i det maksimale antal cyklusser af chlorambucil på tværs af studierne. I iLLUMINATE, MaBLE, CLL11 og ELEVATE-TN blev der maksimalt anvendt 6 cyklusser, mens der i COMPLEMENT1, RESONATE-2, CAM-307 og CLL14 blev anvendt op til 12 cyklusser. Det var ikke muligt at justere for denne forskel i NMA'en, og der bør tages forbehold for den usikkerhed, forskellene i behandlingslængde kan medføre for effektestimaterne. Det er dog usikkert, om 12 cyklusser medfører bedre effekt af chlorambucil, eller om det medfører flere bivirkninger, så patienterne ikke har gavn af en eventuel øget effekt.

Overkrydsning ved progression var tilladt i tre studier (RESONATE-2, ALLIANCE og ELEVATE-TN), men analyserne i studierne og NMA'en justerer ikke herfor. Det kan have betydning for OS-analysen og analysen af bivirkninger, idet den relative



behandlingseffekt kan påvirkes til fordel for det dårligere behandlingsalternativ, mens der også kan være flere bivirkninger i denne gruppe.

Der er stor forskel på studierne med hensyn til andelen af patienter med del(17p), del(11q) og p53-mutation. RESONATE-2 ekskluderede helt patienter med del(17p), og information om p53-mutation mangler for COMPLEMENT1, CAM-307, CLL11 og MaBL. Disse forskelle og manglende data er problematiske og kan have indflydelse på effektmålene, idet fagudvalget forventer, at patienter uden disse mutationer har en bedre prognose.

Andelen af patienter, som ikke er IGHV-muterede, er rapporteret for alle studier på nær CAM-307. Der ses betydelige forskelle i andel af patienter med IGHV-mutation mellem studierne, bl.a. bemærkes, at færre patienter er ikke-muterede i RESONATE-2 og MaBL. Patienter, som ikke er IGHV-muterede, klarer sig dårligere ved behandling med kemoimmunterapi. Fagudvalget tager derfor forbehold for usikkerheden forbundet med forskel i IGHV-mutationsstatus mellem studierne.

Andelen af patienter med CIRS-score > 6 varierer mellem studierne og kan have indflydelse på analysen, idet patienter med CIRS-score > 6 er mindre *fit*, hvilket har indflydelse på prognose og behandlingsmuligheder. ELEVATE-TN, RESONATE-2 og iLLUMINATE inkluderer få patienter med CIRS-score > 6 sammenlignet med CLL11 og CLL14. Denne skævhed i data er en svaghed i analysen.

Ansøger har undersøgt muligheden for at justere analysen (meta-regression) for overkrydsning, forskelle i andelen af patienter med del(17p), del(11q) og p53-mutation og forskelle i andelen af patienter, som ikke er IGHV-muterede, og andelen af patienter med CIRS-score > 6. Ansøger har dog ikke vurderet det muligt grundet det lave antal studier sammenlignet med antal behandlinger (9 studier, som undersøger 12 behandlinger).

#### Fagudvalgets samlede vurdering af analysens anvendelighed

Fagudvalget vurderer, at der er flere vigtige forskelle mellem studierne i patientkarakteristika og studiedesign, som potentielt kan påvirke effektestimaterne. Det er uklart, om forskelle i behandlingstid for chlorambucil kan være til fordel for chlorambucil relativt til de respektive komparatorer i de studier, hvor der gives 12 fremfor 6 cyklusser chlorambucil. Ligeledes er der et væsentligt forbehold vedr. muligheden for overkrydsning i tre studier, som kan påvirke de relative effektestimater til fordel for de ringere behandlingsalternativer i studierne og dermed også for NMA'ens estimater. Der ses også betydelige forskelle i baseline-patientkarakteristika, som har betydning for prognose, behandlingsrespons og behandlingsmuligheder. Slutteligt er OS-data generelt umodne – og til dels også umodne for PFS.

Som konklusion er der væsentlige forbehold vedr. analysen, som betyder, at den primært vil blive anvendt som supplement til øvrige analyser i vurderingen af acalabrutinib.



### **5.2.3 Effektestimater og kategorier**

I Tabel 10 og Tabel 11 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.





**Table 10. Resultater for klinisk spørgsmål 1: acalabrutinib monoterapi vs. obinutuzumab + chlorambucil (GCIB)**

Effekt mål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effekt målet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid (MKRF: 5 %-point)	Kritisk	ELEVATE-TN ITT-population: 5,4 %-point	Kan ikke kategoriseres	ELEVATE-TN ITT-population: HR = 0,60 (95 % CI: 0,28-1,27)	Kan ikke kategoriseres	Kan ikke kategoriseres
Progressionsfri overlevelse (PFS)	Forskel i andel, der opnår PFS efter 3 år eller længst mulig opfølgningstid (MKRF: 10 %-point)	Vigtig	ELEVATE-TN ITT-population: 32,6 %-point ved 3 år  ELEVATE-TN ITT-population: 37,9 %-point ved 46 mdr.	Kan ikke kategoriseres	ELEVATE-TN ITT-population: HR = 0,20 (95 % CI: 0,13-0,30)  ELEVATE-TN subgruppe uden del(17p)/p53-mutation: HR = 0,19 (95 % CI: 0,11-0,31)	Stor merværdi	Stor merværdi
Bivirkninger	Andel patienter, der oplever én eller flere uønskede hændelser af grad 3-4 (MKRF: 10 %-point) (+ kvalitativ gennemgang)	Vigtig	ELEVATE-TN ITT-population: -20,1 %-point (95 % CI: -9,9 – -31,1)	Merværdi af ukendt størrelse	ELEVATE-TN ITT-population: RR = 0,71 (95 % CI: 0,60-0,85)	Moderat merværdi	Lille merværdi
Livskvalitet	EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	-	-	-	-	Kan ikke kategoriseres

### Konklusion

**Samlet kategori for lægemidlets værdi** Moderat merværdi

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.



**Tabel 11. Resultater for klinisk spørgsmål 1: acalabrutinib monoterapi vs. bendamustin + rituximab (BR)**

Effekt mål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid (MKRF: 5 %-point)	Kritisk	-	-	MAIC ITT-population: HR = 1,18 (0,51-2,71)	Kan ikke kategoriseres	Kan ikke kategoriseres
Progressionsfri overlevelse (PFS)	Forskel i andel, der opnår PFS efter 3 år eller længst mulig opfølgningstid (MKRF: 10 %-point)	Vigtig	-	-	MAIC ITT-population: HR = 0,38 (0,20-0,72)	Stor merværdi	Stor merværdi
Bivirkninger	Andel patienter, der oplever en eller flere uønskede hændelser af grad 3-4 (MKRF: 10 %-point) (+ kvalitativ gennemgang)	Vigtig	-	-	-	-	Kan ikke kategoriseres
Livskvalitet	EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	-	-	-	-	Kan ikke kategoriseres

### Konklusion

**Samlet kategori for lægemidlets værdi**      Moderat merværdi

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.



## Acalabrutinib monoterapi vs. obinutuzumab + chlorambucil

### Overlevelse (OS)

Som beskrevet i protokollen er effektmålet *Overlevelse (OS)* kritisk for vurderingen af lægemidlets værdi for patienterne, idet forbedring af patientens overlevelse er det primære mål for behandling af CLL.

Overlevelsesdata i ELEVATE-TN var ikke modent, og median OS var ikke nået i nogen af behandlingsarmene efter hhv. 28,3 og 46,9 måneders median opfølgning. Punktestimatet for OS efter 28,3 måneders median opfølgning indikerer en positiv effekt af acalabrutinib monoterapi, HR = 0,60 (95 % CI 0,28-1,27) for ITT-populationen.

Ved en median opfølgningstid på 28,3 måneder i ELEVATE-TN var der registreret 11 (6,1 %) dødsfald i acalabrutinib monoterapi-armen vs. 17 (9,6 %) dødsfald i chlorambucil + obinutuzumab-armen. Den beregnede OS-rate for ITT-populationen ved 12 måneder baseret på Kaplan-Meier-kurverne var 98,3 % (95 % CI 94,8-99,4) i acalabrutinib monoterapi-armen vs. 96,5 % (95 % CI 92,4-98,4) i chlorambucil + obinutuzumab-armen. Ligeledes var OS-raten ved 36 måneder hhv. 93,5 % (95 % CI: 88,6-96,3) og 88,1 % (95 % CI: 80,7-92,8), hvilket svarer til en forskel på 5,4 %-point.

Efter 46,9 måneders median opfølgning var de estimerede 48 måneders OS-rater 88 % for både acalabrutinib monoterapi og chlorambucil + obinutuzumab.

Det skal bemærkes, at ELEVATE-TN tillod overkrydsning fra chlorambucil + obinutuzumab til acalabrutinib monoterapi ved progression. En betydelig del af patienterne (45 ud af de 177 behandlet med chlorambucil + obinutuzumab) krydsede over til acalabrutinib monoterapi, hvilket kan have påvirket resultaterne til fordel for chlorambucil + obinutuzumab, idet patienterne, som krydsede over, indgik i chlorambucil + obinutuzumab-armen i OS-analysen.

Punktestimatet for den absolutte effektforskel (5,4 %-point) ved 36 måneder afspejler en klinisk relevant effektforskel, mens der ikke ses forskel ved 48 måneder. Dog kan værdien ikke kategoriseres pga. manglende konfidensinterval. Desuden er datagrundlaget ved 36 og 48 måneders opfølgning sparsomt i ELEVATE-TN, hvilket medfører usikkerhed om estimerne.

Baseret på den relative effektforskel for OS (HR = 0,60 (95 % CI 0,28-1,27)), kan acalabrutinib monoterapi ikke kategoriseres, da estimatet er behæftet med betydelig usikkerhed.

Fagudvalget vurderer, at acalabrutinib monoterapi samlet set har en værdi vedr. overlevelse (OS), som ikke kan kategoriseres efter Medicinrådets metoder, da data er umodent. Punktestimatet for hazard ratioen (HR = 0,60 (95 % CI 0,28-1,27)) indikerer dog en forskel mellem behandlingerne til fordel for acalabrutinib monoterapi.

### Progressionsfri overlevelse (PFS)

Som beskrevet i protokollen er effektmålet progressionsfri overlevelse (PFS) vigtigt for vurderingen af lægemidlets værdi for patienterne.



For ITT-populationen var median PFS ikke nået i acalabrutinib monoterapi-armen, og i chlorambucil + obinutuzumab-armen var median PFS 22,6 måneder ved en median opfølgningstid på 28,3 måneder (HR = 0,20 (95 % CI 0,13-0,30)). Ved en median opfølgningstid på 46,9 måneder var median PFS i chlorambucil + obinutuzumab-armen 28,3 måneder, mens den fortsat ikke var nået i acalabrutinib monoterapi-armen.

For subgruppen uden del(17p)/p53-mutation var 20 ud af 156 (12,8 %) af patienterne progredieret i acalabrutinib monoterapi-armen vs. 77 ud af 152 (50,7 %) af patienterne i chlorambucil + obinutuzumab-armen ved en median opfølgningstid på 28,3 måneder (HR = 0,19 (95 % CI 0,11-0,31)).

3 års PFS-rater var ikke tilgængelige for subgruppen uden del(17p)/p53-mutation, men fagudvalget vurderer, at effekten i ITT-populationen er en god indikator for PFS i gruppen uden p17/del53.

Estimeret ud fra Kaplan-Meier-kurverne ved en median opfølgningstid på 28,3 måneder var PFS i ITT-populationen i ELEVATE-TN efter 3 år 63,9 % (95 % CI 29,4-84,9) i acalabrutinib monoterapi-armen og 31,3 % (95 % CI 21,8-41,3) i chlorambucil + obinutuzumab-armen. Det svarer til en forskel på 32,6 %-point. Disse data skal dog fortolkes med forsigtighed, da datagrundlaget er yderst spinkelt, idet *number at risk* på dette tidspunkt kun er 4 i acalabrutinib monoterapi-armen (149 censurerede) og 3 i chlorambucil + obinutuzumab-armen (81 censurerede). Ved et efterfølgende datacut med en median opfølgningstid på 46,9 måneder blev PFS-raten ved 48 måneder estimeret til 78 % i acalabrutinib monoterapi-armen og 25 % i chlorambucil + obinutuzumab-armen. Det svarer til en forskel på 53 %-point, hvilket er væsentligt mere end den fastsatte mindste klinisk relevante forskel på 10 %-point, og understøtter de observerede data ved 28,3 måneders opfølgning.

Punktestimaterne på 32,6 %-point efter 3 år og 53 %-point efter 48 måneder for den absolutte effektforskel for ITT-populationen afspejler en klinisk relevant effektforskel, idet den mindste klinisk relevante forskel var sat til 10 %-point. Pga. manglende konfidensinterval for forskellen kan den foreløbige værdi af acalabrutinib monoterapi vedr. PFS dog ikke bestemmes på den absolutte skala.

Baseret på den relative effektforskel for subgruppen uden P17/del53 (HR = 0,19 (95 % CI 0,11-0,31)) har acalabrutinib monoterapi foreløbigt en stor merværdi vedr. PFS.

Fagudvalget vurderer, at acalabrutinib monoterapi samlet set har en stor merværdi vedr. PFS, idet hazard ratioen for subgruppen uden del(17p)/p53-mutation viser en markant forskel på behandlingerne til fordel for acalabrutinib monoterapi (HR = 0,19 (95 % CI 0,11-0,31)). Dette underbygges af PFS-raterne for ITT-populationen, hvor der efter 48 måneder ses en forskel på 53 %-point mellem grupperne. Fagudvalget forventer, at PFS-gevinsten ved acalabrutinib vil blive afspejlet i en OS-gevinst, når OS-data er mere modne.

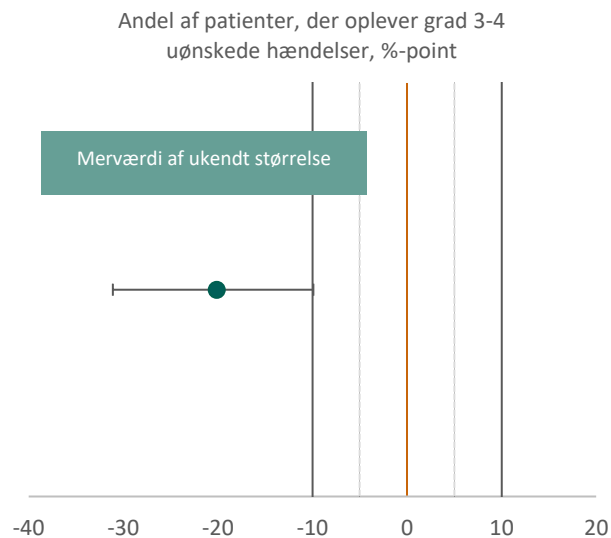


### Bivirkninger

Fagudvalget ønskede sikkerheden ved acalabrutinib belyst ved en opgørelse af andelen af patienter, der oplever mindst én grad 3-4 bivirkning. En forskel mellem grupperne på 10 %-point anses som klinisk relevant.

Data er ikke tilgængeligt for subgruppen uden del(17p)/p53-mutation, men fagudvalget vurderer, at data for ITT-populationen er en god indikator for gruppen uden del(17p)/p53-mutation.

Baseret på data fra ELEVATE-TN med en median opfølgningstid på 28,3 måneder oplevede 49,7 % i acalabrutinib monoterapi-armen en grad  $\geq 3$  uønsket hændelse, mens den tilsvarende andel i chlorambucil + obinutuzumab-armen var 69,8 %. Dette svarer til en forskel på -20,1 % (95 % CI: -9,9 – -31,1) til fordel for acalabrutinib monoterapi og en relativ risiko på 0,71 (95 % CI: 0,6-0,85).



**Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel patienter, der oplever én eller flere uønskede hændelser af grad 3-4. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.**

Fagudvalget har desuden foretaget en kvalitativ gennemgang af bivirkningstyperne for at vurdere, om der er klinisk betydende forskelle i bivirkningsprofilerne mellem acalabrutinib monoterapi og chlorambucil + obinutuzumab. Gennemgangen har taget udgangspunkt i hele *safety*-populationen, da data ikke er opgjort for subpopulationen uden del(17p)/p53-mutation. Fagudvalget forventer ikke, at der er forskel i bivirkningsprofilen mellem *safety*-populationen og subpopulationen uden del(17p)/p53-mutation.



Andelen af patienter, som oplevede uønskede hændelser (*treatment-emergent adverse events* (TEAEs)), var sammenlignelig mellem acalabrutinib monoterapi og chlorambucil + obinutuzumab (95,0 % vs. 98,8 %). Alvorlige uønskede hændelser (*Serious adverse events* (SAEs)) forekom hos 31,8 % og 21,9 % af patienter behandlet med hhv. acalabrutinib monoterapi og chlorambucil + obinutuzumab. Neutropeni (9,5 %), anæmi (6,7 %) og trombocytopeni (2,8 %) var de hyppigste grad  $\geq 3$  uønskede hændelser for acalabrutinib monoterapi. Mere information fremgår af Tabel 12.

**Tabel 12. Uønskede hændelser rapporteret i ELEVATE-TN for acalabrutinib monoterapi og chlorambucil + obinutuzumab (median opfølgningstid 28,3 måneder\*)**

Event	Acalabrutinib monoterapi, n=179, n (%)	Chlorambucil + obinutuzumab, n=169, n (%)
Uønskede hændelser, enhver grad	170 (95,0 %)	167 (98,8 %)
Grad $\geq 3$	89 (49,7 %)	118 (69,8 %)
Alvorlige uønskede hændelser	57 (31,8 %)	37 (21,9 %)
<b>Grad <math>\geq 3</math> uønskede hændelser med en forekomst <math>\geq 2</math> % i en af grupperne</b>		
Neutropeni	17 (9,5 %)	70 (41,4 %)
Trombocytopeni	5 (2,8 %)	20 (11,8 %)
Anæmi	12 (6,7 %)	12 (7,1 %)
Pneumoni	4 (2,2 %)	3 (1,8 %)
Infusionsrelaterede reaktioner	0	9 (5,3 %)

\*Tilgængeligt data for hændelsesfrekvenser efter en median opfølgningstid på 46,9 måneder afviger ikke i betydende grad fra tal i tabellen.

De to behandlinger medfører uønskede hændelser hos 95,0 % (acalabrutinib monoterapi) og 98,8 % (chlorambucil + obinutuzumab) af patienterne. Andelene, som oplevede grad  $\geq 3$  uønskede hændelser, var hhv. 49,7 % og 69,8 %. Forskellen i andele drives her primært af neutropeni, hvor der ses langt flere hændelser ved chlorambucil + obinutuzumab sammenlignet med acalabrutinib (41,4 % vs. 9,5 %). Den større forekomst af neutropeni vurderes dog ikke at have klinisk betydning, da der ikke ses flere alvorlige infektioner såsom lungebetændelse ved chlorambucil + obinutuzumab. Begge behandlinger medfører sammenlignelige frekvenser af grad  $\geq 3$  anæmi (6,7 % og 7,1 %). Ved grad  $\geq 3$  trombocytopeni ses der en mindre forskel (2,8 % og 11,8 %).

Det bemærkes, at der ses mere hovedpine (grad 1-2) ved acalabrutinib (35,8 % vs. 11,8 %), men der er erfaring for, at hovedpine forsvinder inden for 3-4 uger efter opstart af behandlingen.



Ved anvendelse af chlorambucil + obinutuzumab er det velkendt, at der opstår infusionsrelaterede reaktioner ved første infusion. I ELEVATE-TN ses grad  $\geq 3$  infusionsrelaterede hændelser hos 5,3 % af patienter behandlet med chlorambucil + obinutuzumab (0 hændelser for acalabrutinib monoterapi). Her varer reaktionen typisk ikke mere end en dag, men kan i enkelte tilfælde føre til indlæggelse.

I Medicinrådets protokol for vurderingen af acalabrutinib er det defineret, at en forskel på 10 %-point i andelen af patienter, som oplever grad  $\geq 3$  uønskede hændelser, vurderes klinisk relevant. Data fra ELEVATE-TN viser, at 49,7 % og 69,8 % af patienterne behandlet med hhv. acalabrutinib monoterapi og chlorambucil + obinutuzumab oplevede grad  $\geq 3$  uønskede hændelser. Den absolutte effektforskel mellem grupperne er -20,1 %-point (95 % CI -9,9 – -31,1), og acalabrutinib monoterapi har dermed en foreløbig merværdi af ukendt størrelse.

Baseret på den relative effektforskel (RR = 0,71, 95 % CI: 0,6-0,85), har acalabrutinib monoterapi foreløbigt en moderat merværdi vedr. effektmålet bivirkninger, da risikoen for at få en grad  $\geq 3$  uønsket hændelse er mindre ved behandling med acalabrutinib monoterapi end med chlorambucil + obinutuzumab.

Overordnet set vurderer fagudvalget, at acalabrutinib monoterapi har en favorabel bivirkningsprofil sammenlignet med chlorambucil + obinutuzumab. Chlorambucil + obinutuzumab er den forventeligt mildeste form for kemoterapi, som anvendes til CLL-patienter. Det er samtidig en behandling, som klinikerne har lang erfaring med, og som generelt er veltolereret.

Fagudvalget vurderer, at acalabrutinib monoterapi samlet set har en lille merværdi for effektmålet bivirkninger, idet merværdien justeres fra moderat. Justeringen foretages, da der ses flere alvorlige uønskede hændelser ved acalabrutinib sammenlignet med chlorambucil + obinutuzumab (31,8 % vs. 21,9 %).

#### Helbredsrelateret livskvalitet

Data for helbredsrelateret livskvalitet er ikke opgjort for subgruppen uden p17/del53. I stedet har ansøger leveret data for ITT-populationen fra ELEVATE-TN med median opfølgningstid på 28,3 måneder.

Der blev ikke fundet nogen signifikante forskelle i ændring fra baseline mellem de to arme målt med spørgeskemaet EORTC QLQ-C30.

Tid til klinisk relevant forbedring i *Global Health Status (GHS)* var sammenlignelig mellem acalabrutinib monoterapi og chlorambucil + obinutuzumab (2,07 vs. 2,33 måneder; HR: 1,08 (95 % CI: 0,81-1,42)). Der var ingen forskel i tid til forbedring mellem de to arme inden for nogen domæner af EORTC QLQ-C30.

Data for livskvalitet er ikke opgjort som ønsket i protokollen for vurderingen af acalabrutinib, og acalabrutinib monoterapi kan derfor formelt set ikke kategoriseres for effektmålet helbredsrelateret livskvalitet. Det bemærkes dog, at der på baggrund af data til rådighed ingen forskel ses i tid til forbedring af helbredsrelateret livskvalitet mellem



intervention og komparator. Chlorambucil + obinutuzumab er i modsætning til mange andre kemoterapeutika forholdsvis veltolereret, og det er således positivt, at tid til forbedret helbredsrelateret livskvalitet er sammenlignelig mellem de to behandlinger. Fagudvalget ville dog foretrække, at effektmålet i stedet var opgjort over tid, da det ikke kan udelukkes, at der kan forekomme forskel i livskvalitet efter længere opfølgning. Det skyldes, at acalabrutinib gives kontinuerligt (i modsætning til chlorambucil + obinutuzumab), hvilket betyder, at risikoen for at få en bivirkning stiger over tid, og at der ses tidligere progression ved chlorambucil + obinutuzumab, hvilket også ville kunne påvirke livskvaliteten i negativ retning.

#### 5.2.4 Fagudvalgets konklusion

Fagudvalget vurderer samlet set, at behandling med acalabrutinib monoterapi til patienter med CLL giver en moderat merværdi sammenlignet med chlorambucil + obinutuzumab.

I vurderingen er der lagt vægt på den store forskel i PFS mellem de to behandlingsarme. Efter 28,3 måneders median opfølgning var 12,8 % af patienterne uden del(17p)/p53-mutation progredieret eller døde i acalabrutinib monoterapi-armen sammenlignet med 50,7 % i chlorambucil + obinutuzumab-armen (HR = 0,19 (95 % CI 0,11-0,31)). Data for OS var endnu umodne, men viste en tendens til forbedret overlevelse i ITT-populationen ved acalabrutinib monoterapi sammenlignet med chlorambucil + obinutuzumab. Fagudvalget forventer, at forskellen i PFS vil medføre en klinisk relevant forskel i OS ved længere opfølgningstid. Baseret på det nuværende datagrundlag er OS ved 36 måneder (beregnet ud fra Kaplan-Meier-kurverne): 93,5 % (95 % CI: 88,6-96,3) for acalabrutinib monoterapi og 88,1 % (95 % CI: 80,7-92,8) for chlorambucil + obinutuzumab, HR = 0,60 (95 % CI 0,28-1,27). Det bør bemærkes, at 45 ud af 177 patienter behandlet med chlorambucil + obinutuzumab krydsede over til acalabrutinib monoterapi ved progression. Der er ikke justeret for overkrydsning i OS-analysen, hvilket vurderes at være til fordel for chlorambucil + obinutuzumab.

Fagudvalget lægger i vurderingen også vægt på, at acalabrutinib monoterapi er et veltolereret lægemiddel, hvilket har stor betydning, da en del af de lægemidler, som i øvrigt anvendes til at behandle CLL, er kemoterapeutika, som har mange bivirkninger. Dog bemærkes acalabrutinib monoterapi at gives kontinuerligt i modsætning til chlorambucil + obinutuzumab, hvilket betyder, at der potentielt kan forekomme flere bivirkninger over tid.

#### Acalabrutinib monoterapi vs. bendamustin + rituximab

##### Overlevelse (OS)

Det har ikke været muligt at udføre en OS-analyse på subpopulationen uden del(17p)/p53-mutation, og ansøger har derfor udført MAIC-analysen baseret på ITT-populationen i ELEVATE-TN (opfølgningstid i studierne 28,1-31,3 måneder). OS-data er som forventet ikke modent, og median OS var ikke nået i CLL11, CLL14, ELEVATE-TN, ILLUMINATE og RESONATE-2, mens median OS ikke blev evalueret i ALLIANCE.





### MAIC

MAIC-analysen viser en hazard ratio på 1,18 (95 % CI: 0,51-2,71), hvilket indikerer dårligere overlevelse ved acalabrutinib monoterapi sammenlignet med bendamustin + rituximab. Til sammenligning viser ansøgers NMA en HR på 0,61 (95 % CI: 0,23-1,60), hvilket indikerer bedre overlevelse ved acalabrutinib monoterapi. Men i analysen er der ikke taget hensyn til, at der er væsentlige forskelle i patientkarakteristika mellem studierne, hvorfor data skal tolkes med forbehold og kun anvendes som supplement i vurderingen af acalabrutinib.

Overkrydsning ved progression var tilladt i flere studier, som indgik i både MAIC og NMA (ELEVATE-TN, ILLUMINATE, CLL11 og ALLIANCE). Dette gør det sværere at vurdere analysernes resultater, da OS kan blive påvirket til fordel for det ringere behandlingsalternativ i de respektive studier.

### Naiv narrativ gennemgang af data fra relevante studier

I ELEVATE-TN var den beregnede 3-års OS-rate (baseret på Kaplan-Meier-kurven) 93,5 % og den beregnede 48 måneders overlevelseshastighed 88 %. I ALLIANCE-studiet var den beregnede 3-års OS-rate (baseret på Kaplan-Meier-kurven) 88 %, og OS-raten efter 2 år var 95 % med bendamustin + rituximab. I MaBLE-studiet blev rapporteret en 2-års OS-rate (baseret på Kaplan-Meier-kurven) på 89 % efter en median opfølgningstid på 23,5 måneder med bendamustin + rituximab. Data er opsummeret i Tabel 13.

**Tabel 13. OS-rater fra ELEVATE-TN, ALLIANCE og MaBLE**

Effekt mål	Måleenhed	Acalabrutinib ITT n=179 (ELEVATE-TN)	BR (ALLIANCE)	BR (MaBLE)
Overlevelse	Overlevelse 24 måneder	95 %	95 %	89 % (fra KM kurven)
	Overlevelse 36 måneder	93,5 % (fra KM kurven)	88 % (fra KM kurven)	-
	Overlevelse 48 måneder	88 % (estimeret)*	-	-

BR= bendamustin + rituximab, KM = Kaplan-Meier, \*Estimeret ud fra data med 46,9 måneders median opfølgning.

Data ved 36 måneders opfølgning i ELEVATE-studiet viser en højere OS-rate end i ALLIANCE, men da data er forholdsvis spinkelt (acalabrutinib monoterapi *number at risk*: 19, censurerede: 149), skal estimererne tolkes med forsigtighed. OS-raten ved 48 måneders opfølgning for acalabrutinib monoterapi på 88 % understøtter, at acalabrutinib monoterapi er mere effektivt end bendamustin + rituximab.

Da der ikke findes et komparativt estimat med konfidensinterval for forskellen i overlevelseshastighed efter 3 år, kan effekt målet ikke tildeles en foreløbig merværdi. Baseret på den relative effekt forskel fra MAIC-analysen (HR = 1,18 (95 % CI: 0,51-2,71)) har acalabrutinib monoterapi foreløbigt en værdi, som ikke kan kategoriseres vedr. OS.



Fagudvalget vurderer, at værdien af acalabrutinib monoterapi samlet set ikke kan kategoriseres vedr. OS, da data er inkonklusivt og umodent, hvilket kommer til udtryk i et meget bredt konfidensinterval for hazard ratioen (HR = 1,18 (95 % CI: 0,51-2,71)).

#### Progressionsfri overlevelse (PFS)

##### MAIC

PFS-data var umodent, idet median PFS ikke var nået i ELEVATE-TN (acalabrutinib monoterapi-armen), ALLIANCE (ibrutinib og ibrutinib + rituximab-armene), CLL14, RESONATE-2 (ibrutinib-armen) og iLLUMINATE (ibrutinib + obinutuzumab-armen).

Det har ikke været muligt at udføre en PFS-analyse på subpopulationen uden del(17p)/p53-mutation. Ansøgers MAIC-analyse (opfølgningstid i studierne 28,1-31,3 måneder) tager derfor udgangspunkt i ITT-populationen fra ELEVATE-TN. Hazard ratioen for PFS var HR = 0,38 (0,20-0,72). Til sammenligning var hazard ratioen i NMA'en (også baseret på ITT-populationen) HR: 0,15 (0,08-0,27).

##### Naiv narrativ gennemgang af data fra relevante studier

I ELEVATE-TN var 2-års raten for PFS 87,3 %, og den beregnede 3-års rate var 63,9 % for acalabrutinib monoterapi. Ved en median opfølgningstid på 46,9 måneder var 48 måneders raten 78 %. Median PFS var fortsat ikke nået.

I ALLIANCE var PFS-raten ved 2 år 74 % med bendamustin + rituximab og den beregnede 3-års rate 61 %. Median PFS var 43 måneder. I MaBLE var den beregnede 2-års PFS-rate 79 % for bendamustin + rituximab ved en median opfølgningstid på 23,5 måneder. Median PFS var 39,6 måneder. Data er opsummeret i Tabel 14.

**Tabel 14. PFS-rater fra ELEVATE-TN, ALLIANCE og MaBLE**

Effekt mål	Måleenhed	Acalabrutinib (ELEVATE-TN)	BR (ALLIANCE)	BR (MaBLE)
Progressionsfri overlevelse	24 måneder	87,3 %	74 %	79 % (fra KM-kurven)
	36 måneder	63,9 % (fra KM-kurven)	61 % (fra KM-kurven)	-
	48 måneder	78 % (estimeret)	-	-

BR= bendamustin + rituximab, KM = Kaplan-Meier.

Med forbehold for, at raterne ikke kan sammenlignes direkte, da de stammer fra forskellige studier, ses højere PFS-rate ved 24 måneder for acalabrutinib monoterapi (87,3 %) sammenlignet med bendamustin + rituximab i ALLIANCE (74 %) og MaBLE (79 %). Ved 36 måneder ses en mindre forskel i PFS-rate (63,9 % over for 61 % i ALLIANCE). Datagrundlaget ved 36 måneder er imidlertid så spinkelt i acalabrutinib monoterapi-armen i ELEVATE-TN (*number at risk* er 4 og 149 censurerede), at dette ikke kan tillægges vægt. Til sammenligning var der ved 36 måneder 59 patienter *at risk* i bendamustin + rituximab-armen i ALLIANCE. Median PFS var ikke nået i nogen af armene. Raten ved 48 måneder på 78 % for acalabrutinib monoterapi er baseret på et senere *data cut* (median 46,9 måneder) og indikerer bedre effekt af acalabrutinib monoterapi ved sammenligning med raterne for bendamustin + rituximab.



Da der ikke findes et komparativt estimat for forskellen i PFS-rate efter 3 år, kan der ikke tildeles en foreløbig merværdi på den absolutte skala.

Baseret på den relative effektforskel fra MAIC-analysen (HR = 0,38 (95 % CI: 0,20-0,72)) har acalabrutinib monoterapi foreløbigt en stor merværdi vedr. PFS.

Fagudvalget vurderer, at acalabrutinib monoterapi samlet set har en stor merværdi vedr. PFS, fordi hazard ratioen for PFS (HR = 0,38 (0,20-0,72)) viser en signifikant forskel til fordel for acalabrutinib monoterapi. PFS-raterne, som dog er behæftet med usikkerhed, indikerer også, at acalabrutinib er et bedre behandlingsalternativ end bendamustin + rituximab.

### Bivirkninger

I alt oplevede 49,7 % af patienterne behandlet med acalabrutinib monoterapi en grad  $\geq 3$  uønsket hændelse efter en median opfølgningstid på 28,3 måneder i ELEVATE -TN. De hyppigste grad  $\geq 3$  hændelser var neutropeni (9,5 %), anæmi (6,7 %) og trombocytopeni (2,8 %). Pneumoni blev rapporteret hos 2,2 % af patienterne. 8,9 % af patienterne ophørte med behandlingen grundet grad  $\geq 3$  hændelser, og alvorlige uønskede hændelser (SAE) blev rapporteret for 31,8 % af patienterne. Det var ikke muligt at foretage en komparativ analyse af uønskede hændelser, og i det følgende er acalabrutinib monoterapi derfor sammenlignet narrativt med bendamustin + rituximab.

I CLL10-studiet blev grad  $\geq 3$  uønskede hændelser rapporteret for 84 % af patienterne i bendamustin + rituximab-armen. De hyppigste hændelser var neutropeni (55 %), trombocytopeni (14 %), anæmi (11 %) og pneumoni (9 %).

I ALLIANCE rapporterede 62 % grad  $\geq 3$  AEs hæmatologiske hændelser, mens andelen med non-hæmatologiske hændelser var 63 %. Grad  $\geq 3$  anæmi blev rapporteret for 12 % af patienterne, neutropeni for 22 %, trombocytopeni for 9 %, pneumoni for 15 % og febril neutropeni for 7 %.

Grad  $\geq 3$  hændelser blev rapporteret for 75 % af patienterne i MaBLE. De hyppigste grad  $\geq 3$  hændelser i bendamustin + rituximab-armen var neutropeni (43 %), trombocytopeni (10 %), anæmi (10 %) og pneumoni (5 %). Alvorlige uønskede hændelser (SAE) blev rapporteret for 41 %. Se oversigt over andel patienter med uønskede hændelser i de forskellige studier i Tabel 15.

**Tabel 15. Andel patienter, der oplever én eller flere uønskede hændelser af grad 3-4 i ELEVATE-TN, ALLIANCE, CLL10 og MaBLE**

Effekt mål	Måleenhed	Acalabrutinib (ELEVATE-TN) n=179	BR (ALLIANCE) n=183	BR (CLL10) n=279	BR (MaBLE) n=121
Bivirkninger	Andel patienter, der oplever én eller flere uønskede hændelser af grad 3-4	49,7 %	Hæmatologiske: 62 % Non-hæmatologiske: 63 %	84 %	75 %

BR= bendamustin + rituximab.



Fagudvalget vurderer, at merværdien af acalabrutinib monoterapi vedr. bivirkninger formelt set ikke kan kategoriseres, da der ikke foreligger en komparativ analyse af hændelsesfrekvenserne. Dog viser raterne for uønskede hændelser, at acalabrutinib monoterapi har en mere favorabel bivirkningsprofil sammenlignet med bendamustin + rituximab, idet acalabrutinib monoterapi er associeret med færre uønskede hændelser. Forskellen i rater ser ud til at være drevet af en større andel af hæmatologiske bivirkninger ved bendamustin + rituximab, hvilket er i overensstemmelse med fagudvalgets forventninger baseret på erfaring og lægemidlernes virkningsmekanismer. Fagudvalget bemærker, at de hæmatologiske bivirkninger ved bendamustin + rituximab er relevante at inddrage i vurderingen, idet der ses alvorlig infektion såsom pneumoni. Denne tendens ses ikke ved acalabrutinib monoterapi.

#### Helbredsrelateret livskvalitet

Ansøger har ikke leveret komparative data for effektmålet.

#### 5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer samlet set, at acalabrutinib monoterapi til patienter med CLL giver en moderat merværdi sammenlignet med bendamustin + rituximab.

I vurderingen er der lagt vægt på hazard ratioen for PFS (HR = 0,38 (0,20-0,72)), som viser, at acalabrutinib monoterapi er et bedre behandlingsalternativ end bendamustin + rituximab. Estimatet betyder, at acalabrutinib monoterapi for PFS indplaceres i kategorien "stor merværdi".

Overlevelsesdata var endnu umodent, hvilket var forventeligt baseret på opfølgningstiden i studierne i ansøgers analyse (28,1-31,3 måneder). Fagudvalget finder det sandsynligt, at PFS-gevinsten ved acalabrutinib monoterapi vil afspejles i en øget overlevelse ved længere opfølgningstid, hvilket understøttes af overlevelsesraterne i ELEVATE-TN, ALLIANCE og MaBLE, som indikerer en tendens til bedre overlevelse ved acalabrutinib monoterapi.

Fagudvalget lægger også stor vægt på, at acalabrutinib monoterapi er et bedre tolereret lægemiddel end bendamustin + rituximab. Acalabrutinib medfører færre grad  $\geq 3$  uønskede hændelser (49,7 % vs. 84 % og 75 %), og der ses færre klinisk betydende hæmatologiske bivirkninger, som kan medføre øget infektionsrisiko. Fagudvalget bemærker, at acalabrutinib monoterapi, i modsætning til bendamustin + rituximab, gives kontinuert, hvilket potentielt kan medføre flere bivirkninger over tid.

### 5.3 Klinisk spørgsmål 2

*Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med kemoimmunterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion (17p)/p53-mutation?*



### 5.3.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

#### **Acalabrutinib + obinutuzumab vs. obinutuzumab + chlorambucil**

##### Direkte analyser

Det direkte studie ELEVATE-TN, som er beskrevet ovenfor i afsnit 5.2.1, vil blive anvendt til at besvare denne del af klinisk spørgsmål 2. Udvalgte baselinekarakteristika for populationerne inkluderet i den direkte sammenligning mellem acalabrutinib + obinutuzumab og obinutuzumab + chlorambucil i ELEVATE-TN-studiet kan findes i Bilag 2, Tabel 40.

##### Indirekte analyser

Ansøgers MAIC- og NMA-analysen, som er beskrevet ovenfor i afsnit 5.2.1, indgår i besvarelsen af det kliniske spørgsmål.

#### **Acalabrutinib + obinutuzumab vs. bendamustin + rituximab**

##### Indirekte analyser

Der findes ikke et direkte sammenlignende studie af acalabrutinib + obinutuzumab og bendamustin + rituximab. Denne del af klinisk spørgsmål 2 vil derfor udelukkende blive besvaret vha. MAIC- og NMA-analyserne, som er beskrevet i afsnit 5.2.1, samt ved en narrativ sammenligning. Denne narrative gennemgang anvender data fra de samme studier, som den narrative gennemgang i klinisk spørgsmål 1, dvs. at data for acalabrutinib + obinutuzumab stammer fra ELEVATE-TN, og data for bendamustin + rituximab stammer fra hhv. ALLIANCE, CLL10 og MaBL. Oversigten over studierne kan findes i Tabel 5 i afsnit 5.2.1. Studierne er beskrevet yderligere i Bilag 1. Udvalgte baselinekarakteristika for populationerne i studierne kan ses i Tabel 43 i Bilag 2.

### 5.3.2 Databehandling og analyse

Vurderingen er baseret på ELEVATE-TN, MAIC og NMA-analyser, som blev beskrevet i afsnit 5.2.1 og 5.2.2, samt på en narrativ sammenligning.

### 5.3.3 Effektestimater og kategorier

I Tabel 16 og Tabel 17 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.



**Tabel 16. Resultater for klinisk spørgsmål 2: acalabrutinib + obinutuzumab vs. obinutuzumab + chlorambucil (GCIB)**

Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid (MKRF: 5 %-point)	Kritisk	ELEVATE-TN ITT-population: 6,8 %-point	Kan ikke kategoriseres	ELEVATE-TN ITT-population: HR = 0,47 (0,21-1,06)	Kan ikke kategoriseres	Kan ikke kategoriseres
Progressionsfri overlevelse (PFS)	Forskel i andel patienter, der opnår PFS efter 3 år eller længst mulig opfølgningstid (MKRF: 10 %-point)	Vigtig	ELEVATE-TN ITT-population: 58,3 %-point	Kan ikke kategoriseres	ELEVATE-TN ITT-population: HR = 0,10 (0,06-0,17)  ELEVATE-TN subgruppe uden del(17p)/p53mutation: HR = 0,10 (0,5-0,18)	Stor merværdi	Stor merværdi
Bivirkninger	Andel patienter, der oplever én eller flere uønskede hændelser grad 3-4 (MKRF: 10 %-point) (+ kvalitativ gennemgang)	Vigtig	ELEVATE-TN ITT-population: 0,4 %-point	Kan ikke kategoriseres	ELEVATE-TN ITT-population: RR: 1,00 (0,88-1,15)	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	-	-	-	-	-

### Konklusion

**Samlet kategori for lægemidlets værdi** Lille merværdi

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.



**Tabel 17. Resultater for klinisk spørgsmål 2: acalabrutinib + obinutuzumab vs. bendamustin + rituximab (BR)**

Effekt mål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid (MKRF: 5 %-point)	Kritisk	-	Kan ikke kategoriseres	ITT-population: HR = 0,55 (0,20-1,50) (MAIC)	Kan ikke kategoriseres	Kan ikke kategoriseres
Progressionsfri overlevelse (PFS)	Forskel i andel patienter, der opnår PFS efter 3 år eller længst mulig opfølgningstid (MKRF: 10 %-point)	Vigtig	-	Kan ikke kategoriseres	ITT-population: HR = 0,21 (0,10-0,43) (MAIC)	Stor merværdi	Stor merværdi
Bivirkninger	Andel patienter, der oplever en eller flere uønskede hændelser grad 3-4 (MKRF: 10 %-point) (+ kvalitativ gennemgang)	Vigtig	-	-	-	-	Kan ikke kategoriseres
Livskvalitet	EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	-	-	-	-	-
<b>Konklusion</b>							
<b>Samlet kategori for lægemidlets værdi</b>		Lille merværdi					

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.



## **Acalabrutinib + obinutuzumab vs. obinutuzumab + chlorambucil**

### **Overlevelse (OS)**

Efter en median opfølgningstid på hhv. 28,3 og 46,9 måneder i ELEVATE-TN var OS-data ikke modent og median OS ikke nået i nogen af behandlingsarmene. Data for subgruppen uden del(17p)/p53-mutation var ikke til rådighed. For ITT-populationen er punktestimatet for OS til fordel for acalabrutinib + obinutuzumab HR = 0,47 (95 % CI 0,21-1,06), men ikke statistisk signifikant (median opfølgningstid 28,3 måneder).

Efter en median opfølgningstid på 28,3 måneder var den beregnede OS-rate for ITT-populationen ved 12 måneder (baseret på Kaplan-Meier-kurverne) 96,1 % (95 % CI: 91,9-98,1) for acalabrutinib + obinutuzumab vs. 96,5 % (95 % CI: 92,4-98,4) for chlorambucil + obinutuzumab. Ligeledes var OS-raten ved 36 måneder hhv. 94,9 % (95 % CI: 90,5-97,3) og 88,1 % (95 % CI: 80,7-92,8), hvilket svarer til en forskel på 6,8 %-point. Ved en median opfølgningstid på 46,9 måneder var den beregnede OS for ITT-populationerne ved 48 måneder hhv. 93 % for acalabrutinib + obinutuzumab og 88 % for chlorambucil + obinutuzumab.

Det skal bemærkes, at ELEVATE-TN tillod overkrydsning fra chlorambucil + obinutuzumab til acalabrutinib givet som monoterapi ved progression. En betydelig del af patienterne (28,3 måneders opfølgning: 45 ud af 177 behandlet med chlorambucil + obinutuzumab) krydsede over til acalabrutinib, hvilket kan have påvirket resultaterne til fordel for chlorambucil + obinutuzumab, idet disse patienter indgik i chlorambucil + obinutuzumab-armen i OS-analysen.

Punktestimaterne for den absolutte effektforskel ved 36 måneder (6,8 %-point) og ved 48 måneder (5 %-point) afspejler en klinisk relevant forskel til fordel for acalabrutinib + obinutuzumab. Men eftersom vi ikke har et konfidensinterval for forskellene, kan værdien af den absolutte forskel ikke kategoriseres. Derudover er datagrundlaget ved 36 måneders opfølgning sparsomt i ELEVATE-TN, hvorfor der er usikkerhed om estimatet. Baseret på den relative effektforskel (HR = 0,47; 95 % CI: 0,21-1,06) kan acalabrutinib + obinutuzumab ikke kategoriseres vedr. overlevelse (OS), da konfidensintervallet er for bredt.

Fagudvalget vurderer, at acalabrutinib + obinutuzumab samlet set har en værdi, som ikke kan kategoriseres vedr. effektmålet overlevelse (OS), fordi data er umodent. Punktestimatet for hazard ratioen (HR = 0,47 (95 % CI: 0,21-1,06)) indikerer en forskel mellem behandlingerne til fordel for acalabrutinib + obinutuzumab, og det forventes, at længere opfølgningstid vil understøtte dette.

### **Progressionsfri overlevelse (PFS)**

I ITT-populationen var median PFS i chlorambucil + obinutuzumab-armen 22,6 måneder, mens median PFS ikke var nået i acalabrutinib + obinutuzumab-armen efter en median opfølgningstid på 28,1 måneder (HR = 0,10 (95 % CI: 0,06-0,17)). Efter en median opfølgning på 46,9 måneder var median PFS fortsat ikke nået i acalabrutinib + obinutuzumab-armen, mens den i chlorambucil + obinutuzumab-armen var ændret til 27,8 måneder.





For subgruppen uden del(17p)/p53-mutation var 11 ud af 154 (7,1 %) patienter progredieret eller døde i acalabrutinib + obinutuzumab-armen vs. 77 ud af 152 (50,7 %) af patienterne i chlorambucil + obinutuzumab-armen ved en median opfølgningstid på 28,1 måneder (HR = 0,10 (95 % CI: 0,05-0,18)).

3 års PFS-resultater var ikke tilgængelige for subgruppen uden del(17p)/p53-mutation. Beregnet ud fra Kaplan-Meier-kurverne var PFS-raterne i ITT-populationen efter 3 år på 89,6 % (95 % CI: 82,0-94,1) for acalabrutinib + obinutuzumab og 31,3 % (95 % CI: 21,8-41,3) for chlorambucil + obinutuzumab, hvilket svarer til en forskel på 58,3 %-point. Disse data skal dog fortolkes med forsigtighed, da datagrundlaget er yderst spinkelt, idet *number at risk* på dette tidspunkt kun er 4 i acalabrutinib + obinutuzumab-armen (161 censurerede) og 3 i chlorambucil + obinutuzumab-armen (81 censurerede). Ved det efterfølgende *data cut* med en median opfølgningstid på 46,9 måneder var 48 måneders raten i acalabrutinib + obinutuzumab-armen 87 % og i chlorambucil + obinutuzumab-armen 25 %, hvilket svarer til en forskel på 62 %-point.

Punktestimaterne på 58,3 %-point efter 3 år og 62 %-point efter 4 år for den absolutte effektforskel afspejler en klinisk relevant effektforskel, idet den mindste klinisk relevante forskel var sat til 10 %-point. Ved 2 år ses også en klinisk relevant effektforskel på 46 %-point. Men da konfidensintervallet for forskellene mangler, kan den foreløbige værdi af acalabrutinib + obinutuzumab ikke bestemmes på den absolutte skala. Baseret på den relative effektforskel for subgruppen uden del(17p)/p53-mutation (HR = 0,10 (95 % CI: 0,05-0,18)) har acalabrutinib + obinutuzumab foreløbigt en stor merværdi vedr. PFS.

Fagudvalget vurderer, at acalabrutinib + obinutuzumab samlet set har en stor merværdi vedr. PFS, fordi hazard ratioen for subgruppen uden del(17p)/p53-mutation viser en markant forskel på behandlingerne til fordel for acalabrutinib monoterapi (HR = 0,10 (95 % CI: 0,05-0,18)). Dette underbygges af PFS-raterne, hvor der efter 2 år ses en forskel på 46 %-point, efter 3 år en forskel på 58,3 %-point og efter 4 år en forskel på 62 %-point mellem grupperne. Fagudvalget forventer, at PFS-gevinsten ved acalabrutinib + obinutuzumab vil afspejle sig i en gevinst på overlevelse, når overlevelseshdata er mere modent.

#### Bivirkninger

Data er ikke tilgængeligt for subgruppen uden del(17p)/p53-mutation, og vurderingen er derfor baseret på data fra ITT-populationen i ELEVATE-TN (median opfølgningstid 28,3 måneder).

I acalabrutinib + obinutuzumab-armen oplevede 70,2 % af patienterne en grad  $\geq 3$  uønsket hændelse, mens den tilsvarende andel i chlorambucil + obinutuzumab-armen var 69,8 %. Dette svarer til en forskel på 0,4 %-point og en relativ risiko (RR) på 1,00 (95 % CI: 0,88-1,15)

38,8 % af patienterne behandlet med acalabrutinib + obinutuzumab oplevede en SAE, og i chlorambucil + obinutuzumab-armen oplevede 21,9 % en SAE. Den hyppigste SAE i gruppen behandlet med acalabrutinib + obinutuzumab var pneumoni, hvilket forekom hos 12 patienter (6,7 %). Den hyppigste alvorlige uønskede hændelse i gruppen



behandlet med chlorambucil + obinutuzumab var *tumor lysis* syndrom, som forekom hos 8 patienter (4,7 %).

Ophør af behandling som følge af uønskede hændelser var hyppigst i chlorambucil + obinutuzumab-armen (14,2 %) sammenlignet med acalabrutinib + obinutuzumab (10,7 %). De hyppigste grad  $\geq 3$  uønskede hændelser er vist i Tabel .

**Tabel 18. Uønskede hændelser rapporteret i ELEVATE-TN for acalabrutinib + obinutuzumab og chlorambucil + obinutuzumab baseret på median opfølgningstid på 28,3 måneder\***

Event	Acalabrutinib + obinutuzumab n=179, n (%)	Chlorambucil + obinutuzumab n=169, n (%)
Uønskede hændelser, alle grader	171 (96,1 %)	167 (98,8 %)
Grad $\geq 3$	125 (70,2 %)	118 (69,8 %)
Alvorlige uønskede hændelser	69 (38,8 %)	37 (21,9 %)
<b>Grad <math>\geq 3</math> uønskede hændelser med en forekomst <math>\geq 2</math> % i en af grupperne</b>		
Neutropeni	53 (29,8 %)	70 (41,4 %)
Trombocytopeni	15 (8,4 %)	20 (11,8 %)
Anæmi	10 (5,6 %)	12 (7,1 %)
Øvre luftvejsinfektion	4 (2,2 %)	1 (0,6 %)
Pneumoni	10 (5,6 %)	3 (1,8 %)
Infusionsrelaterede reaktioner	4 (2,2 %)	9 (5,3 %)
Diarré	8 (4,5 %)	3 (1,8 %)

\*Tilgængelige data for hændelsesfrekvenser efter en median opfølgningstid på 46 måneder afviger ikke i betydende grad fra tal i tabellen.

Fagudvalget vurderer, at der generelt set ikke er forskelle i forekomsten af grad  $\geq 3$  uønskede hændelser mellem de to behandlinger. Dog ses der flere tilfælde af neutropeni ved behandling med chlorambucil + obinutuzumab (41,4 %) sammenlignet med acalabrutinib + obinutuzumab (29,8 %). Det bemærkes, at tillægget af obinutuzumab til acalabrutinib øger forekomsten af neutropeni, idet der var færre tilfælde ved acalabrutinib monoterapi (9,5 %). Neutropeni er klinisk relevant i de tilfælde, hvor det medfører flere infektioner hos patienten. En sammenligning af grad  $\geq 3$  infektioner viser en overvægt af hændelser i gruppen behandlet med acalabrutinib + obinutuzumab



(n=38, 20,8 %) sammenholdt med gruppen behandlet med chlorambucil + obinutuzumab (n=14, 8,3 %). Ved behandling med acalabrutinib monoterapi er andelen 14,0 % (n=25).

Punktestimatet for den absolutte forskel i grad  $\geq 3$  uønskede hændelser i ITT-populationen (0,4 %-point) afspejler ikke en klinisk relevant forskel, idet den mindste klinisk relevante forskel var sat til 10 %-point. Da konfidensintervallet for forskellen ikke er til rådighed, kan den foreløbige værdi af acalabrutinib + obinutuzumab vedr. bivirkninger ikke kategoriseres på den absolutte skala.

Baseret på den relative forskel for ITT-populationen RR = 1,00 (95 % CI: 0,88-1,15) kan den foreløbige værdi af acalabrutinib + obinutuzumab ikke kategoriseres, da konfidensintervallet for forskellen er for bredt, og estimatet derfor er usikkert. Fagudvalget vurderer samlet set, at værdien af acalabrutinib + obinutuzumab ikke kan kategoriseres vedr. bivirkninger baseret på det absolutte og relative effektestimat. Ved gennemgang af bivirkningsprofilerne fremhæver fagudvalget, at der forekommer et sammenligneligt antal grad  $\geq 3$  uønskede hændelser ved acalabrutinib + obinutuzumab og chlorambucil + obinutuzumab, men at behandling med acalabrutinib + obinutuzumab medfører med flere alvorlige uønskede hændelser (38,8 % vs. 21,9 %). Samtidig ses der flere tilfælde af neutropeni ved chlorambucil + obinutuzumab (41,4 % vs. 29,8 %), men ved gennemgang af grad  $\geq 3$  infektioner ses en tendens til en større forekomst ved brug af acalabrutinib + obinutuzumab (20,8 %) vs. chlorambucil + obinutuzumab (8,3 %). Fagudvalget vurderer på baggrund af de tilgængelige data, at de to behandlingsalternativer er sammenlignelige, hvad angår bivirkninger.

#### Helbredsrelateret livskvalitet

Acalabrutinib + obinutuzumab var associeret med forbedringer fra baseline i helbredsrelateret livskvalitet målt med EORTC QLQ-C30. Acalabrutinib + obinutuzumab viste forbedring på de fleste domæner af EORTC QLQ-C30, herunder på *global health status* (GHS)-skalaen og vedr. *fatigue*, *role functioning*, *emotional functioning*, *pain*, *dyspnoea*, *insomnia* og *appetite loss*. Tilsvarende forbedringer sås ved behandling med chlorambucil + obinutuzumab.

Data for helbredsrelateret livskvalitet er ikke tilgængeligt for populationen uden del(17p)/p53-mutation, og data er ikke opgjort som ønsket i protokollen for vurderingen af acalabrutinib. Der kan derfor formelt set ikke tildeles en merværdi for effektmålet. Det bemærkes, at der på baggrund af det tilgængelige data ingen forskel ses i tid til forbedring af livskvalitet, når acalabrutinib + obinutuzumab sammenlignes med chlorambucil + obinutuzumab.

#### 5.3.4 Fagudvalgets konklusion

Fagudvalget vurderer samlet set, at acalabrutinib + obinutuzumab til patienter med CLL uden del(17p)/p53-mutation giver en lille merværdi sammenlignet med chlorambucil + obinutuzumab.



I vurderingen er der lagt vægt på PFS-data for subgruppen uden del(17p)/p53-mutation, som efter 28,3 måneders median opfølgning viser en stor forskel mellem de to behandlingsalternativer. I gruppen behandlet med acalabrutinib + obinutuzumab var 7,1 % progredieret eller døde sammenlignet med 50,7 % i gruppen behandlet med chlorambucil + obinutuzumab (HR = 0,10 (95 % CI: 0,05-0,18)).

Data for overlevelse var endnu umodent, men viser en tendens til øget OS ved acalabrutinib + obinutuzumab (HR = 0,47 (95 % CI: 0,21-1,06)). Fagudvalget forventer, at forskellen i PFS vil medføre en klinisk relevant forskel på overlevelse ved længere opfølgningstid. Dette skal også ses i lyset af, at 45 ud af 177 patienter behandlet med chlorambucil + obinutuzumab krydsede over til acalabrutinib monoterapi ved progression. Der er ikke justeret for overkrydsning i OS-analysen, hvilket er til fordel for chlorambucil + obinutuzumab.

Fagudvalget vurderer, at de to behandlingsalternativer er sammenlignelige angående bivirkningsprofiler, om end der ses flere alvorlige uønskede hændelser og grad  $\geq 3$  infektioner ved acalabrutinib + obinutuzumab. Da det er uvist, hvilken betydning denne forskel har i klinisk praksis, vælger fagudvalget at nedgradere den samlede merværdi til lille.

#### **Acalabrutinib + obinutuzumab vs. bendamustin + rituximab**

##### **Overlevelse (OS)**

###### *MAIC*

Ansøger har udført en MAIC-analyse baseret på ITT-populationen i ELEVATE-TN for at belyse OS (opfølgningstid i studierne 28,1-31,3 måneder). OS-data er forventeligt ikke modent på dette tidspunkt, og median OS var ikke nået i CLL11, CLL14, ELEVATE-TN, iLLUMINATE og RESONATE-2, mens median OS ikke blev evalueret i ALLIANCE.

MAIC-analysen viser en hazard ratio på HR = 0,55 (95 % CI: 0,20-1,50) uden statistisk signifikant forskel mellem acalabrutinib + obinutuzumab og bendamustin + rituximab. Til sammenligning viser ansøgers NMA en HR på 0,36 (95 % CI: 0,12-1,05), dog uden hensyn til, at der er væsentlige forskelle i patientkarakteristika mellem studierne, hvorfor data skal tolkes med forbehold.

Overkrydsning ved progression var tilladt i flere af studierne, som indgik i både MAIC og NMA (ELEVATE-TN, iLLUMINATE, CLL11 og ALLIANCE). Dette gør det sværere at vurdere analysernes resultater, da OS kan blive påvirket til fordel for det ringere behandlingsalternativ i de respektive studier.

###### *Naiv narrativ gennemgang af data fra relevante studier*

I ELEVATE-TN var den beregnede 3-års OS (baseret på Kaplan-Meier-kurven) 94,9 %, og 2-års OS-raten var 95 % for acalabrutinib + obinutuzumab ved en median opfølgningstid på 28,3 måneder. Ved et efterfølgende *data cut* med en median opfølgningstid på 46,9 måneder var den beregnede OS ved 48 måneder 93 %. I ALLIANCE-studiet var den beregnede 3-års OS med bendamustin + rituximab (baseret på Kaplan-Meier-kurven) 88 %, og OS efter 2 år var 95 %. MaBLE-studiet rapporterede en 2-års OS (baseret på



Kaplan-Meier-kurven) på 89 % ved en median opfølgningstid på 23,5 måneder. Data er opsummeret i Tabel .

**Tabel 19. OS-rater fra ELEVATE-TN, ALLIANCE og MaBLE**

Effekt mål	Måleenhed	AO (ELEVATE-TN)	BR (ALLIANCE)	BR (MaBLE)
Overlevelse	Overlevelse 24 måneder	95 %	95 %	89 % (fra KM-kurven)
	Overlevelse 36 måneder	94,9 % (fra KM-kurven)	88 % (fra KM-kurven)	-
	Overlevelse 48 måneder	93 % (estimeret)	-	-

AO = acalabrutinib + obinutuzumab, BR= bendamustin + rituximab, KM = Kaplan-Meier.

Ved naiv sammenligning af overlevelsesseraterne fra ITT-populationerne efter 3 år i ELEVATE-TN over for ALLIANCE ses en forskel på 6,9 %-point. Den mindste klinisk relevante forskel var sat til 5 %-point. Dog er data ikke direkte sammenligneligt, og datagrundlaget for acalabrutinib + obinutuzumab er spinkelt (*number at risk*: 15, censurerede: 155). Overlevelsesseraten ved 48 måneder understøtter, at acalabrutinib + obinutuzumab muligvis er mere effektivt end bendamustin + rituximab. Det er således ikke muligt at tildele en foreløbig værdi på den absolutte skala for acalabrutinib + obinutuzumab baseret på det nuværende datagrundlag.

Baseret på den relative effektforskel for ITT-populationen (MAIC HR = 0,55 (95 % CI: 0,20-1,50)) kan den foreløbige værdi af acalabrutinib + obinutuzumab ikke kategoriseres, da konfidensintervallet er meget bredt.

Fagudvalget vurderer, at værdien af acalabrutinib + obinutuzumab samlet set ikke kan kategoriseres vedr. OS, fordi data er umodent.

### Progressionsfri overlevelse (PFS)

#### MAIC

PFS-data var til dels umodent, idet median PFS ikke var nået i acalabrutinib + obinutuzumab-armen i ELEVATE-TN ved de tilgængelige *data cuts*. Median PFS var heller ikke nået i ALLIANCE (ibrutinib og ibrutinib + rituximab-armene), CLL14, RESONATE-2 (ibrutinib-armen) og iLLUMINATE (ibrutinib + obinutuzumab-armen).

Det har ikke været muligt at udføre en PFS-analyse på subpopulationen uden del(17p)/p53-mutation. Ansøgers MAIC-analyse (opfølgningstid i studierne 28,1-31,3 måneder) tager derfor udgangspunkt i ITT-populationen fra ELEVATE-TN. Hazard ratioen (HR) var 0,21 (95 % CI: 0,10-0,43), hvilket indikerer, at acalabrutinib + obinutuzumab er et bedre behandlingsalternativ end bendamustin + rituximab. Ansøgers NMA viser et lignende resultat med en HR på 0,08 (95 % CI: 0,04-0,16).



#### Naiv narrativ gennemgang af data fra relevante studier

I ELEVATE-TN var 2-års raten for PFS 93 %, den beregnede 3-års PFS-rate 89,9 % og den beregnede 4-års rate 87 % for acalabrutinib + obinutuzumab. Median PFS var endnu ikke nået ved de tilgængelige *data cuts* (median opfølgningstid 28,3 og 46,9 måneder). I ALLIANCE var PFS-raten ved 2 år 74 % med bendamustin + rituximab, og den beregnede 3-års PFS var 61 %. Median PFS-rate var 43 måneder. I MaBLE var den beregnede 2-års PFS rate 79 % for bendamustin + rituximab ved en median opfølgningstid på 23,5 måneder. Median PFS var 39,6 måneder. Data er opsummeret i Tabel 20.

**Tabel 20. PFS-raterne fra ELEVATE-TN, ALLIANCE og MaBLE**

Effekt mål	Opfølgning	AO (ELEVATE-TN)	BR (ALLIANCE)	BR (MaBLE)
	24 måneder	93 %	74 %	79 % (fra KM-kurven)
Progressionsfri overlevelse	36 måneder	89,9 % (fra KM-kurven)	61 % (fra KM-kurven)	-
	48 måneder	87 % (estimeret)	-	-

AO = acalabrutinib + obinutuzumab, BR = bendamustin + rituximab, KM = Kaplan-Meier.

Med forbehold for, at raterne ikke kan sammenlignes direkte, ses en højere PFS-rate ved 24 måneder for acalabrutinib + obinutuzumab (93 %) sammenlignet med bendamustin + rituximab i ALLIANCE (74 %) og MaBLE (79 %).

Ved 36 måneder ses en forskel i PFS-rate (89,9 % over for 61 % i ALLIANCE) på 28,9 %-point. Den mindste klinisk relevante forskel var sat til 10 %-point. Datagrundlaget ved 36 måneder er imidlertid så spinkelt i acalabrutinib + obinutuzumab-armen i ELEVATE-TN (*number at risk* er 4, og 161 er censurerede), at dette skal fortolkes med forsigtighed. Til sammenligning var der ved 36 måneder 59 patienter *at risk* i bendamustin + rituximab-armen i ALLIANCE. Median PFS var ikke nået i nogen af armene. Baseret på det nuværende datagrundlag er det samlet set ikke muligt at tildele acalabrutinib + obinutuzumab en foreløbig værdi på den absolutte skala.

Baseret på den relative effektforskel for ITT-populationen (MAIC HR = 0,21 (95 % CI: 0,10-0,43)) er den foreløbige værdi af acalabrutinib + obinutuzumab vedr. PFS en stor merværdi.

Fagudvalget vurderer, at acalabrutinib + obinutuzumab samlet set har en stor merværdi vedr. PFS, fordi hazard ratioen for PFS viser en signifikant forskel til fordel for acalabrutinib monoterapi, som indplacerer acalabrutinib monoterapi i kategorien "stor merværdi". PFS-raterne, som dog er behæftet med usikkerhed, indikerer også, at acalabrutinib er et bedre behandlingsalternativ.



### Bivirkninger

Det var ikke muligt at foretage en komparativ analyse af acalabrutinib + obinutuzumab vs. bendamustin + rituximab vedr. andelen af patienter, som oplevede en grad  $\geq 3$  uønsket hændelse. I stedet gennemgås data narrativt.

I alt oplevede 70,2 % af patienterne behandlet med acalabrutinib + obinutuzumab en grad  $\geq 3$  uønsket hændelse og 38,8 % en alvorlig uønsket hændelse i ELEVATE-TN (median opfølgningstid 28,3 måneder). De hyppigste grad  $\geq 3$  hændelser var neutropeni (29,8 %), anæmi (5,6 %) og trombocytopeni (8,4 %). Behandlingsophør grundet en uønsket hændelse forekom hos 11,2 % af patienterne.

I CLL10-studiet blev grad  $\geq 3$  uønskede hændelser rapporteret for 84 % af patienterne behandlet med bendamustin + rituximab. De hyppigste grad  $\geq 3$  hændelser var neutropeni (55 %), trombocytopeni (14 %), anæmi (11 %) og pneumoni (9 %). I ALLIANCE rapporterede 62 % af patienterne grad  $\geq 3$  AEs hæmatologiske hændelser, mens andelen med non-hæmatologiske hændelser var 63 %. Grad  $\geq 3$  anæmi blev rapporteret for 12 % af patienterne, neutropeni for 22 %, trombocytopeni for 9 %, pneumoni for 15 % og febril neutropeni for 7 %.

Grad  $\geq 3$  uønskede hændelser blev rapporteret for 75 % af patienterne i MaBL. De hyppigste grad  $\geq 3$  hændelser blandt patienter behandlet med bendamustin + rituximab var neutropeni (43 %), trombocytopeni (10 %), anæmi (10 %) og pneumoni (5 %). Alvorlige uønskede hændelser (SAE) blev rapporteret for 41 %.

**Tabel 21. Andel patienter, der oplevede én eller flere uønskede hændelser grad 3-4 i ELEVATE-TN, ALLIANCE, CLL10 og MaBL**

Effekt mål	Måleenhed	AO (ELEVATE-TN) n=179	BR (ALLIANCE) n=183	BR (CLL10) n=279	BR (MaBL) n=121
Bivirkninger	Andel patienter, der oplever én eller flere uønskede hændelser af grad 3-4	70,2 %	Hæmatologiske: 62 % Non-hæmatologiske: 63 %	84 %	75 %

AO = acalabrutinib + obinutuzumab, BR = bendamustin + rituximab, KM = Kaplan-Meier.

Fagudvalget vurderer, at merværdien af acalabrutinib + obinutuzumab vedr. bivirkninger ikke kan kategoriseres, da der ikke er foretaget en komparativ analyse af hændelsesfrekvenserne. Ved sammenligning af andelen af patienter, der oplever én eller flere uønskede hændelser af grad 3-4, ses, at der er en smule færre hændelser ved acalabrutinib + obinutuzumab sammenlignet med bendamustin + rituximab (70,2 % vs. 84 % (CLL10-studiet) og 75 % (MaBL-studiet)).

Forskellen i rater ser ud til at være drevet af en lidt større andel hæmatologiske bivirkninger ved bendamustin + rituximab, hvilket er i god overensstemmelse med fagudvalgets forventninger baseret på erfaring og virkningsmekanismer ved



lægemidlerne. Fagudvalget hæfter sig ved, at de hæmatologiske bivirkninger ved bendamustin + rituximab har klinisk relevans, idet der ses alvorlig infektion såsom pneumoni. I MaBLé er forekomsten af infektioner 10 % af grad 3, 3 % af grad 4 og 2 % af grad 5. I CLL10 oplevede 19 % af patienterne en infektion kategoriseret som en SAE. I acalabrutinib + obinutuzumab-armen i ELEVATE-TN fik 21 % af patienterne også en grad  $\geq 3$  infektion.

Fagudvalget vurderer samlet set, at værdien af acalabrutinib + obinutuzumab ikke kan kategoriseres vedr. bivirkninger, da der ikke findes komparative estimater at basere kategoriseringen på. Det vurderes, at acalabrutinib + obinutuzumab og bendamustin + rituximab er omtrent lige toksiske. Det bemærkes, at der var færre behandlingsophør grundet en uønsket hændelse hos patienterne behandlet med acalabrutinib + obinutuzumab (11,2 %) sammenlignet med patienterne behandlet med bendamustin + rituximab (MaBLé 18 %).

#### Livskvalitet

Ansøger har ikke leveret komparative data for effektmålet.

### 5.3.5 Fagudvalgets konklusion

Fagudvalget vurderer samlet set, at acalabrutinib + obinutuzumab til patienter med CLL giver en lille merværdi sammenlignet med bendamustin + rituximab til patienter uden del(17p)/p53-mutation.

I vurderingen er der lagt vægt på hazard ratioen (HR = 0.21 (95 % CI: 0,10-0,43)) for PFS, som viser, at acalabrutinib + obinutuzumab er et bedre behandlingsalternativ end bendamustin + rituximab. Estimatet indplacerer acalabrutinib + obinutuzumab i kategorien "stor merværdi" for PFS. Efter 36 måneders opfølgning ses en forskel i PFS-rate på 28,9 %-point (89,9 % vs. 61 % i ALLIANCE). Den mindste klinisk relevante forskel var fastsat til 10 %-point. Datagrundlaget ved 36 måneder er yderst spinkelt, men underbygges af 48 måneders data fra et senere *data cut*.

Data for OS var endnu umodent (HR = 0,55 (95 % CI: 0,20-1,50)), hvilket var forventeligt baseret på opfølgningstiden i studierne (28,1-31,3 måneder). Fagudvalget finder det sandsynligt, at PFS-gevinsten ved acalabrutinib vil afspejles i en klinisk relevant øget OS ved længere opfølgningstid.

Fagudvalget vælger at justere den samlede merværdi til lille, da acalabrutinib + obinutuzumab ikke vurderes at tolereres bedre end bendamustin + rituximab. Fagudvalget bemærker, at acalabrutinib + obinutuzumab, i modsætning til bendamustin + rituximab, gives kontinuerligt, hvilket potentielt kan medføre flere bivirkninger over tid.





## 5.4 Klinisk spørgsmål 3

*Hvilken værdi har acalabrutinib som monoterapi sammenlignet med dansk standardbehandling hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion (17p)/p53-mutation?*

### 5.4.1 Litteratur

I det følgende beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

#### Acalabrutinib monoterapi vs. ibrutinib

##### Direkte analyser

Vurderingen af bivirkninger baseres på data fra ELEVATE-RR, som inkluderer en direkte sammenligning af acalabrutinib monoterapi over for ibrutinib til 2. linjebehandling af CLL.

**ELEVATE-RR** er et internationalt, multicenter, open-label, randomiseret fase 3-studie, som inkluderer tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL. Patienterne skulle have del(17p) og/eller del(11q) for at indgå i studiet. Patienterne blev randomiseret 1:1 til acalabrutinib monoterapi (n=268) eller ibrutinib (n=265). Acalabrutinib 100 mg p.o. blev administreret to gange dagligt indtil sygdomsprogression eller uacceptabel toksicitet. Ibrutinib 420 mg p.o. blev administreret én gang dagligt, ligeledes til sygdomsprogression eller uacceptabel toksicitet. Det primære endepunkt var PFS. Median opfølgningstid var 40,9 måneder [45].

##### Indirekte analyser

Der findes ikke et direkte sammenlignende studie af acalabrutinib monoterapi vs. ibrutinib i 1. linje. Vurderingen af OS og PFS i klinisk spørgsmål 3 vil derfor blive baseret på MAIC og NMA-analyserne, som blev beskrevet i afsnit 5.2.1 og 5.2.2, samt på en narrativ sammenligning. I den narrative sammenligning stammer data for acalabrutinib monoterapi fra ELEVATE-TN, som også er beskrevet i afsnit 5.2.1. Data for ibrutinib stammer fra de to studier Ahn 2018 og RESONATE-2. Disse studier er kort præsenteret i Tabel 22 og yderligere beskrevet i Bilag 1. Udvalgte baselinekarakteristika for populationerne kan ses i Bilag 2.

**Tabel 22. Oversigt over studier for klinisk spørgsmål 3 + 4, der indgår i den narrative sammenligning af OS og PFS (acalabrutinib +/- obinutuzumab vs. ibrutinib)**

Klinisk forsøg	Lægemidler	Population
ELEVATE-TN NCT02475681	Acalabrutinib + obinutuzumab vs. acalabrutinib vs. obinutuzumab + chlorambucil	Tidligere ubehandlede CLL-patienter > 65 år eller mellem 18 og 65 år og med komorbiditet (kreatinin- clearance på 30-69 ml/min. eller CIRS-G > 6)
RESONATE-2 NCT01722487	Ibrutinib vs. chlorambucil	Tidligere ubehandlede patienter ≥ 65 år med CLL eller småcellet lymfocytært lymfom



Klinisk forsøg	Lægemidler	Population
Ahn 2018 NCT01500733	Ibrutinib vs. chlorambucil	Tidligere ubehandlede voksne patienter med CLL, der enten havde deletion 17p/p53-mutation eller var 65 år eller ældre

#### 5.4.2 Databehandling og analyse

##### Direkte analyse (ELEVATE-RR)

ELEVATE-RR inkluderer en direkte sammenligning af acalabrutinib monoterapi vs. ibrutinib og anvendes til at belyse bivirkninger ved de to behandlinger.

##### Fagudvalgets kommentarer til datagrundlaget for den direkte analyse og analysens anvendelighed

Dosering og behandlingstid med ibrutinib er i overensstemmelse med dansk klinisk praksis. Patienterne inkluderet i ELEVATE-RR er patienter med relaps eller refraktær sygdom, hvilket afviger fra populationen i klinisk spørgsmål 3, som omhandler patienter i 1. linje. Patienterne i ELEVATE-RR har desuden alle del(17p) og/eller del(11q), da dette var et inklusionskriterie. Fagudvalget vurderer, at patienterne i ELEVATE-RR afviger fra den danske population med del(17p)/p53-mutation på følgende punkter:

- Andelen med del(17p) var 45,1 % og 45,3 % i de to studiearme, mens p53-mutation forekom hos 37,3 % og 42,3 %. Andelen med én eller begge mutationer er større i den danske population, hvor alle patienter har enten del(17p) eller p53-mutation.
- Flere patienter i studiet var IGHV-umuterede (82,1 % og 89,4 %), end hvad der forventes i klinikken.
- Patienterne i studiet har tidligere modtaget behandling, hvilket patienterne i den danske førstelinjepopulation ikke har. En stor andel i studiet har modtaget purin-analoger (64,2 % og 59,6 %), som er kendt for at give længerevarende knoglemarvspåvirkning, hvilket kan prædisponere for hæmatologiske bivirkninger, også ved efterfølgende behandling. Forekomsten af hæmatologiske bivirkninger såsom penier er derfor formodentlig overrepræsenteret i studiet.
- Patienterne i studiet er yngre.

Fagudvalget forventer, at bivirkninger ved acalabrutinib monoterapi, som blev observeret i studiet, kan genfindes ved behandling af danske patienter med del(17p)/p53-mutation. Der tages forbehold for, at forskelle i patientkarakteristika mellem patienterne i studiet og i den danske patientpopulation kan have indflydelse på hændelsesfrekvenserne. Specielt har det betydning, at mange patienter i studiet tidligere er behandlet med purin-analoger, og at der derfor muligvis ses flere hæmatologiske bivirkninger, end hvad der forventes i dansk klinisk praksis i 1. linje.



#### **Indirekte analyser (MAIC og NMA)**

Vurderingen af OS og PFS er baseret på MAIC og NMA-analyser, som blev beskrevet i afsnit 5.2.1 og 5.2.2, samt en narrativ sammenligning. Ansøger har ikke leveret data, som belyser helbredsrelateret livskvalitet.

#### **Fagudvalgets kommentarer til datagrundlaget for de indirekte analyser samt analysernes anvendelighed**

Både MAIC og NMA er baseret på ITT-populationerne, som inkluderer patienter både med og uden del(17p) og p53-mutation. Fagudvalget vurderer, at data kan anvendes til at belyse OS og PFS i populationen med del(17p)/p53-mutation, dog med det forbehold, at OS og PFS formentlig er overestimeret, idet ITT-populationen forventeligt har en bedre prognose end populationen med del17p/p53. Det forventes dog, at overestimeringen sker i samme grad for acalabrutinib monoterapi og ibrutinib, hvorfor det tillægges mindre betydning.

#### **5.4.3 Effektestimater og kategorier**

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 3.



**Tabel 23. Resultater for klinisk spørgsmål 3: acalabrutinib monoterapi vs. ibrutinib**

Effekt mål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid (MKRF: 5 %-point)	Kritisk	-	Kan ikke kategoriseres	MAIC ITT-population: HR = 0,73 (95 % CI: 0,27-2,02)	Kan ikke kategoriseres	Kan ikke kategoriseres
Progressionsfri overlevelse (PFS)	Forskel i andel af patienter, der opnår PFS efter 3 år eller længst mulig opfølgningstid (MKRF: 10 %-point)	Vigtig	-	Kan ikke kategoriseres	MAIC ITT-population: HR = 0,94 (95 % CI: 0,44-1,95)	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel af patienter, der oplever én eller flere uønskede hændelser af grad 3-4 (MKRF: 10 %-point) (+ kvalitativ gennemgang)	Vigtig	-6,1 %-point	Kan ikke kategoriseres	ELEVATE-RR: RR: 0,92 (95 % CI: 0,83-1,02)	Ingen dokumenteret merværdi	Kan ikke kategoriseres
Livskvalitet	EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	-	-	-	-	-
<b>Konklusion</b>							
<b>Samlet kategori for lægemidlets værdi</b>		Kan ikke kategoriseres					

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.



## Acalabrutinib monoterapi vs. ibrutinib

### Overlevelse (OS)

Der findes ingen direkte sammenlignende studier af acalabrutinib monoterapi og ibrutinib i 1. linje, og der findes heller ikke komparative data for populationen med del(17p)/p53-mutation. Fagudvalget vurderer, at data for ITT-populationerne kan anvendes til at belyse effekten i subgruppen med del17p/p53, dog med det forbehold, at OS og PFS formentlig er overestimeret, idet ITT-populationen forventeligt har en bedre prognose end populationen med del(17p)/p53. Det forventes, at overestimeringen forekommer i samme grad for acalabrutinib monoterapi og ibrutinib, hvorfor det tillægges mindre betydning.

### MAIC

Ansøgers MAIC-analyse, som er baseret på ITT-populationerne, viser en hazard ratio på 0,73 (95 % CI: 0,27-2,02), hvilket ikke indikerer forskel mellem behandlingerne. Ansøgers NMA (baseret på ITT-populationer) er i overensstemmelse hermed (HR = 0,44 (95 % CI: 0,16-1,27). OS-data var umodent for størstedelen af studierne (herunder ELEVATE-TN) inkluderet i ansøgers analyser.

### Naiv gennemgang af data fra relevante studier

Ved en median opfølgningstid på 28,3 måneder i ELEVATE-TN var der registreret 11 (6,1 %) dødsfald i acalabrutinib monoterapi-armen. Den beregnede OS for ITT-populationen ved 24 måneder baseret på Kaplan-Meier-kurverne var 95 % (95 % CI: 90-97) for acalabrutinib monoterapi-armen. Ligeledes var OS ved 36 måneder 93,5 % (95 % CI: 88,6-96,3). Ved et efterfølgende *data cut* med en median opfølgningstid på 46,9 måneder var den beregnede 48 måneders OS på 88 %.

Efter 2 års median opfølgningstid var den estimerede 2-års overlevelse i en population af tidligere behandlede patienter med p53-mutation behandlet med ibrutinib på 84 % i Ahn 2018-studiet. Efter en median opfølgning på 4,8 år var den estimerede 5-års overlevelse 85,3 % (95 % CI: 74,2-98,1). Til sammenligning havde ITT-populationen behandlet med ibrutinib i RESONATE-2 en overlevelse på 98 % efter 2 år, mens den efter 5 år var 83 % (median opfølgningstid 60 måneder). Se data i Tabel .

**Tabel 24. OS-rater fra ELEVATE-TN, Ahn 2018 og RESONATE-2**

Effekt mål	Opfølgning	Acalabrutinib ITT-population n=179 (ELEVATE-TN)	Ibrutinib p53-mutation n=51 (Ahn 2018)	Ibrutinib ITT-population n=136 (RESONATE-2)
Overlevelse	2 år	95 %	84 %	98 %
	3 år	93,5 % (fra KM-kurven)	-	-
	48 måneder	88 % (estimeret)	-	-
	5 år	-	85,3 %	83 %*

\*Dette tal er 84 % for patienter behandlet med ibrutinib med prognostisk højrisiko CLL (p53-mutation, del(11q) og/eller umuteret IGHV), uden censorering for overkrydsning til ibrutinib.



Baseret på overlevelsesraterne er det ikke muligt at bestemme værdien af acalabrutinib på den absolutte skala, da data ikke tillader en direkte sammenligning.

Baseret på den relative effektforskel (MAIC HR = 0,73 (95 % CI: 0,27-2,02)) kan merværdien af acalabrutinib monoterapi foreløbigt ikke kategoriseres vedr. OS, da konfidensintervallet er for bredt.

Fagudvalget vurderer samlet set, at merværdien af acalabrutinib monoterapi ikke kan kategoriseres vedr. OS, idet OS-data er umodent. Dette er forventeligt baseret på studierne opfølgningstid (28,1-31,3 måneder), som er for kort til indsamling af et tilstrækkeligt antal events. Det vurderes – baseret på det nuværende datagrundlag – at de to behandlinger er lige gode, hvad angår overlevelse.

### Progressionsfri overlevelse (PFS)

#### MAIC

Ansøgers MAIC-analyse for ITT-populationen viser ingen signifikant forskel på de to behandlinger (HR = 0,94 (95 % CI: 0,44-1,95)). NMA'en, som også er baseret på ITT-populationerne, viser, at acalabrutinib monoterapi er signifikant bedre, hvad angår PFS sammenlignet med ibrutinib monoterapi (HR = 0,35 (95 % CI: 0,18-0,66)). Imidlertid er der ikke justeret for forskelle i patientpopulationerne i de studier, der indgår i analysen, hvorfor data skal tolkes med forsigtighed og tillægges mindre vægt i vurderingen.

#### Naiv gennemgang af data fra relevante studier

I ELEVATE-TN var 2-års PFS-raten for acalabrutinib monoterapi i subgruppen med p53-mutation 71 % og 2-års PFS-raten i subgruppen med del(17p) 74 %. Disse estimater er baseret på en aflæsning af Kaplan-Meier-kurverne.

I Ahn 2018-studiet var 2-års PFS-raten 85 % i den behandlingsnaive population med p53-mutation (aflæst på KM-kurven). 5-års PFS-raten var 74,4 %. I RESONATE-2 var 5 års PFS-raten på 56 % i p53-populationen, mens den i den samlede population var 70 %. Se data i Tabel . Fagudvalget bemærker, at der ikke kan konkluderes noget om PFS på baggrund af raterne fra de enkelte studier, da disse er svære at tolke, hvilket formentlig skyldes forskelle i patientpopulationerne i studierne samt et lille datagrundlag (n).

**Tabel 25. PFS-rater fra subpopulationer i ELEVATE, Ahn 2018 og RESONATE-2**

Effekt mål	Opfølgning	Acalabrutinib (ELEVATE-TN)		Ibrutinib (Ahn 2018)	Ibrutinib (RESONATE-2)	
		p53 (n=19)	del17p (n=16)	p53 (n=34)	p53 (n=12)	All (n=136)
Progressionsfri overlevelse	2 år	71 % (fra KM-kurven)	74 % (fra KM-kurven)	85 %	-	-
	5 år	-	-	74,4 %	56 %	70 %

KM = Kaplan-Meier.



Fagudvalget har noteret sig, at et dansk multicenter retrospektivt studie har undersøgt effekt og bivirkninger hos 205 patienter med CLL eller småcellet lymfocytært lymfom (SLL), som blev behandlet med ibrutinib uden for kliniske forsøg [46]. Medianalderen for patienter i studiet var 73 år, og 54,4 % havde muteret p53 eller deletion 17p (19 % var behandlingsnaive). Ved en median opfølgningstid på 21,4 måneder var den estimerede 12 måneders PFS-rate 86,3 % (95 % CI: 81,3-91,2). Der var ingen signifikant forskel i PFS mellem behandlingsnaive patienter (1. linje) og patienter med relaps/refraktær sygdom (2. linje). Der sås heller ingen signifikant forskel i PFS mellem patienter hhv. med og uden del(17p)/p53-mutation.

Fagudvalget har noteret sig, at et dansk multicenter retrospektivt studie har undersøgt effekt og bivirkninger hos 205 patienter med CLL eller småcellet lymfocytært lymfom (SLL), som blev behandlet med ibrutinib uden for kliniske forsøg [46]. Medianalderen for patienter i studiet var 73 år, og 54,4 % havde muteret p53 eller deletion 17p (19 % var behandlingsnaive). Ved en median opfølgningstid på 21,4 måneder var den estimerede 12 måneders PFS-rate 86,3 % (95 % CI: 81,3-91,2 %). Der var ingen signifikant forskel i PFS mellem behandlingsnaive patienter (1. linje) og patienter med relaps/refraktær sygdom (2. linje). Der sås heller ingen signifikant forskel i PFS mellem patienter hhv. med og uden del(17p)/p53-mutation. Da data imidlertid ikke er opgjort ved enten 2 eller 5 års opfølgning, er det ikke muligt at sammenligne direkte med studiedata i Tabel 24.

Baseret på den relative effektforskel (HR = 0,94 (95 % CI: 0,44-1,95)) kan den foreløbige værdi af acalabrutinib monoterapi ikke kategoriseres vedr. PFS, da konfidensintervallet er for bredt. Baseret på overlevelsesraterne er det ikke muligt at bestemme den foreløbige værdi af acalabrutinib monoterapi på den absolutte skala, da data ikke tillader en direkte sammenligning.

Fagudvalget vurderer, at værdien af acalabrutinib monoterapi samlet set ikke kan kategoriseres vedr. PFS jf. Medicinrådets metoder. Hazard ratioen fra MAIC-analysen indikerer, at de to behandlinger er omtrent ligeværdige, hvad angår PFS. I MAIC-analysen er der taget højde for forskelle i patientkarakteristika i studierne, hvorfor denne analyse tillægges størst betydning i vurderingen.

### Bivirkninger

Baseret på data fra ELEVATE-RR er det muligt at foretage en komparativ analyse af andelen, som oplevede en grad  $\geq 3$  uønsket hændelse hos patienter behandlet med hhv. acalabrutinib monoterapi og ibrutinib. Derudover gennemgås data fra ELEVATE-RR og ELEVATE-TN (acalabrutinib-armen) narrativt. Data fra ELEVATE-TN anvendes primært som supplement, da ELEVATE-TN ikke inkluderer en direkte sammenligning med ibrutinib, og da patienterne i mindre grad ligner patienterne i klinisk spørgsmål 3 (forskelle i prognostika).

Uønskede hændelser rapporteret i ELEVATE-RR og ELEVATE-TN fremgår af Tabel 26.



**Tabel 26. Uønskede hændelser rapporteret i ELEVATE-RR og ELEVATE-TN for acalabrutinib monoterapi og ibrutinib**

Event	ELEVATE-TN	ELEVATE-RR*	
	Acalabrutinib monoterapi n=179, n (%) Opfølgningstid: 28,3 mdr.	Acalabrutinib monoterapi n=266, n (%) Opfølgningstid: 38,3 mdr.	Ibrutinib n=263, n (%) Opfølgningstid: 35,5 mdr.
Uønskede hændelser, enhver grad	170 (95,0 %)	260 (97,7 %)	256 (97,3 %)
Grad ≥ 3	89 (49,7 %)	183 (68,8 %)	197 (74,9 %)
Alvorlige uønskede hændelser (SAE)	57 (31,8 %)	143 (53,8 %)	154 (58,6 %)
Behandlingsophør grundet uønskede hændelser	16 (8,9 %)	39 (14,7 %)	56 (21,3 %)
<b>Grad ≥ 3 uønskede hændelser</b>			
Neutropeni	17 (9,5 %)	21 (19,5 %)	60 (22,8 %)
Trombocytopeni	5 (2,8 %)	26 (9,8 %)	18 (6,8 %)
Anæmi	12 (6,7 %)	31 (11,7 %)	34 (12,9 %)
Perifært ødem	1 (0,6 %)	0	1 (0,4 %)
Øvre luftvejsinfektion	0	5 (1,9 %)	1 (0,4 %)
Urinvejsinfektion	3 (1,7 %)	3 (1,1 %)	6 (2,3 %)
Pneumoni	4 (2,2 %)	28 (10,5 %)	23 (8,7 %)
Opkastning	1 (0,6 %)	1 (0,4 %)	3 (1,1 %)
Forstoppelse	0	0	2 (0,8 %)
Træthed	2 (1,1 %)	<b>9 (3,4 %)</b>	0
Feber	1 (0,6 %)	8 (3,0 %)	2 (0,8 %)
Diarré	1 (0,6 %)	3 (1,1 %)	<b>13 (4,9 %)</b>
Arthralgi	1 (0,6 %)	0	2 (0,8 %)
Rygsmerte	2 (1,1 %)	0	2 (0,8 %)
Hovedpine	2 (1,1 %)	<b>4 (1,5 %)</b>	0
Hoste	1 (0,6 %)	2 (0,8 %)	1 (0,4 %)
Dyspnø	3 (1,7 %)	6 (2,3 %)	1 (0,4 %)
Udslæt	1 (0,6 %)	2 (0,8 %)	0
Hypertension	4 (2,0 %)	11 (4,1 %)	<b>23 (8,7 %)</b>
Atrieflimren	7 (4,0 %)	12 (4,5 %)	9 (3,4 %)
Kvalme	0	0	1 (0,4 %)





Event	ELEVATE-TN	ELEVATE-RR*	
	Acalabrutinib monoterapi n=179, n (%) Opfølgningstid: 28,3 mdr.	Acalabrutinib monoterapi n=266, n (%) Opfølgningstid: 38,3 mdr.	Ibrutinib n=263, n (%) Opfølgningstid: 35,5 mdr.
Bronkitis	0	3 (1,1 %)	2 (0,8 %)
Kontusion (blå mærker)	0	0	1 (0,4 %)
Myalgi	NR	2 (0,8 %)	1 (0,4 %)
Næseblødning	NR	1 (0,4 %)	1 (0,4 %)
Muskelspasmer	NR	0	2 (0,8 %)

NR: not reported; **Fed**: Markerer, at eventet har statistisk højere incidens end intervention/komparator i ELEVATE-RR. Se også tabel 27. \*Tilgængelige data for hændelsesfrekvenser efter en median opfølgningstid på 46,9 måneder afviger ikke i betydende grad fra tal i tabellen.

Fagudvalget bemærker, at acalabrutinib monoterapi er associeret med færre grad  $\geq 3$  hændelser (68,8 % vs. 74,9 %, forskel -6,1 %-point) end ibrutinib, men at forskellen ikke er statistisk signifikant (RR: 0,92 (95 % CI: 0,83-1,02)). Ansøger har ikke angivet et konfidensinterval for den absolutte effektforskel på -6,1 %-point, og punkttestimatet for forskellen er mindre end den mindste klinisk relevante forskel på 10 %-point.

Der ses færre alvorlige uønskede hændelser (SAE) (48,6 % vs. 53,8 %) og færre behandlingsophør grundet uønskede hændelser (14,7 % vs. 21,3 %) ved acalabrutinib monoterapi sammenlignet med ibrutinib. Det bemærkes, at frekvenserne for acalabrutinib monoterapi i ELEVATE-TN er lavere end de tilsvarende frekvenser for acalabrutinib monoterapi i ELEVATE-RR. Det kan formentlig forklares af den kortere opfølgningstid i ELEVATE-TN.

Hændelser, som forekommer med statistisk signifikant forskellig incidens i ELEVATE-RR, er angivet i Tabel 27, hvor fed skrift indikerer en højere incidens.

**Tabel 27. Uønskede hændelser, som forekommer med statistisk signifikant højere incidens i ELEVATE-RR (markeret med fed)**

Event	ELEVATE-RR			
	Acalabrutinib monoterapi n=266, n (%) Enhver grad	Grad $\geq 3$	Ibrutinib n=263, n (%) Enhver grad	Grad $\geq 3$
Urinvejsinfektion	22 (8,3 %)	3 (1,1 %)	<b>36 (13,7 %)</b>	6 (2,3 %)
Træthed	54 (20,3 %)	<b>9 (3,4 %)</b>	44 (16,7 %)	0
Diarré	92 (34,6 %)	3 (1,1 %)	<b>121 (46,0 %)</b>	<b>13 (4,9 %)</b>
Arthralgi	42 (15,8 %)	0	<b>60 (22,8 %)</b>	2 (0,8 %)



Event	ELEVATE-RR			
	Acalabrutinib monoterapi n=266, n (%) Enhver grad	Grad ≥ 3	Ibrutinib n=263, n (%) Enhver grad	Grad ≥ 3
Rygsmærter	20 (7,5 %)	0	<b>34 (12,9 %)</b>	2 (0,8 %)
Hovedpine	<b>92 (34,6 %)</b>	<b>4 (1,5 %)</b>	53 (20,2 %)	0
Hoste	<b>77 (28,9 %)</b>	2 (0,8 %)	56 (21,3 %)	1 (0,4 %)
Hypertension	23 (8,6 %)	11 (4,1 %)	<b>60 (22,8 %)</b>	<b>23 (8,7 %)</b>
Atrieflimren	24 (9,0 %)	12 (4,5 %)	<b>41 (15,6 %)</b>	9 (3,4 %)
Kontusion (blå mærker)	31 (11,7 %)	0	<b>48 (18,3 %)</b>	1 (0,4)
Muskelspasmer	16 (6,0 %)	0	<b>35 (13,3 %)</b>	2 (0,8 %)
Dyspepsi	10 (3,8 %)	0	<b>32 (12,2 %)</b>	0

Statistisk signifikant højere incidenser er markeret med **fed**.

Fagudvalget bemærker, at acalabrutinib monoterapi er forbundet med større forekomst af træthed, hovedpine og hoste sammenlignet med ibrutinib. Disse bivirkninger vurderes mindre klinisk relevante. Det er fagudvalgets erfaring, at hovedpine i forbindelse med behandling med acalabrutinib monoterapi primært ses i begyndelsen af behandlingen og er forbigående og forholdsvis kortvarigt.

Ibrutinib er associeret med flest gastrointestinale bivirkninger (diarré og dyspepsi) samt kardiovaskulære bivirkninger (hypertension og atrieflimren). Fagudvalget fremhæver de kardiovaskulære bivirkninger som problematiske, set i lyset af at populationen med CLL i forvejen har en forholdsvis høj forekomst af kardiovaskulær komorbiditet pga. en høj medianalder og en større andel af mænd i populationen. Hypertension kan være asymptomatisk og dermed vanskeligt at opdage og få håndteret tilstrækkeligt i klinikken og kan således over tid føre til flere kardiovaskulære problematikker. Atrieflimren er også en betydende bivirkning, idet der ses øget risiko for gentagne hændelser. Ibrutinib er desuden associeret med muskuloskeletale smerter (artragi, rygsmerter og muskelsmerter), som kan have indvirkning på patientens livskvalitet.

Efter markedsføring af ibrutinib har flere studier undersøgt effekt og bivirkninger ved ibrutinib i klinisk praksis, og disse peger på, at tolerabilitet er en relevant problematik. Der ses væsentlig højere rater for behandlingsophør af ibrutinib grundet uønskede hændelser i klinisk praksis sammenlignet med, hvad der er rapporteret i de kliniske studier. I RESONATE-2 var 21 % af patienterne ophørt med behandlingen grundet uønskede hændelser efter 5 års opfølgning, og i RESONATE var andelen 7 % efter 26 måneders opfølgning [23][28]. Et dansk retrospektivt multicenter studie har vist, at 54,7 % af patienterne behandlet med ibrutinib (i 1. og 2. linje) ophører behandlingen grundet uønskede hændelser [46], hvilket indikerer, at behandlingsophør oftere skyldes



lægemiddeltoksicitet end progression. En mulig forklaring er, at patienterne i klinisk praksis er ældre og har mere komorbiditet end patienterne i de kliniske forsøg. Efter markedsføring af ibrutinib har flere studier undersøgt effekt og bivirkninger ved ibrutinib i klinisk praksis, hvilke peger på, at tolerabilitet er en relevant problematik. Der ses væsentlig højere rater for behandlingsophør af ibrutinib grundet uønskede hændelser i klinisk praksis sammenlignet med, hvad der er rapporteret i de kliniske studier. I RESONATE-2 var 21 % af patienterne ophørt med behandlingen grundet uønskede hændelser efter 5 års opfølgning og i RESONATE var andelen 7 % efter 26 måneders opfølgning [23][28]. Et dansk retrospektivt multicenter studie har vist at 54,7 % af patienterne behandlet med ibrutinib (i 1. og 2. linje) ophører behandlingen grundet uønskede hændelser [46], hvilket indikerer, at behandlingsophør oftere skyldes lægemiddeltoksicitet end progression. En mulig forklaring er, at patienterne i klinisk praksis er ældre og har mere komorbiditet end patienterne i de kliniske forsøg. Det er endnu uvist, om behandling med acalabrutinib vil medføre samme høje rate for behandlingsophør som følge af uønskede hændelser som set ved brug af ibrutinib i klinisk praksis. Ibrutinib og acalabrutinib har samme virkningsmekanisme, idet begge hæmmer Brutons tyrosinkinase (BTK), men acalabrutinib er mere selektiv og dermed muligvis bedre tolereret.

Studier har vist, at patienter, som ikke tåler ibrutinib, kan have gavn af behandling med acalabrutinib, da toksicitetsprofilerne er forskellige. Et studie undersøgte effekt og bivirkninger ved acalabrutinib i en population af patienter, som var intolerante over for ibrutinib [47]. Ud af 61 bivirkninger til ibrutinib, som førte til behandlingsophør, gentog kun 28 % sig ved brug af acalabrutinib, mens 13 % gentog sig i mindre svær grad (median opfølgningstid 19 måneder). 3 ud af 33 patienter i studiet ophørte behandling med acalabrutinib som følge af behandlingsrelateret uønsket hændelse. Validiteten af disse fund er efterfølgende blevet bekræftet i et andet studie [48].

Baseret på den relative risiko for at opleve en grad  $\geq 3$  uønsket hændelse (RR: 0,92 (95 % CI: 0,83-1,02)) er der ingen merværdi af behandling med acalabrutinib monoterapi. Baseret på punkttestimatet for den absolutte effektforskel -6,1 %-point kan værdien ikke kategoriseres, da der ikke foreligger et konfidensinterval.

Fagudvalget vurderer samlet set, at værdien af acalabrutinib monoterapi ikke kan kategoriseres vedr. bivirkninger, da datamaterialet ikke tillader dette jf. Medicinrådets metoder.

Der ses færre grad  $\geq 3$  hændelser (68,8 % vs. 74,9 %, ikke statistisk signifikant forskel), færre alvorlige uønskede hændelser (SAE) (53,8 % vs. 48,6 %) samt færre behandlingsophør grundet uønskede hændelser (14,7 % vs. 21,3). Ligeledes ses der signifikant flere kardiovaskulære bivirkninger ved ibrutinib. Ved anvendelse af ibrutinib i klinikken ses højt behandlingsophør grundet uønskede hændelser. Behandlingsophør ved brug af acalabrutinib vil muligvis være mere begrænset, da acalabrutinib er en mere selektiv BTK-hæmmer og dermed muligvis bedre tolereret.

#### Helbredsrelateret livskvalitet

Ansøger har ikke leveret komparative data for effektmålet.



#### 5.4.4 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af acalabrutinib monoterapi sammenlignet med ibrutinib til patienter med CLL og del(17p)/p53-mutation ikke kan kategoriseres.

Der ses færre grad  $\geq 3$  hændelser (68,8 % vs. 74,9 %) færre alvorlige uønskede hændelser (SAE) (53,8 % vs. 58,6 %) og færre behandlingsophør grundet uønskede hændelser (14,7 % vs. 21,3 %), og der ses signifikant flere kardiovaskulære bivirkninger ved ibrutinib. Samlet ses vurderer fagudvalget, at acalabrutinib og ibrutinib er sammenlignelige hvad angår bivirkninger.

OS-data er umodent, hvilket afspejles i det brede konfidensinterval for ansøgers MAIC (HR = 0,73 (95 % CI: 0,27-2,02)), og indikerer på nuværende tidspunkt ikke forskel mellem behandlingerne. Dette er forventeligt baseret på studierne begrænsede opfølgningstid (28,1-31,3 måneder. PFS-data viser også, at de to behandlinger er omtrent ligeværdige (MAIC HR = 0,94 (95 % CI: 0,44-1,95)).

### 5.5 Klinisk spørgsmål 4

*Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med dansk standardbehandling hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion 17p/p53-mutation?*

#### 5.5.1 Litteratur

I det følgende beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

#### **Acalabrutinib + obinutuzumab vs. ibrutinib**

##### Indirekte analyser

Der findes ikke et direkte sammenlignende studie af acalabrutinib + obinutuzumab og ibrutinib. Medicinrådets vurdering af OS og PFS er derfor baseret på MAIC og NMA-analyserne, som blev beskrevet i afsnit 5.2.1 og 5.2.2, samt på en narrativ sammenligning. Den narrative sammenligning anvender data fra de samme studier som den narrative sammenligning i klinisk spørgsmål 3. Dvs. at data for acalabrutinib + obinutuzumab stammer fra studiet ELEVATE-TN, og data for ibrutinib stammer fra de tre studier ELEVATE-RR, Ahn 2018 og RESONATE-2. Oversigten over studierne kan findes i afsnit 5.4.1. Alle studierne er beskrevet yderligere i Bilag 1. Udvalgte baselinekarakteristika for populationerne i disse studier kan ses i Tabel 8 i Bilag 2.

Bivirkninger vurderes ved en narrativ gennemgang af data fra ELEVATE-TN og ELEVATE-RR.



## 5.5.2 Databehandling og analyse

### Indirekte analyser (MAIC og NMA)

Vurderingen af OS og PFS er baseret på MAIC og NMA-analyser, som blev beskrevet i afsnit 5.2.1 og 5.2.2, samt på en narrativ sammenligning. Ansøger har ikke leveret data, som belyser helbredsrelateret livskvalitet.

### Fagudvalgets kommentarer til datagrundlaget for de indirekte analyser og analysernes anvendelighed

Både MAIC og NMA er baseret på ITT-populationerne, som inkluderer patienter både med og uden del(17p) og p53-mutation. Fagudvalget vurderer, at data kan anvendes til at belyse OS og PFS i populationen med del(17p)/p53-mutation, dog med det forbehold, at OS og PFS formentlig er overestimeret, idet ITT-populationen forventeligt har en bedre prognose end populationen med del17p/p53. Det forventes, at overestimeringen er af samme grad for acalabrutinib + obinutuzumab og ibrutinib, hvorfor det tillægges mindre betydning

### Narrativ gennemgang af bivirkninger

Ansøger har ikke fundet det muligt at foretage en indirekte komparativ analyse af andelen af patienter, som oplevede en grad  $\geq 3$  uønsket hændelse baseret på ELEVATE-TN og ELEVATE-RR. Ansøger begrundet det med følgende:

- Der er forskelle i patientpopulationerne i ELEVATE-TN og ELEVATE-RR, idet patienterne i ELEVATE-TN er ældre, og patienterne i ELEVATE-RR har mere *bulky disease*  $\geq 5$  cm og flere cytogenetiske abnormaliteter (del(17p), del(11q), kompleks karyotype, p53-mutation samt umuteret IGHV). Samtidig viser subgruppeanalyser baseret på ELEVATE-RR, at disse faktorer påvirker risikoen for at få grad  $\geq 3$  uønskede hændelser.
- Behandlingsvarigheden er forskellig i ELEVATE-TN og ELEVATE-RR (median behandlingsvarighed for acalabrutinib monoterapi i ELEVATE-RR er 38,3 måneder, mens den i ELEVATE-TN er 27,7 måneder i første *data cut* og 45,7 måneder i et efterfølgende *data cut*).

Ansøgers konklusion er, at der er forskellig risiko for at opleve en uønsket hændelse i ELEVATE-TN og ELEVATE-RR, og at risikoen er associeret til patientkarakteristika. Behandlingsvarigheden kan også have betydning for forekomsten af uønskede hændelser. En indirekte analyse bør derfor justere for forskelle i patientkarakteristika og behandlingsvarighed. Imidlertid er datamaterialet for spinkelt til at udføre en indirekte komparativ analyse, idet populationen med del(17p)/p53-mutation i ELEVATE-TN, som blev behandlet med acalabrutinib + obinutuzumab, er for begrænset (n=25).

### Fagudvalgets betragtninger

Fagudvalget tager ansøgers betragtninger til efterretning, men finder det dog besynderligt, at ansøgers subgruppeanalyser viser, at fx forekomsten af del(17p) har betydning for bivirkningsforekomsten.

Effekt målet belyses derfor ved en narrativ gennemgang af bivirkningsdata fra ibrutinib-armen i ELEVATE-RR og acalabrutinib + obinutuzumab-armen i ELEVATE-TN.



Fagudvalget forventer, at bivirkninger associeret med ibrutinib, som blev observeret i ELEVATE-RR, kan genfindes ved behandling af danske patienter i 1. linje med del(17p)/p53-mutation. Der tages forbehold for, at forskelle i patientkarakteristika mellem patienterne i studiet og i den danske patientpopulation kan have indflydelse på hændelsesfrekvenserne. Specielt har det betydning, at mange patienter i studiet tidligere er behandlet med purin-analoger, og at der derfor muligvis ses flere hæmatologiske bivirkninger, end hvad der forventes i dansk klinisk praksis i 1. linje. Se også afsnit 5.4.2. Ligeledes forventes det også, at bivirkninger associeret med acalabrutinib + obinutuzumab, som blev observeret i ELEVATE-TN, kan genfindes ved behandling af danske patienter i 1. linje med del(17p)/p53-mutation, da patienterne i ELEVATE-TN ligner de danske patienter (fraset forskellen i forekomst af del(17p) og p53-mutation).

### **5.5.3 Effektestimater og kategorier**

I Tabel 28 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 4.



**Table 28. Resultater for klinisk spørgsmål 4: acalabrutinib + obinutuzumab vs. ibrutinib**

Effekt mål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid (MKRF: 5 %-point)	Kritisk	-	Kan ikke kategoriseres	ITT-population: HR = 0,88 (95 % CI: 0,31-2,22) (MAIC)	Kan ikke kategoriseres	Kan ikke kategoriseres
Progressionsfri overlevelse (PFS)	Forskel i andel patienter, der opnår PFS efter 3 år eller længst mulig opfølgningstid (MKRF: 10 %-point)	Vigtig	-	Kan ikke kategoriseres	ITT-population: HR = 0,61 (95 % CI: 0,24-1,55)	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der oplever én eller flere uønskede hændelser af grad 3-4 (MKRF: 10 %-point) (+ kvalitativ gennemgang)	Vigtig	-	Kan ikke kategoriseres	-	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	-	-	-	-	-

### Konklusion

**Samlet kategori for lægemidlets værdi** Kan ikke kategoriseres

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.



### Overlevelse (OS)

Der findes ingen direkte sammenlignende studier af acalabrutinib + obinutuzumab og ibrutinib og ingen komparative data for populationen med del17p/p53-mutation.

#### MAIC

Ansøgers MAIC-analyse, som er baseret på ITT-populationerne, viser en hazard ratio på 0,88 (95 % CI: 0,31-2,52), hvilket indikerer ingen forskel mellem behandlingerne. Ansøgers NMA (baseret på ITT-populationer) indikerer, at acalabrutinib + obinutuzumab er et bedre handlingsalternativ end ibrutinib, men forskellen er ikke statistisk signifikant (HR = 0,35 (95 % CI: 0,12-1,04)). OS-data var umodent for størstedelen af studierne (herunder ELEVATE-TN) inkluderet i ansøgers analyser.

#### Narrativ gennemgang af data fra relevante studier

Ved en median opfølgningstid på 28,3 måneder i ELEVATE-TN var den beregnede overlevelsesrate ved 24 måneder 95 % (95 % CI: 91-97) for ITT-populationen behandlet med acalabrutinib + obinutuzumab. Ved et efterfølgende *data cut* med en median opfølgningstid på 46,9 måneder var overlevelsesraten ved 48 måneder 93 %. Ved 24 måneders median opfølgning var den estimerede 2-års overlevelse i en behandlingsnaiv population med p53-mutation behandlet med ibrutinib på 84 % i Ahn 2018-studiet. Efter en median opfølgning på 4,8 år var den estimerede 5-års overlevelse 85,3 % (95 % CI: 74,2-98,1).

Til sammenligning havde ITT-populationen behandlet med ibrutinib i RESONATE-2 en overlevelse efter 2 år på 98 %, mens den efter 5 år var 83 % (median opfølgningstid 60 måneder). Se data i Tabel 29.

**Tabel 29. OS-rater fra ELEVATE-TN, Ahn 2018 og RESONATE-2**

Effektmål	Opfølgning	Acalabrutinib + obinutuzumab ITT-population n=179 (ELEVATE-TN)	Ibrutinib p53 aberration n=51 (Ahn 2018)	Ibrutinib ITT-population n=136 (RESONATE-2)
Overlevelse	2 år	95 %	84 %	98 %
	3 år	-	-	-
	48 måneder	93 %	-	-
	5 år	-	85,3 %	83 %*

\*Dette tal er 84 % for patienter behandlet med ibrutinib med højrisiko CLL (p53-mutation, del(11q) og/eller umuteret IGHV), uden censorering for overkrydsning til ibrutinib.

Baseret på overlevelsesraterne er det ikke muligt at bestemme den foreløbige værdi af acalabrutinib + obinutuzumab på den absolutte skala, da data ikke tillader en direkte sammenligning. Baseret på den relative effektforskel (HR = 0,88 (95 % CI: 0,31-2,22)) kan værdien af acalabrutinib + obinutuzumab foreløbigt ikke kategoriseres vedr. OS, da konfidensintervallet er for bredt.





Fagudvalget vurderer samlet set, at merværdien af acalabrutinib + obinutuzumab ikke kan kategoriseres vedr. OS, idet OS-data er umodne. Dette er forventeligt baseret på studierne begrænsede opfølgningstid (28,1-31,3 måneder). Ud fra det nuværende datagrundlag vurderes det, at de to behandlinger er lige gode, hvad angår OS.

### Progressionsfri overlevelse (PFS)

#### MAIC

Ansøgers MAIC-analyse for ITT-populationen viser ingen signifikant forskel mellem acalabrutinib + obinutuzumab og ibrutinib (HR: 0,61 (95 % CI: 0,24-1,55)). NMA'en viser, at acalabrutinib + obinutuzumab er signifikant bedre end ibrutinib (HR = 0,19 (95 % CI: 0,09-0,38)), hvad angår PFS. Denne analyse er foretaget på ITT-populationen og ikke populationen med del(17p)/p53-mutation. Der er ikke justeret for forskelle i patientpopulationerne i studierne, og data skal derfor tolkes med forsigtighed og tillægges mindre vægt i vurderingen.

#### Narrativ gennemgang af data fra relevante studier

I ELEVATE-TN var 2-års PFS-raten for acalabrutinib + obinutuzumab i subgruppen med p53-mutation 95 % (95 % CI: 70-99) og for subgruppen med del(17p) 88 % (95 % CI: 61-97).

I Ahn 2018-studiet var 2-års PFS-raten 85 % i den behandlingsnaive population med p53-mutation (aflæst på KM-kurven) og 5-års PFS-raten 74,4 %. I RESONATE-2 var 5 års PFS-raten 56 % i populationen med p53-mutation, mens den i den samlede population var 70 % (se data i Tabel 30). Fagudvalget bemærker, at der ikke kan drages konklusioner på baggrund af PFS-raterne fra de enkelte studier, da disse er svære at tolke. Formentlig skyldes det forskelle i patientpopulationerne i studierne samt et lille datagrundlag (n).

**Tabel 30. PFS-rater fra ELEVATE-TN, Ahn 2018 og RESONATE-2**

Effektmål	Opfølgning	A + O	del(17p)	ibrutinib	ibrutinib	p53
		p53 (n=21) (ELEVATE-TN)	(n=17) (ELEVATE-TN)	p53 (n=34 ) (Ahn 2018)	ITT (n=136) (RESONATE-2)	(n=12) (RESONATE-2)
Progressionsfri overlevelse	2 år	95 %	88 %	85 %	98 %	-
	3 år	-	-	-	-	-
	5 år	-	-	74,4 %*	70 %	56 %

\*Behandlingsnaiv kohorte med p53 aberration. A + O: Acalabrutinib plus obinutuzumab

Baseret på raterne for PFS er det ikke muligt at bestemme den foreløbige værdi af acalabrutinib + obinutuzumab på den absolutte skala, da data ikke tillader en direkte sammenligning. Baseret på den relative effektforskel (HR: 0,61 (95 % CI: 0,24-1,55) kan værdien af acalabrutinib + obinutuzumab foreløbigt ikke kategoriseres vedr. PFS, da konfidensintervallet er for bredt.



Samlet set kan værdien af acalabrutinib + obinutuzumab ikke kategoriseres vedr. PFS, da datagrundlaget ikke tillader en formel kategorisering.

Hazard ratioen fra MAIC-analysen (HR: 0,61 (95 % CI: 0,24-1,55)) indikerer, at de to behandlinger er omtrent ligeværdige, hvad angår PFS. I MAIC-analysen er der taget højde for forskelle i patientkarakteristika i studierne, hvorfor MAIC tillægges størst betydning i vurderingen.

### Bivirkninger

Det er ikke muligt at foretage en komparativ analyse af andelen af patienter med uønskede hændelser grad  $\geq 3$ . Data gennemgås derfor i stedet narrativt for acalabrutinib + obinutuzumab baseret på ELEVATE-TN, mens ibrutinib belyses ved hjælp af ELEVATE-RR.

I ELEVATE-TN og ELEVATE-RR blev bivirkninger ikke opgjort særskilt for patienter med p53-mutation eller del(17p). I stedet fremgår data for *safety*-populationen.

Ved en median opfølgningstid på 28,3 måneder i ELEVATE-TN (andelen efter opfølgning på 47 måneder er ikke oplyst) og 40,9 måneder i ELEVATE-RR havde hhv. 70,2 % af patienterne i acalabrutinib + obinutuzumab-armen og 74,9 % af patienterne i ibrutinib-armen oplevet en grad  $\geq 3$  uønsket hændelse.

Ved en median opfølgningstid på 47 måneder i ELEVATE-TN og 40,9 måneder i ELEVATE-RR havde 39,1 % behandlet acalabrutinib + obinutuzumab og 53,8 % behandlet med ibrutinib oplevet en alvorlige uønsket hændelse (SAE). Ligeledes blev behandlingsophør grundet en uønsket hændelse rapporteret hos 12,3 % behandlet med acalabrutinib + obinutuzumab og 21,3 % behandlet med ibrutinib.

De hyppigste grad  $\geq 3$  hændelser rapporteret for acalabrutinib + obinutuzumab og ibrutinib var neutropeni (hhv. 29,8 % og 22,8 %), anæmi (5,6 % og 12,9 %), trombocytopeni (8,4 % og 6,8 %), diarré (4,5 % og 4,9 %), hypertension (2,8 % og 8,7 %) og pneumoni (5,6 % og 8,7 %) samt infektioner (23,6 % og 30 %).

Fagudvalget bemærker, at acalabrutinib + obinutuzumab er forbundet med mere træthed (28,1 % vs. 16,7 %) og hovedpine (39,9 % vs. 20,2 %) af enhver grad. Ibrutinib medfører flest kardiovaskulære bivirkninger (hypertension (22,8 % vs. 7,9 %) og atrieflimren af enhver grad (15,6 % vs. 3,9 %)). Hypertension kan være asymptomatisk og dermed vanskelig at opdage og få håndteret tilstrækkeligt i klinikken og kan således over tid føre til flere kardiovaskulære problematikker, hvis det ikke behandles passende. Også atrieflimren er en betydende bivirkning, idet der ses øget risiko for flere hændelser, hvis det først er opstået én gang.

Værdien af acalabrutinib + obinutuzumab kan ikke kategoriseres vedr. bivirkninger jf. Medicinrådets metode, da der ikke findes komparative estimater at basere kategoriseringen på. Acalabrutinib + obinutuzumab medfører færre hjertekar-



bivirkninger, færre infektioner på trods af mere neutropeni, mindre anæmi samt færre alvorlige uønskede hændelser og behandlingsophør grundet uønskede hændelser.

#### Helbredsrelateret livskvalitet

Ansøger har ikke leveret komparative data for effektmålet.

#### 5.5.4 Fagudvalgets konklusion

Den samlede værdi af acalabrutinib + obinutuzumab sammenlignet med ibrutinib til patienter med CLL og del(17p)/p53-mutation kan ikke kategoriseres.

Der ses færre alvorlige uønskede hændelser (SAE) (47,8 % vs. 58,6 %) samt færre behandlingsophør grundet uønskede hændelser (12,8 % vs. 22,3 %) for acalabrutinib sammenlignet med ibrutinib. Desuden ses der færre kardiovaskulære bivirkninger ved acalabrutinib + obinutuzumab. I vurderingen er der taget hensyn til, at hændelsesraterne ikke er direkte sammenlignelige, og at forskelle i patientkarakteristika i studierne kan have indflydelse på frekvenserne. Samlet set vurderer fagudvalget, at acalabrutinib + obinutuzumab og ibrutinib er sammenlignelige behandlingsalternativer hvad angår bivirkningsprofilen.

OS-data er umodent, hvilket afspejles i det brede konfidensinterval for ansøgers MAIC (HR = 0,88 (95 % CI: 0,31-2,22)), og indikerer ikke forskel mellem behandlinger på nuværende tidspunkt. Dette er forventeligt baseret på studiernes opfølgningstid (28,1-31,3 måneder), som er for kort til indsamling af tilstrækkelig antal events. PFS-data viser også, at de to behandlinger er omtrent ligeværdige (MAIC HR: 0,61 (95 % CI: 0,24-1,55)).

## 5.6 Klinisk spørgsmål 5

*Hvilken værdi har acalabrutinib som monoterapi sammenlignet med ibrutinib til 2. linjebehandling af patienter med kronisk lymfatisk leukæmi?*

### 5.6.1 Litteratur

I det følgende beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i direkte (ELEVATE-RR) og indirekte analyser (MAIC og NMA) til besvarelse af klinisk spørgsmål 5.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt de studier, som fremgår af Tabel 31. Publikationerne, som er relateret til disse studier, fremgår i afsnit 5.1.

#### Direkte analyser

ELEVATE-RR sammenligner acalabrutinib med ibrutinib til 2. linjebehandling af CLL. Se beskrivelse af studiet under klinisk spørgsmål 3 i afsnit 5.4.1.



## Indirekte analyser

### MAIC

Ansøger har udført en systematisk litteratursøgning og har her identificeret to studier, som vurderes relevante i en sammenligning med ASCEND-studiet, se Tabel 31. ELEVATE-RR indgår ikke i analysen, da ELEVATE-RR først blev publiceret efter ansøgning til Medicinrådet. Studierne er fase 3-randomiserede kliniske forsøg og inkluderer den aktuelle patientpopulation (tidligere behandlede CLL-patienter) samt relevante effektmål og komparatorer. Se Bilag 1 for en beskrivelse af studierne. Oversigt over udvalgte baselinekarakteristika for de relevante populationer inkluderet i MAIC-analysen kan findes i Tabel 49 i Bilag 2.

**ASCEND**-studiet er registreringsstudiet for acalabrutinib til 2. linjebehandling. ASCEND er et internationalt, multicenter, open-label, randomiseret fase 3-studie, som inkluderede tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL. Patienterne blev randomiseret 1:1 til acalabrutinib monoterapi (n=155) eller *investigator's choice* terapi (idelalisib + rituximab (n=119) eller bendamustin + rituximab (n=36)). Oral acalabrutinib 100 mg blev administreret to gange dagligt indtil sygdomsprogression eller uacceptabel toksicitet. Oral idelalisib 150 mg blev administreret to gange dagligt indtil sygdomsprogression eller uacceptabel toksicitet i kombination med intravenøs rituximab efter regimet: 375 mg/m<sup>2</sup> på dag 1 i første cyklus, 500 mg/m<sup>2</sup> hver anden uge i fire doser efterfulgt af 500 mg/m<sup>2</sup> hver fjerde uge i tre doser indtil i alt otte infusioner var givet. Alternativt blev intravenøs bendamustin 70 mg/m<sup>2</sup> administreret på dag 1 og 2 i hver cyklus i kombination med intravenøs rituximab givet efter regimet: 375 mg/m<sup>2</sup> på dag 1 i den første cyklus efterfulgt af 500 mg/m<sup>2</sup> på dag 1 i cyklus 2-6. Oral chlorambucil 10 mg/m<sup>2</sup> blev givet på dag 1-7 i hver cyklus. Alle cykler var på 28 dage. Patienterne, der modtog én af de to *investigator's choice*-behandlinger, og som oplevede bekræftet sygdomsprogression, havde mulighed for at krydse over til acalabrutinib-armen. Median opfølgningstid var 16,1 måneder [49]. En artikel, der inkluderer ekstra *follow-up*-data, er publiceret i 2020 [20].

### NMA

Ansøger har på baggrund af en systematisk litteratursøgning identificeret syv studier, som er inkluderet i en NMA. Studierne er fase 3-randomiserede kliniske forsøg og inkluderer tidligere behandlede CLL-patienter samt relevante effektmål og komparatorer. Se Bilag 1 for en beskrivelse af studierne. Se også Tabel 31 nedenfor for overblik over studierne. En oversigt over udvalgte baselinekarakteristika for de relevante populationer, som er inkluderet i NMA-analysen, kan findes i Tabel 50 i Bilag 2.



**Tabel 31. Oversigt over studier for klinisk spørgsmål 5 inkluderet i de indirekte sammenligninger (MAIC og NMA) og den narrative sammenligning af acalabrutinib vs. ibrutinib**

Klinisk forsøg	Lægemidler	Population	Indgår i
ELEVATE-RR*	Acalabrutinib vs. ibrutinib	Tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL og enten del(17p) eller del(11q)	Direkte sammenligning
ASCEND NCT02970318	Acalabrutinib vs. idelalisib + rituximab vs. bendamustin + rituximab	Tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL	MAIC NMA Narrativ sammenligning
RESONATE NCT01578707	Ibrutinib vs. ofatumumab	Tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL eller småcellet lymfocytært lymfom	MAIC NMA Narrativ sammenligning
MURANO NCT02005471	Venetoclax + rituximab vs. bendamustin + rituximab	Tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL	MAIC NMA
Furman 2014 NCT01539512	Idelalisib + rituximab vs. placebo + rituximab	Tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL, som samtidig led af større komorbiditet, fx nedsat nyrefunktion, behandlingsindiceret myelosuppression eller CIRS > 6	NMA
Jones 2017 NCT01659021	Idelalisib + ofatumumab vs. ofatumumab	Tidligere behandlede voksne patienter (> 18 år) med relaps CLL inden for 24 måneder fra sidste behandling	NMA
HELIOS NCT01611090	Ibrutinib + bendamustin + rituximab vs. placebo + bendamustin + rituximab	Tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL eller småcellet lymfocytært lymfom	NMA
Zelenetz 2017 NCT01569295	Idelalisib + bendamustin + rituximab vs. placebo + bendamustin + rituximab	Tidligere behandlede voksne patienter (> 18 år) med relaps CLL	NMA

\*ELEVATE-RR indgår ikke i ansøgers MAIC og NMA, da studiet blev publiceret efter tidspunktet for ansøgning til Medicinrådet.



## 5.6.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet. Ansøger har udført en direkte sammenlignende analyse, en MAIC samt en NMA og dertil beskrevet data narrativt. Besvarelsen af klinisk spørgsmål 5 vil primært bygge på den direkte sammenligning af acalabrutinib over for ibrutinib i ELEVATE-RR. MAIC og NMA-analyser vil blive inddraget som supplement.

### Direkte analyse (ELEVATE-RR)

ELEVATE-RR inkluderer en direkte sammenligning af acalabrutinib vs. ibrutinib.

#### Fagudvalgets kommentarer til datagrundlaget for den direkte analyse og analysens anvendelighed

Fagudvalget bemærker, at data for OS er umodent ved den tilgængelige opfølgningstid på median 46,9 måneder. Dosering og behandlingstid med ibrutinib er i overensstemmelse med dansk klinisk praksis. Patienterne inkluderet i ELEVATE-RR er patienter med relaps eller refraktær sygdom. Patienterne i ELEVATE-RR har desuden alle del(17p) og/eller del(11q), da dette var et inklusionskriterie i studiet.

Fagudvalget vurderer, at patienterne i ELEVATE-RR afviger fra den danske population i 2. linje på følgende punkter:

- Andelen med del(17p) og p53-mutation var større i studiet. Del(17p) forekom hos 45,1 % og 45,3 % i de to studiearme, mens p53-mutation forekom hos 37,3 % og 42,3 %.
- Flere patienter i studiet var IGHV-umuterede (82,1 % og 89,4 %), end hvad der forventes i klinikken.
- Patienterne i studiet havde modtaget flere tidligere behandlinger, end hvad der ses i dansk klinisk praksis.
- En mindre andel i studiet havde modtaget alemtuzumab i tidligere behandlingslinje (6 % og 4,2 %). Alemtuzumab bruges stort set ikke i dansk klinisk praksis.
- En stor andel i studiet havde tidligere modtaget behandling med purinanaloger (64,2 % og 59,6 %), som er kendt for at give længerevarende knoglemarvspåvirkning, hvilket kan prædisponere for hæmatologiske bivirkninger, også ved efterfølgende behandling. Forekomsten af hæmatologiske bivirkninger såsom cytopenier er derfor formodentlig overrepræsenteret i studiet.
- Patienterne i studiet var yngre.

Fagudvalget forventer, at effekten af acalabrutinib på OS og PFS, som blev observeret i studiet, er underestimeret, da patienterne i studiet har dårligere cytogenetiske prognostika og samtidig har modtaget flere tidligere behandlinger end de danske patienter.

Fagudvalget forventer også, at bivirkninger associeret med acalabrutinib og ibrutinib, som blev observeret i studiet, kan genfindes ved behandling af danske patienter i 2. linje. Der tages forbehold for, at forskelle i patientkarakteristika mellem patienterne i studiet



og i den danske patientpopulation kan han indflydelse på hændelsesfrekvenserne. Specielt har det betydning, at mange patienter i studiet tidligere er behandlet med purinanaloger, og at der derfor muligvis ses flere hæmatologiske bivirkninger, end hvad der forventes i dansk klinisk praksis.

#### MAIC

Analysen, som ansøger har udført for 2. linjebehandling, er *un-anchored*, idet der ikke findes fælles komparator, som kan knytte acalabrutinib og komparator(erne) sammen. Ansøger har identificeret og justeret analysen for følgende effektmodifikatorer og prognostiske faktorer.

**Tabel 32. Effektmodifikatorer og prognostiske faktorer, som justeres i analysen mellem ASCEND (acalabrutinib) og RESONATE (ibrutinib)\***

MAIC – 2. linje
<ul style="list-style-type: none"><li>• Alder</li><li>• Køn</li><li>• Bulky disease (<math>\geq 5</math> cm)</li><li>• del(17p)</li><li>• p53-mutation</li><li>• 11q mutation Eastern Cooperative Oncology Group Performance Score (ECOG PS) 0</li><li>• Eastern Cooperative Oncology Group Performance Score (ECOG PS) 1</li><li>• <math>\beta 2</math> mikroglobulin ved baseline (<math>&gt; 3,5</math> mg/L)</li><li>• Rai stage 1 eller 2</li><li>• Rai stage 3 eller 4</li><li>• Én tidligere behandlingslinje</li><li>• To tidligere behandlingslinjer</li><li>• Tre eller flere tidligere behandlingslinjer</li><li>• Kompleks karyotype</li><li>• Immunoglobulin heavy-chain variable (IGHV) gene mutation status</li><li>• CrCl <math>&lt; 60</math> ml/min.**</li></ul>

\*Information om del(11q), kompleks karyotype og IGHV var kun tilgængelig for 97 %, 78 % og 69 % af populationen i RESONATE, som blev behandlet med ibrutinib. Information om p53 status var desuden kun tilgængelig for 62 %, men denne er korreleret med del(17p), som er inkluderet i base-case.

\*\*En subgruppeanalyse anvendte ikke CrCl. I stedet blev anvendt p53-mutationsstatus og race.

Fagudvalget vurderer, at der overordnet set er matchet for relevante effektmodifikatorer og prognostiske faktorer i ansøgers MAIC for 2. linjebehandling. Dog vurderer fagudvalget, at det er problematisk, at der ikke justeres for forskelle i forekomsten af p53 aberration, da denne er associeret med nedsat respons på kemoimmunterapi. Ligeledes er tid til relaps ved tidligere behandling en relevant faktor med betydning for prognose, som der ikke er justeret for. Af mindre betydning bemærkes, at køn ikke forventes at have betydning for effekt eller prognose, hvorfor der ikke bør matches for det. Det kan diskuteres, om det er relevant at matche alder, da der i øvrigt matches for flere faktorer, som relaterer til komorbiditet.

Fagudvalget fremhæver del(17p)-mutation, p53-mutation og IGHV-mutationsstatus som de vigtigste faktorer med betydning for prognose og behandlingseffekt. Se Tabel 7 i afsnit 5.2.2 med fagudvalgets betragtninger vedr. faktorer med betydning for prognose og/eller effekt.



I analysen er anvendt de *data cuts* fra RESONATE og MURANO, som er mest sammenlignelige med data, der er til rådighed fra ASCEND (median opfølgning 16,1 måneder). Se median opfølgningstider i Tabel 33.

**Tabel 33. Opfølgningstid, median**

Klinisk forsøg	Lægemidler	Median opfølgningstid (måneder)
ASCEND	Acalabrutinib vs. idelalisib + rituximab vs. bendamustin + rituximab	16,1
RESONATE	Ibrutinib vs. ofatumumab	16,1 (PFS) 19,0 (OS)
MURANO	Venetoclax + rituximab vs. bendamustin + rituximab	23,8

Ved de anvendte *data cuts* var median OS og PFS ikke nået i studierne.

#### Fagudvalgets kommentarer til datagrundlaget for analysen

De anvendte *data cuts* i MAIC'en vurderes tilstrækkelig ens set fra et klinisk perspektiv, dog er opfølgningstiden for specielt ASCEND og RESONATE meget kort. OS- og PFS-data er forventeligt ikke modne med denne opfølgningstid, og datagrundlaget for OS- og PFS-analyserne er således meget spinkelt.

Overkrydsning ved progression var tilladt i RESONATE og ASCEND. I RESONATE kunne patienter behandlet med ofatumumab skifte til ibrutinib-behandling, mens det i ASCEND var muligt at skifte fra *investigator's choice* til acalabrutinib ved progression. I ASCEND skiftede 23 % af patienterne behandling, og der justeres ikke for overkrydsning i analyserne. I RESONATE blev patienter, som krydsede over, censureret i OS-analysen. Ved overkrydsning bliver det sværere at vurdere resultaterne, da både OS- og bivirkningsestimater kan blive påvirket til fordel for det ringere behandlingsalternativ i studierne. Eftersom der ikke justeres for overkrydsning i ASCEND, vil effektforskellen formentlig være underestimeret i studiet, hvilket også vil påvirke effektestimaterne fra MAIC-analysen.

#### Fagudvalgets samlede vurdering af analysens anvendelighed

Fagudvalget vurderer, at der er matchet for relevante faktorer, som har indflydelse på prognose og/eller behandlingseffekt, hvilket betyder, at forskelle i baseline-patientkarakteristika mellem studierne formentlig ikke får indflydelse på analysens resultater. Dog er det problematisk, at der ikke er justeret for p53 aberration, da denne har betydning for prognose og behandlingseffekt. Fagudvalget så også gerne, at der var justeret for tid til relaps.

Det bemærkes, at der i ASCEND indgår 132 patienter i acalabrutinib monoterapi-armen med tilstrækkeligt baselinedata til at indgå i MAIC-analysen. Efter matching er ESS (*effective sample size*) reduceret til kun 44 patienter, hvilket er et spinkelt datagrundlag





for at belyse effekten af acalabrutinib. I RESONATE indgår 195 patienter i ibrutinib-armen. Efter matching i MAIC-analysen indgår fortsat 195 patienter. Her er datagrundlaget altså større.

Manglende justering for overkrydsning i ASCEND betyder, at det relative effektestimat i studiet kan være påvirket til fordel for det ringere behandlingsalternativ (*investigator's choice*), og dermed kan effekten af acalabrutinib også være underestimeret i MAIC-analysen. Slutteligt er data umodne for både PFS og OS. Ved en længere opfølgningstid vil man opnå større sikkerhed omkring resultaterne. Specielt toksicitet kan spille ind på effektestimaterne tidligt i behandlingsforløbet, hvorfor lang opfølgningstid ønskes. Dernæst indsætter effekten af visse lægemidler hurtigere end ved andre, hvilket også understøtter behovet for lang opfølgningstid.

Analysen vurderes overordnet anvendelig, dog med forbehold.

#### Netværksmetaanalyse

Da der ikke findes en direkte sammenlignende analyse mellem acalabrutinib over for ibrutinib til 2. linjebehandling, har ansøger udført en indirekte sammenlignende analyse i form af en NMA baseret på data fra 7 studier, se Tabel 34.

Forudsætningen for en netværksmetaanalyse er, at karakteristika ved studierne (populationer, interventioner, fælles komparatorer, opfølgning m.m.) er tilstrækkelig ens, for at analysen er metodisk forsvarlig.

I analysen er anvendt *data cuts*, hvor den mediane opfølgningstid så vidt muligt ligner opfølgningstiden fra de andre studier, se Tabel 34.

**Tabel 34. Opfølgningstid, median**

Klinisk forsøg	Median opfølgningstid (måneder)
RESONATE	19 måneder
ASCEND	~16 måneder
Furman 2014	NR
Jones 2017	16,1 måneder
HELIOS	17 måneder
Zeneletz 2017	14 måneder
Seymour 2018	23,8 måneder

NR: Not reached, ikke nået.

Ved de anvendte *data cuts* var den mediane OS ikke nået i ASCEND, Furman 2014, Jones 2017, HELIOS, RESONATE, Seymour 2018 samt i den ene arm af Zelenetz 2017-studiet (idelalisib i kombination med bendamustin og rituximab).



Median PFS var ikke nået i den ene arm i Furman 2014 (idelalisib + rituximab), HELIOS (ibrutinib + bendamustin + rituximab-arm), RESONATE (ibrutinib-arm), ASCEND (acalabrutinib-arm) og Seymour 2018 (venetoclax + rituximab-arm).

#### Fagudvalgets kommentarer til datagrundlaget for analysen

For at binde netværket af studier sammen i analysen har ansøger antaget, at idelalisib + ofatumumab (Jones 2017) og idelalisib + rituximab (Furman 2014) er ækvivalente, hvad angår effekt. Fagudvalget vurderer ud fra det nuværende datagrundlag, at denne antagelse er plausibel.

De anvendte *data cuts* i NMA'en vurderes tilstrækkelig ens set fra klinisk perspektiv. Dog er OS-data forventeligt ikke modne på grund af utilstrækkelig opfølgningstid, og datagrundlaget for OS-analysen er således meget spinkelt. Det bemærkes også, at data for median PFS er umodent, men dog knap så spinkelt som for OS. Ved en længere opfølgningstid vil man opnå større sikkerhed omkring resultaterne. Specielt toksicitet kan spille ind på effektestimaterne tidligt i behandlingsforløbet, hvorfor længere opfølgningstid ønskes. Dernæst indsætter effekten af visse lægemidler hurtigere end ved andre, hvilket også understøtter behovet for lang opfølgningstid. Det vurderes dog samlet set, at opfølgningstider i studierne er anvendelige.

Overkrydsning var tilladt ved progression i to studier (RESONATE og ASCEND), men dataanalyserne i ASCEND justerer ikke herfor. NMA'en justerer heller ikke for overkrydsning, hvilket har betydning for OS-analysen og opgørelsen af bivirkninger, idet den relative behandlingseffekt kan påvirkes til fordel for det dårligere behandlingsalternativ.

Der er forskel på studierne ved sammenligning af andelen af patienter med del(17p) og p53-mutation. Disse mutationer har betydning for effekten af kemoterapi og antistoffer, som er væsentligt ringere hos patienter med disse forandringer. Ved targeteret behandling ses ikke tilsvarende ringere effekt, men dog stadig kortere tid til progression. I ASCEND havde forholdsvis få patienter del(17p) (16 %), mens den tilsvarende andel i RESONATE var 33 %. Patienter med del(17p) var helt ekskluderet i HELIOS. Andelen med p53-mutation varierede fra 13,2 % i Jones 2017 (idelalisib + ofatumumab-armen) til 45,5 % i Furman 2014 (rituximab-armen). Information om p53-mutation mangler i HELIOS. Disse forskelle samt manglende data er problematiske og kan have indflydelse på effektmålene, idet fagudvalget forventer, at patienter uden disse mutationer har en bedre prognose, bl.a. grundet bedre behandlingseffekt.

Andelen af patienter med kompleks karyotype (defineret som 3 eller flere kromosomale forandringer) rapporteres kun i ASCEND, HELIOS og RESONATE, hvor der rapporteres i spændet 6,2 % i HELIOS (bedamustin + rituximab + ibrutinib-armen) op til 32,3 % (acalabrutinib-armen) i ASCEND. Kompleks karyotype vil ofte være associeret med en dårligere prognose, og den ulige fordeling og manglende information om karyotype i de resterende studier er derfor problematisk. Fx kan det forventes, at patienterne i ASCEND og RESONATE har dårligere prognose end patienterne i HELIOS, hvilket i sidste ende kan påvirke de relative effektestimater i netværksmetaanalysen for både PFS og OS.



Andelen af patienter, som ikke er IGHV-muterede, er rapporteret i alle studier. Der ses betydelige forskelle i andelen mellem studierne, bl.a. bemærkes, at færrest patienter er ikke-muterede i RESONATE (42,3 %) sammenlignet med flest ikke-muterede i ASCEND (86,1 %). Patienter, som ikke er IGHV-muterede klarer sig dårligere ved behandling med kemoimmunterapi, og denne forskel i IGHV-mutationsstatus mellem studierne tager fagudvalget forbehold for.

Ansøger har undersøgt muligheden for at justere analysen (meta-regression) for forskelle i patientkarakteristika og studiedesign, men har ikke fundet mulighed herfor på grund af det lave antal studier sammenlignet med antal behandlinger.

#### Fagudvalgets samlede vurdering af analysens anvendelighed

Fagudvalgets vurderer, at der er flere vigtige forskelle mellem studierne patientkarakteristika og studiedesign, som potentielt kan påvirke effektestimaterne. Der er forbehold vedr. muligheden for overkrydsning i to studier, som kan påvirke de relative effektestimater til fordel for de ringere behandlingsalternativer i studierne og dermed også for NMA'ens estimater. Der ses også betydelige forskelle i baseline-patientkarakteristika (IGHV-status, del(17p), p53-mutation og kompleks karyotype), som har betydning for prognose, behandlingsrespons og behandlingsmuligheder. Slutteligt er OS-data generelt umodne, og til dels også umodne for PFS.

Som konklusion er der væsentlige forbehold vedr. analysen, som betyder, at den primært vil blive anvendt som supplement til øvrige analyser i vurderingen af acalabrutinib.

### 5.6.3 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 5.



**Table 35. Resultater for klinisk spørgsmål 5: komparator ibrutinib**

Effekt mål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Forskel i overlevelseshastighed ved 3 år eller ved længst mulig opfølgningstid (MKRF: 5 %-point)	Kritisk	ELEVATE-RR: 4 %-point	Kan ikke kategoriseres	ELEVATE-RR: HR = 0,82 (95 % CI: 0,59-1,15) MAIC HR = 0,92 (95 % CI: 0,38-2,27)	Kan ikke kategoriseres	Kan ikke kategoriseres
Progressionsfri overlevelse (PFS)	Forskel i andel patienter, der opnår PFS efter 3 år eller længst mulig opfølgningstid (MKRF: 10 %-point)	Vigtig	ELEVATE-RR: ~0 %-point	Kan ikke kategoriseres	ELEVATE-RR: HR = 1,00 (95 % CI: 0,79-1,27) MAIC HR = 0,72 (95 % CI: 0,33-1,60)	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der oplever én eller flere uønskede hændelser af grad 3-4 (MKRF: 10 %-point) (+ kvalitativ gennemgang)	Vigtig	-6,1 %-point	Kan ikke kategoriseres	ELEVATE-RR: RR: 0,92 (95 % CI: 0,83-1,02)	Ingen dokumenteret merværdi	Kan ikke kategoriseres
Livskvalitet	EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	-	-	-	-	-
<b>Konklusion</b>							
<b>Samlet kategori for lægemidlets værdi</b>		Kan ikke kategoriseres					

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.



## Overlevelse (OS)

### *ELEVATE-RR*

I ELEVATE-RR er median OS ikke nået efter en median opfølgningstid på 40,9 måneder. På opgørelsestidspunktet var 23,5 % af patienterne behandlet med acalabrutinib monoterapi døde, og tilsvarende var 27,5 % behandlet med ibrutinib døde, svarende til en forskel på -4 %-point (HR: 0,82 (95 % CI: 0,59-1,15)).

### *MAIC og NMA*

Ansøgers MAIC-analyse, som er baseret på ITT-populationerne, viser en hazard ratio på [REDACTED], hvilket indikerer ingen forskel mellem behandlingerne. Ansøgers NMA (også baseret på ITT-populationerne) er i overensstemmelse hermed (HR = 1,30 (95 % CI: 0,49-3,48)). I begge analyser er konfidensintervallerne brede, hvilket kan forklares med, at OS-data var umodent i størstedelen af studierne i ansøgers analyser.

Baseret på overlevelsesraterne fra ELEVATE-RR er det ikke muligt at bestemme værdien af acalabrutinib monoterapi på den absolutte skala, da der mangler et konfidensinterval for forskellen.

Baseret på den relative effektforskel HR: 0,82 (95 % CI: 0,59-1,15) fra ELEVATE-RR, som fremgår af Tabel 35 kan værdien af acalabrutinib ikke kategoriseres vedr. OS, da konfidensintervallet er for bredt. Fagudvalget vurderer, at hazard ratioen indikerer, at acalabrutinib monoterapi og ibrutinib er sammenlignelige i effekt, hvad angår OS, hvilket understøttes af resultaterne fra MAIC- og netværksmetaanalysen. Der tages forbehold for, at data er umodent, hvilket afspejles i brede konfidensintervaller for hazard ratioerne.

## Progressionsfri overlevelse (PFS)

### *ELEVATE-RR*

I ELEVATE-RR er median PFS ens i acalabrutinib monoterapi-armen (38,4 måneder (95 % CI: 33,0-38,6)) og ibrutinib-armen (38,4 måneder (95 % CI: 33,0-41,6)), HR = 1,00 (95 % CI: 0,79-1,27) efter en median opfølgningstid på 40,9 måneder. Ved aflæsning på Kaplan-Meier-kurven er ~55 % af patienterne i begge arme i live efter 36 måneder.

### *MAIC og NMA*

Ansøgers MAIC viser ingen signifikant forskel mellem acalabrutinib og ibrutinib [REDACTED] og ansøgers NMA er i overensstemmelse med dette HR = 0,79 (95 % CI: 0,40-1,54).

Baseret på PFS-raterne er det ikke muligt at bestemme den foreløbige værdi af acalabrutinib på den absolutte skala jf. Medicinrådets metoder.

Baseret på den relative effektforskel fra ELEVATE-RR (HR = 1,00 (95 % CI: 0,79-1,27)), kan værdien af acalabrutinib foreløbigt ikke kategoriseres vedr. PFS, da konfidensintervallet er for bredt. Fagudvalget vurderer, at merværdien af acalabrutinib samlet set ikke kan kategoriseres vedr. PFS, men at effekten af acalabrutinib monoterapi og ibrutinib er sammenlignelig, hvad angår PFS ud fra det nuværende datagrundlag.



### Bivirkninger

Baseret på data fra ELEVATE-RR er det muligt at foretage en komparativ analyse mellem acalabrutinib monoterapi og ibrutinib af andelen, som oplevede en grad  $\geq 3$  uønsket hændelse. Desuden gennemgås data narrativt fra ELEVATE-RR.

Fagudvalget vurderer, at data fra ELEVATE-RR kan anvendes til at belyse bivirkninger i klinisk spørgsmål 5 (den fulde 2. linjepopulation), selvom ELEVATE-RR inkluderer en stor andel patienter med højriskosygdom. Der tages dog forbehold for, at hændelsesfrekvenserne kan være influeret af forskelle i patientkarakteristika. Uønskede hændelser rapporteret i ELEVATE-RR fremgår af Tabel 36.

**Tabel 36. Uønskede hændelser rapporteret i ELEVATE-RR for acalabrutinib monoterapi og ibrutinib**

Uønskede hændelser	ELEVATE-RR	
	Acalabrutinib monoterapi n=266, n (%) Opfølgningstid: 38,3 måneder	Ibrutinib n=263, n (%) Opfølgningstid: 35,5 måneder
Uønsket hændelse (enhver grad)	260 (97,7 %)	256 (97,3 %)
Uønsket hændelse (Grad $\geq 3$ )	183 (68,8 %)	197 (74,9 %)
Alvorlig uønsket hændelse (SAE)	143 (53,8 %)	154 (58,6 %)
Behandlingsophør grundet uønsket hændelse	39 (14,7 %)	56 (21,3 %)
<b>Grad <math>\geq 3</math> uønskede hændelser</b>		
Neutropeni	52 (19,5 %)	60 (22,8 %)
Trombocytopeni	26 (9,8 %)	18 (6,8 %)
Anæmi	31 (11,7 %)	34 (12,9 %)
Perifært ødem	0	1 (0,4 %)
Øvre luftvejsinfektion	5 (1,9 %)	1 (0,4 %)
Urinvejsinfektion	3 (1,1 %)	6 (2,3 %)
Pneumoni	28 (10,5 %)	23 (8,7 %)
Opkastning	1 (0,4 %)	3 (1,1 %)
Forstoppelse	0	2 (0,8 %)
Træthed	<b>9 (3,4 %)</b>	0
Feber	8 (3,0 %)	2 (0,8 %)
Diarré	3 (1,1 %)	<b>13 (4,9 %)</b>
Arthralgi	0	2 (0,8 %)
Rygsmerte	0	2 (0,8 %)
Hovedpine	<b>4 (1,5 %)</b>	0



ELEVATE-RR		
Uønskede hændelser	Acalabrutinib monoterapi n=266, n (%) Opfølgningstid: 38,3 måneder	Ibrutinib n=263, n (%) Opfølgningstid: 35,5 måneder
Hoste	2 (0,8 %)	1 (0,4 %)
Dyspnoø	6 (2,3 %)	1 (0,4 %)
Udslæt	2 (0,8 %)	0
Hypertension	11 (4,1 %)	<b>23 (8,7 %)</b>
Atrieflimren	12 (4,5 %)	9 (3,4 %)
Kvalme	0	1 (0,4 %)
Bronkitis	3 (1,1 %)	2 (0,8 %)
Kontusion (blå mærker)	0	1 (0,4)
Myalgi	2 (0,8 %)	1 (0,4 %)
Næseblødning	1 (0,4 %)	1 (0,4 %)
Muskelspasmer	0	2 (0,8 %)

NR: not reported; **Fed**: Markerer, at eventet har statistisk højere incidens end intervention/komparator i ELEVATE-RR. Se også tabel nedenfor.

Baseret på data fra ELEVATE-RR er acalabrutinib monoterapi associeret med færre grad  $\geq 3$  hændelser (68,8 % vs. 74,9 %, forskel -6,1 %-point) end ibrutinib, men forskellen er ikke statistisk signifikant (RR: 0,92 (95 % CI: 0,83-1,02)). Ansøger har ikke angivet et konfidensinterval for estimatet for den absolutte effektforskel på -6,1 %-point, og punkttestimatet for forskellen er mindre end den mindste klinisk relevante forskel på 10 %-point.

Der ses også færre alvorlige uønskede hændelser (SAE) (53,8 % vs. 48,6 %) samt færre behandlingsophør grundet uønskede hændelser (14,7 % vs. 21,3 %) ved acalabrutinib monoterapi sammenlignet med ibrutinib. Det bemærkes, at frekvenserne for acalabrutinib monoterapi i ELEVATE-TN er lavere end de tilsvarende frekvenser for acalabrutinib monoterapi i ELEVATE-RR. Det kan sandsynligvis forklares med den kortere opfølgningstid i ELEVATE-TN.

Hændelser, som forekommer med statistisk signifikant forskellig incidens i ELEVATE-RR, er angivet i Tabel 37, hvor fed skrift indikerer en højere incidens.



**Tabel 37. Uønskede hændelser, som forekommer med statistisk signifikant højere incidens i ELEVATE-RR (markeret med fed)**

Event	ELEVATE-RR			
	Acalabrutinib monoterapi n=266, n (%) Enhver grad	Grad ≥ 3	Ibrutinib n=263, n (%) Enhver grad	Grad ≥ 3
Urinvejsinfektion	22 (8,3 %)	3 (1,1 %)	<b>36 (13,7 %)</b>	6 (2,3 %)
Træthed	54 (20,3 %)	<b>9 (3,4 %)</b>	44 (16,7 %)	0
Diarré	92 (34,6 %)	3 (1,1 %)	<b>121 (46,0 %)</b>	<b>13 (4,9 %)</b>
Artralgi	42 (15,8 %)	0	<b>60 (22,8 %)</b>	2 (0,8 %)
Rygsmærter	20 (7,5 %)	0	<b>34 (12,9 %)</b>	2 (0,8 %)
Hovedpine	<b>92 (34,6 %)</b>	<b>4 (1,5 %)</b>	53 (20,2 %)	0
Hoste	<b>77 (28,9 %)</b>	2 (0,8 %)	56 (21,3 %)	1 (0,4 %)
Hypertension	23 (8,6 %)	11 (4,1 %)	<b>60 (22,8 %)</b>	<b>23 (8,7 %)</b>
Atrieflimren	24 (9,0 %)	12 (4,5 %)	<b>41 (15,6 %)</b>	9 (3,4 %)
Kontusion (blå mærker)	31 (11,7 %)	0	<b>48 (18,3 %)</b>	1 (0,4)
Muskelspæsmen	16 (6,0 %)	0	<b>35 (13,3 %)</b>	2 (0,8 %)
Dyspepsi	10 (3,8 %)	0	<b>32 (12,2 %)</b>	0

Statistisk signifikant højere incidenser er markeret med fed.

Fagudvalget bemærker, at acalabrutinib monoterapi er forbundet med mere træthed samt hovedpine og hoste sammenlignet med ibrutinib. Disse bivirkninger vurderes at være af mindre klinisk relevans. Det er fagudvalgets erfaring, at hovedpine i forbindelse med behandling med acalabrutinib monoterapi primært ses i begyndelsen af behandlingen, er forbigående og forholdsvis kortvarigt.

Ibrutinib er forbundet med flere gastrointestinale bivirkninger (diarré og dyspepsi) samt kardiovaskulære bivirkninger (hypertension og atrieflimren) end acalabrutinib. Ibrutinib er desuden associeret med muskuloskeletale smerter (artralgi, rygsmærter og muskelsmerter), som kan have betydning for patientens livskvalitet.

Efter markedsføring af ibrutinib har flere studier undersøgt effekt og bivirkninger ved ibrutinib i klinisk praksis, og disse peger på, at tolerabilitet af behandlingen er en relevant problematik i klinikken. Der ses væsentlig højere rater for behandlingsophør af ibrutinib grundet uønskede hændelser i klinisk praksis sammenlignet med, hvad der er rapporteret i de kliniske studier. I RESONATE-2 ophørte 21 % behandlingen grundet uønskede hændelser efter 5 års opfølgning, og i RESONATE var andelen 7 % efter 26





måneders opfølgning [23][28]. Bl.a. har et dansk retrospektivt multicenter studie vist, at 54,7 % af patienterne behandlet med ibrutinib (i 1. og 2. linje) ophører behandlingen grundet uønskede hændelser [46], hvilket betyder, at behandlingsophør oftere skyldes lægemiddeltoksicitet end progression. En mulig forklaring kan være, at patienterne i klinisk praksis er ældre og har mere komorbiditet end patienterne i de kliniske forsøg. Det er endnu uvist, om behandling med acalabrutinib vil medføre samme høje rate for behandlingsophør som følge af uønskede hændelser, som er set i klinisk praksis ved brug af ibrutinib. Ibrutinib og acalabrutinib har samme virkningsmekanisme, idet begge hæmmer Brutons tyrosinkinase (BTK), men acalabrutinib er mere selektiv og dermed muligvis bedre tolereret.

I forlængelse af dette har studier vist [47][48], at patienter, som ikke tåler ibrutinib, kan have gavn af behandling med acalabrutinib, da toksicitetsprofilerne ikke er ens (se klinisk spørgsmål 3, Bivirkninger).

Baseret på den relative risiko for at opleve en grad  $\geq 3$  uønsket hændelse RR: 0,92 (95 % CI: 0,83-1,02) er der ingen merværdi af acalabrutinib monoterapi.

Baseret på punkttestimatet for den absolutte effektforskel -6,1 %-point kan værdien ikke kategoriseres, da der ikke foreligger et konfidensinterval.

Fagudvalget vurderer samlet set, at værdien af acalabrutinib monoterapi ikke kan kategoriseres vedr. bivirkninger, da datamaterialet ikke tillader dette, jf. Medicinrådets metoder.

Der ses færre grad  $\geq 3$  hændelser (68,8 % vs. 74,9 %), færre alvorlige uønskede hændelser (SAE) (53,8 % vs. 48,6 %) samt færre behandlingsophør grundet uønskede hændelser (14,7 % vs. 21,3 %) ved acalabrutinib monoterapi end ved ibrutinib. Ligeledes ses der signifikant flere kardiovaskulære bivirkninger ved ibrutinib. Ved anvendelse af ibrutinib i klinikken ses højt frafald grundet uønskede hændelser. Frafaldet ved brug af acalabrutinib vil måske være mindre, da denne er en mere selektiv BTK-hæmmer og dermed muligvis bedre tolereret.

#### Helbredsrelateret livskvalitet

Ansøger har ikke leveret komparative data for effektmålet.

#### 5.6.4 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af acalabrutinib monoterapi sammenlignet med ibrutinib til 2. linjebehandling af patienter med kronisk lymfatisk leukæmi ikke kan kategoriseres.

Der ses færre grad  $\geq 3$  hændelser (68,8 % vs. 74,9 %), færre alvorlige uønskede hændelser (SAE) (53,8 % vs. 48,6 %) samt færre behandlingsophør grundet uønskede hændelser (14,7 % vs. 21,3 %).

Desuden ses signifikant flere kardiovaskulære bivirkninger ved ibrutinib. Samlet set vurderer fagudvalget, at acalabrutinib og ibrutinib er sammenlignelige hvad angår bivirkninger.



I fagudvalgets overvejelser indgår også, at OS-data indikerer, at acalabrutinib monoterapi og ibrutinib er sammenlignelige i effekt. OS-data er fortsat umodne efter en opfølgningstid på 40,9 måneder i ELEVATE-RR, HR: 0,82 (95 % CI: 0,59-1,15). Median PFS er 38,4 måneder i begge studiearme, og med HR = 1,00 (95 % CI: 0,79-1,27) vurderes acalabrutinib monoterapi og ibrutinib at være sammenlignelige i effekt, hvad angår PFS.

## 6. Andre overvejelser

I Medicinrådets protokol for vurderingen af acalabrutinib har fagudvalget udbedt sig oplysninger fra ansøger vedr. IGHV-mutationsstatus, kombination af acalabrutinib og obinutuzumab i 1. linje samt behandling med acalabrutinib før eller efter ibrutinib. Ansøgers svar fremgår nedenfor.

### **IGHV-mutationsstatus**

Ansøger bedes, med henblik på eventuel differentiering af effekt, bidrage med separate effektopgørelser for patienter, hhv. umuteret og hypermuteret IGHV-status for alle effektmål i sammenligningen med kemoimmunterapi. Opdeling af populationen ift. IGHV-mutationsstatus bør også kunne tilgodeses i den sundhedsøkonomiske model.

Ansøger har leveret data fra NMA'en, som blev udført for 1. linjebehandling. I populationen med IGHV-mutation var behandling med acalabrutinib + obinutuzumab associeret med en lavere risiko for progression ved sammenligning med bendamustin + rituximab og chlorambucil + obinutuzumab. Ved behandling med acalabrutinib monoterapi var der tendens til lavere risiko for progression, men denne var ikke statistisk signifikant.



**Tabel 38. PFS-resultater i subgruppen med IGHV-mutation i 1. linje**

HR	Bendamustin + rituximab	Chlorambucil + obinutuzumab
Acalabrutinib monoterapi	0,31 (0,06-1,57)	0,69 (0,31-1,56)
Acalabrutinib + obinutuzumab	0,09 (0,01-0,54)	0,20 (0,07-0,62)

I populationen uden IGHV-mutation var behandling med acalabrutinib monoterapi og acalabrutinib + obinutuzumab associeret med en signifikant lavere risiko for progression ved sammenligning med bendamustin + rituximab og chlorambucil + obinutuzumab.

**Tabel 39. PFS-resultater i subgruppen uden IGHV-mutation i 1. linje**

HR	Bendamustin + rituximab	Chlorambucil + obinutuzumab
Acalabrutinib monoterapi	0,10 (0,03-0,32)	0,12 (0,07-0,20)
Acalabrutinib + obinutuzumab	0,08 (0,02-0,25)	0,09 (0,05-0,16)

Baseret på de præsenterede HR, vurderer fagudvalget, at subgruppen med IGHV-mutation vil have størst gavn af behandling med acalabrutinib + obinutuzumab fremfor acalabrutinib monoterapi, da kombinationen medførte en signifikant lavere risiko for progression ved sammenligning med bendamustin + rituximab og chlorambucil + obinutuzumab. Ved acalabrutinib monoterapi sås ingen signifikant forskel.

I populationen uden IGHV-mutation havde patienterne gavn (signifikant) af både acalabrutinib monoterapi og i kombination med obinutuzumab.

Ansøger har også leveret IGHV-subgruppeanalyser for 2. linje, men her er alle data inkonklusive grundet brede konfidensintervaller.

#### **Kombination med obinutuzumab**

Fagudvalget ønsker at undersøge værdien af at kombinere acalabrutinib med obinutuzumab til patienter i 1. linje, og dette ønske bedes afspejlet i den sundhedsøkonomiske model.

Ansøger har bidraget med data fra en post hoc PFS-analyse fra ELEVATE-TN, som er til fordel for acalabrutinib + obinutuzumab sammenlignet med acalabrutinib monoterapi, HR: 0,49 (95 % CI: 0,26-0,95).

Median OS var ikke nået i behandlingsarmene i ELEVATE-TN, men der var en trend mod, at OS var til fordel for acalabrutinib + obinutuzumab (HR: 0,47; p = 0,0577) og acalabrutinib monoterapi (HR: 0,60; p = 0,1556) ved sammenligning med chlorambucil + obinutuzumab.



En opgørelse af andelen af patienter med grad  $\geq 3$  uønskede hændelser viste en lavere forekomst ved behandling med acalabrutinib monoterapi (49,7 %) sammenlignet med acalabrutinib + obinutuzumab (70,2 %). Alvorlige uønskede hændelser forekom hos 31,8 % og 38,8 % af patienterne behandlet med acalabrutinib monoterapi og acalabrutinib + obinutuzumab.

Fagudvalget tager ansøgers informationer til efterretning.

#### **Behandling med acalabrutinib før eller efter ibrutinib**

Tidligere behandling med en B-celle-receptorhæmmer er et eksklusionskriterium i ASCEND-studiet. Da acalabrutinib og ibrutinib begge tilhører denne gruppe og har samme target (BTK), ønsker fagudvalget, at ansøger redegør for evidensen for at anvende de to behandlinger efter hinanden. Fagudvalget ønsker, at ansøger inddrager viden om mutation af C481-sitet i forbindelse med behandlingssvigt på ibrutinib, og hvorvidt det har betydning for eventuel efterfølgende effekt af acalabrutinib.

Ansøger har i sin ansøgning inkluderet data, som viser, at resistens over for acalabrutinib primært medieres af mutationer i det samme site (C481), som oftest er involveret i resistens over for ibrutinib. Fagudvalget konkluderer, at ved resistensudvikling – som følge af behandling med acalabrutinib eller ibrutinib – er det ikke gavnligt med efterfølgende behandling med ibrutinib eller acalabrutinib.

Som tidligere diskuteret i klinisk spørgsmål 3 findes der data, som underbygger, at acalabrutinib med fordel kan anvendes hos patienter, som er intolerante over for ibrutinib [47,48].

## 7. Relation til behandlingsvejledning

Der foreligger en RADS behandlingsvejledning for CLL fra 2016, men denne er ikke opdateret med de nyeste lægemidler, og der findes ikke en lægemiddelrekommandation.

## 8. Evidensens kvalitet

Analyserne, som anvendes i vurderingen af acalabrutinib, bygger på både direkte og indirekte evidens. Overordnet er studierne der indgår i de indirekte analyser sammenlignelige. Der er ikke foretaget systematisk vurdering af risiko for bias i studierne og evidensens kvalitet. Der er foretaget vurdering af risiko for bias for ELEVATE-TN og ELEVATE-RR, som anvendes til direkte sammenligninger.



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# 10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

## Medicinrådets fagudvalg vedrørende kronisk lymfatisk leukæmi (CLL)

Sammensætning af fagudvalg	
Formand	Indstillet af
Robert Schou Pedersen <i>Overlæge</i>	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
Medlemmer	Udpeget af
Thor Høyer <i>Afdelingslæge</i>	Region Nordjylland
Annika Rewes <i>Afdelingslæge</i>	Region Syddanmark
Rasmus Bo Dahl-Sørensen <i>Afdelingslæge</i>	Region Sjælland
Jindrich Mourek <i>Overlæge</i>	Region Hovedstaden
Stine Trolle Poulsen <i>Farmaceut</i>	Dansk Selskab for Sygehusapoteksledelse
Samuel Azuz <i>Afdelingslæge</i>	Dansk Selskab for Klinisk Farmakologi
<i>Deltager ikke</i>	Dansk Sygepleje Selskab
<i>Kan ikke udpege</i>	Danske Patienter

### Medicinrådets sekretariat

Medicinrådet  
Dampfærgevej 21-23, 3. sal  
2100 København Ø  
+45 70 10 36 00  
[medicinraadet@medicinraadet.dk](mailto:medicinraadet@medicinraadet.dk)



# 11. Versionslog

## Versionslog

Version	Dato	Ændring
1.0	20. april 2022	Godkendt af Medicinrådet.



## 12. Bilag

### Bilag 1: Gennemgang af de kliniske studier og Cochrane risk of bias

#### **Ahn-studiet (NCT01500733)**

Ahn-studiet er et single-center, single-armet, open-label fase 2-studie, der inkluderede tidligere ubehandlede voksne patienter med CLL, der enten havde deletion 17p/p53-mutation (n=51) eller var  $\geq 65$  år (n=35). Oral ibrutinib 420 mg blev givet én gang dagligt indtil sygdomsprogression eller uacceptabel toksicitet i 6 cykler af 28 dage. Studiets mediane opfølgningstid var ca. 58 måneder (4,8 år) [25].

#### **ALLIANCE (NCT01886872)**

ALLIANCE er et open-label, multicenter, randomiseret fase 3-studie, der blev udført i Canada og USA og inkluderede voksne patienter over 65 år med tidligere ubehandlet CLL uanset mutationstype. Patienterne blev randomiseret 1:1:1 til hhv. bendamustin + rituximab (n=183), ibrutinib (n=182) eller ibrutinib + rituximab (n=182). Intravenøs bendamustin 90 mg/m<sup>2</sup> blev administreret på dag 1 og 2 i cyklus 1-6 i kombination med intravenøs rituximab 375 mg/m<sup>2</sup>, som blev administreret på dag 1 i første cyklus efterfulgt af 500 mg/m<sup>2</sup> på dag 1 i cyklus 2-6. Oral ibrutinib blev administreret som 420 mg dagligt indtil sygdomsprogression eller uacceptabel toksicitet. Patienterne i ibrutinib + rituximab-armen modtog ibrutinib i samme regime som ibrutinib-gruppen, men fik derudover intravenøs rituximab 375mg/m<sup>2</sup> på dag 1, 8, 15 og 22 i anden cyklus og på dag 1 i cyklus 3-6. Behandlingerne blev givet i cykler af 28 dage. Patienterne i bendamustin + rituximab-gruppen kunne krydse over til ibrutinib ved sygdomsprogression. Median opfølgningstid var 38 måneder [24].

#### **ASCEND (NCT02970318)**

ASCEND er et internationalt, multicenter, open-label, randomiseret fase 3-studie, som inkluderede tidligere behandlede voksne patienter (> 18 år) med relaps/refraktær CLL. Patienterne blev randomiseret 1:1 til acalabrutinib monoterapi (n=155) eller *investigator's choice*-terapi (idelalisib + rituximab (n=119) eller bendamustin + rituximab (n=36)). Oral acalabrutinib 100 mg blev administreret to gange dagligt til sygdomsprogression eller uacceptabel toksicitet. Oral idelalisib 150 mg blev administreret to gange dagligt til sygdomsprogression eller uacceptabel toksicitet i kombination med intravenøs rituximab efter regimet: 375 mg/m<sup>2</sup> på dag 1 i første cyklus, 500 mg/m<sup>2</sup> hver anden uge i fire doser efterfulgt af 500 mg/m<sup>2</sup> hver fjerde uge i tre doser indtil i alt otte infusioner var givet. Alternativt blev intravenøs bendamustin 70 mg/m<sup>2</sup> administreret på dag 1 og 2 i hver cyklus i kombination med intravenøs rituximab givet efter regimet: 375 mg/m<sup>2</sup> på dag 1 i den første cyklus efterfulgt af 500 mg/m<sup>2</sup> på dag 1 i cyklus 2-6. Oral chlorambucil 10 mg/m<sup>2</sup> blev givet på dag 1-7 i hver cyklus. Alle cykler var på 28 dage. Patienterne, der modtog én af de to *investigator's choice*-behandlinger, og som oplevede bekræftet sygdomsprogression, havde mulighed for at krydse over til acalabrutinib-armen. Median opfølgningstid var 16,1 måneder [49]. En artikel, der inkluderer ekstra *follow-up*-data, er publiceret i 2020 [20].



### **COMPLEMENT1**

COMPLEMENT 1 er et internationalt, multicenter, open-label, randomiseret fase 3-studie, som inkluderede tidligere ubehandlede voksne patienter ( $\geq 18$  år) med CLL, hvor fludarabin-baseret behandling ikke er mulig. Patienterne blev randomiseret 1:1 til chlorambucil (n=226) eller chlorambucil + ofatumumab (n=221). Oral chlorambucil 10 mg/m<sup>2</sup> blev administreret på dag 1-7 i cyklus 1-12 i begge grupper. Intravenøs ofatumumab 300 mg blev administreret på dag 1 og 1.000 mg på dag 8 i første cyklus. I de efterfølgende cykler blev 1.000 mg ofatumumab givet på dag 1 i cyklus 3-12. Hver cyklus var på 28 dage. Median opfølgningstid var 28,9 måneder [50].

### **CAM-307 (NCT00046683)**

CAM-307 er et internationalt, multicenter, open-label, randomiseret fase 3-studie, der inkluderede tidligere ubehandlede voksne patienter ( $\geq 18$  år) med CLL. Patienterne blev randomiseret 1:1 til alemtuzumab (n=148) eller chlorambucil (n=148). Intravenøs alemtuzumab 30 mg blev givet 3 gange pr. uge i 12 uger. Oral chlorambucil 40 mg/m<sup>2</sup> blev givet hver 28. dag i op til 12 måneder. Median opfølgningstid var 24,6 måneder [32].

### **CLL10 (NCT 00769522)**

CLL10 er et internationalt, multicenter, open-label, non-inferioritets randomiseret fase 3-studie, der inkluderer tidligere ubehandlede patienter i alderen 33-81 med *advanced* CCL. Patienterne blev randomiseret 1:1 til fludarabin, cyklofosamid + rituximab (n=284) eller bendamustin + rituximab (n=280). Intravenøs fludarabin 25 mg/m<sup>2</sup> pr. dag og cyklofosamid 250 mg/m<sup>2</sup> pr. dag blev givet på dag 1-3 i hver cyklus. Intravenøs rituximab 375 mg/m<sup>2</sup> blev administreret på dag 0 i den første cyklus efterfulgt af 500 mg/m<sup>2</sup> på dag 1 i cyklus 2-6. Intravenøs bendamustin 90 mg/m<sup>2</sup> pr. dag blev givet på dag 1 og 2 i hver cyklus i kombination med intravenøs rituximab administreret efter samme regime som nævnt ovenfor. Alle cyklerne var på 28 dage. Median opfølgningstid var 37,1 måneder [34].

### **CLL11 (NCT01010061)**

CLL11 er et internationalt, multicenter, open-label, randomiseret tre-armet fase 3-studie, som inkluderer tidligere ubehandlede voksne patienter med CLL og komorbiditet (CIRS  $> 6$  eller kreatinin-clearance på mellem 30-69 pr. minut). Patienterne blev randomiseret 1:2:2 til chlorambucil givet som monoterapi (n=118/118), obinutuzumab + chlorambucil (n=238/333) eller rituximab + chlorambucil (n=233/330). Oral chlorambucil 0,5 mg/kg blev administreret på dag 1 og 15 i hver cyklus fra cykel 1-6 i alle grupperne. Intravenøs obinutuzumab 1.000 mg blev administreret på dag 1, 8 og 15 i første cyklus og efterfølgende på dag 1 i cyklus 2-6. Intravenøs rituximab 375 mg/m<sup>2</sup> blev administreret på dag 1 i den første cyklus efterfulgt af 500 mg/m<sup>2</sup> på dag 1 i cyklus 2-6. Alle cykler var på 28 dage. Overkrydsning til obinutuzumab-chlorambucil-gruppen var tilladt for de patienter, der modtog chlorambucil givet som monoterapi, som oplevede sygdomsprogression, mens de modtog behandlingen eller inden for de første 6 måneder efter behandlingens ophør. Median opfølgningstid er ikke angivet [33]. En artikel publiceret i 2020 vurderer langtidseffekten og HRQL af behandlingerne givet i CLL11-studiet [35].



### **CLL14 (NCT02242942)**

CLL14 er et internationalt, multicenter, open-label, randomiseret fase 3-studie, som inkluderer tidligere ubehandlede voksne patienter med CLL og komorbiditet (CIRS > 6 eller kreatinin-clearance på < 70 ml/min.). Patienterne blev randomiseret 1:1 til venetoclax + obinutuzumab (n=216) eller chlorambucil + obinutuzumab (n=216). Intravenøs obinutuzumab blev administreret i begge grupper efter følgende regime: 100 mg på dag 1 og 900 mg på dag 2 (eller 1.000 mg på dag 1), 1.000 mg på dag 8 og 15 i første cyklus efterfulgt af 1.000 mg på dag 1 i cyklus 2-6. Oral chlorambucil 0,5 mg/kg blev administreret på dag 1 og 15 i cyklus 1-12. Oral venetoclax blev opstartet på dag 22 i første cyklus med en 5-ugers dosis-optrappingsperiode, hvor 20 mg, 50 mg, 100 mg, 200 mg og 400 mg alle blev administreret én gang dagligt i en uge efterfulgt af 400 mg én gang dagligt de følgende 12 cykler. Hver cyklus var på 28 dage. Median opfølgningstid var 28,1 måneder [38].

### **Furman-studiet (NCT01539512)**

Furman-studiet er et multicenter, randomiseret, dobbelt-blindet, placebokontrolleret fase 3-studie, der inkluderede tidligere behandlede voksne patienter (> 18 år) med relapseret/refraktær CLL, som samtidig led af større komorbiditet, fx nedsat nyrefunktion, behandlingsinduceret myelosuppression eller CIRS > 6. Patienterne blev derudover randomiseret 1:1 til idelalisib + rituximab (n=110) eller placebo + rituximab (n=110). Oral idelalisib 150 mg blev administreret to gange dagligt. Placebo modtog matchende placebo. Alle patienter modtog derudover intravenøs rituximab 375 mg/m<sup>2</sup> efterfulgt af fire doser med 500 mg/m<sup>2</sup> hver anden uge og 500 mg/m<sup>2</sup> hver fjerde uge i tre doser, til de i alt havde modtaget 8 infusioner. Hvis patienterne i placebogruppen oplevede sygdomsprogression, blev de overflyttet til et andet studie og modtog idelalisib i stedet. Hvis patienterne i idelalisibgruppen oplevede sygdomsprogression, kunne dosis af idelalisib øges til 300 mg to gange dagligt. Studiet blev stoppet ved den første interimanalyse grundet overvældende effekt af idelalisib + rituximab [51].

### **HELIOS (NCT01611090)**

HELIOS er et internationalt, multicenter, dobbelt-blindet, placebokontrolleret fase 3-studie, der inkluderede tidligere behandlede voksne patienter (> 18 år) med relapseret/refraktær CLL eller småcellet lymfocytært lymfom. Patienterne blev randomiseret til 1:1 til ibrutinib + bendamustin + rituximab (n=289) eller placebo + bendamustin + rituximab (n=289). Oral ibrutinib 420 mg blev administreret én gang dagligt i kombination med intravenøs bendamustin (70 mg/m<sup>2</sup> på dag 2-3 i første cyklus, og dag 1-2 i cyklus 2-6) og intravenøs rituximab (375 mg/m<sup>2</sup> på dag 1 i første cyklus og 500 mg/m<sup>2</sup> på dag 1 i cyklus 2-6 i maksimum 6 cykler). Alle cykler var af 4 ugers varighed. Placebogruppen modtog bendamustin og rituximab i samme regime som ibrutinib-gruppen. En protokoljustering blev fortaget i starten af 2014 pga. de positive resultater for ibrutinib, som blev fundet i RESONATE-studiet. Det blev derfor muligt for patienter i placebogruppen at krydse over til ibrutinib-gruppen ved sygdomsprogression. Overkrydsning blev først implementeret, efter alle patienter var inkluderet i studiet. Median follow-up var 17 måneder [37].



#### **iLLUMINATE (NCT02264574)**

iLLUMINATE er et internationalt, multicenter, open-label, randomiseret fase 3-studie, der inkluderede patienter med tidligere ubehandlet CLL eller småcellet lymfocytært lymfom, som var  $\geq 65$  år eller under, hvis de led af andre sygdomme. Patienterne blev randomiseret 1:1 til ibrutinib + obinutuzumab (n=113) eller chlorambucil + obinutuzumab (n=116). Oral ibrutinib 420 mg blev givet én gang dagligt og kombineret med intravenøs obinutuzumab 100 mg på dag 1, 900 mg på dag 2, 1.000 mg på dag 8 og dag 15 i første cyklus og på dag 1 i de efterfølgende 6 cykler. Oral chlorambucil 0,5 mg/kg blev givet på dag 1 og 15 i hver af de 6 cykler og kombineret med obinutuzumab doseret i samme regime som beskrevet ovenfor. Alle cykler var på 28 dage. Patienter i chlorambucil + obinutuzumab-gruppen kunne krydse over til ibrutinib-gruppen ved bekræftet sygdomsprogression. Median follow-up var 31,3 måneder [11].

#### **Jones-studiet (NCT01659021)**

Jones-studiet er et internationalt, multicenter, open-label, kontrolleret, randomiseret fase 3-studie, der inkluderede tidligere behandlede voksne patienter ( $> 18$  år) med relapseret CLL inden for 24 måneder fra sidste behandling. Patienterne blev randomiseret 2:1 til idelalisib + ofatumumab (n=174) eller ofatumumab (n=87). Oral idelalisib 150 mg blev administreret to gange dagligt i kombination med intravenøs ofatumumab, som blev administreret efter regimet: 300 mg i uge 1, 1.000 mg ugentligt i 7 uger efterfulgt af 1.000 mg hver fjerde uge i 16 uger. Ofatumumab givet som monoterapi blev administreret efter samme regime som kombinationsgruppen, fraset at 2.000 mg substituerede de 1.000 mg. Median follow-up for idelalisib + ofatumumab-gruppen var 16,1 måneder, mens den for ofatumumab-gruppen var 5,8 måneder [42].

#### **MaBLLe (NCT 01056510)**

MaBLLe er et open-label, randomiseret studie, der inkluderede voksne patienter  $\geq 18$  år med CLL, hvor fludarabin ikke anbefales. Patienterne blev randomiseret 1:1 til rituximab + bendamustin (n=178) eller rituximab + chlorambucil (n=179). I rituximab + bendamustin-gruppen blev intravenøs rituximab 375 mg/m<sup>2</sup> administreret på dag 1 i den første cyklus. Herefter blev 500 mg/m<sup>2</sup> givet hver 4. uge i de følgende 2-6 cykler. Intravenøs bendamustin 90 mg/m<sup>2</sup> (1. linje) eller 70 mg/m<sup>2</sup> (2. linje) blev givet på dag 1 og 2 hver fjerde uge i cyklus 1-6. I rituximab + chlorambucil-gruppen blev samme regime for rituximab fulgt og administreret i kombination med oral chlorambucil 10 mg/m<sup>2</sup> på dag 1-7 i fire uger i op til 12 cykler. Patienter i rituximab + chlorambucil-gruppen uden komplet respons efter sjette cykel modtog chlorambucil givet som monoterapi i mindst 6 derpå følgende cykler eller indtil komplet respons. Median follow-up var 23,5 måneder [52].

#### **MURANO (NCT02005471)**

MURANO er et internationalt, multicenter, open-label, randomiseret fase 3-studie, der inkluderede tidligere behandlede voksne patienter ( $> 18$  år) med relapseret/refraktær CLL. Patienterne blev randomiseret til 1:1 til venetoclax + rituximab (n=194) eller bendamustin + rituximab (n=195). Oral venetoclax blev administreret i overensstemmelse med en 5-ugers optrappingsplan fra 200 mg pr. dag til 400 mg pr. dag. Efter fuldførelse af dosisoptrappingen blev behandlingen kombineret med intravenøs rituximab 375 mg/m<sup>2</sup> på dag 1 i første cyklus efterfulgt af 500 mg/m<sup>2</sup> på dag 1



i 2.-6. cyklus. Behandlingen med venetoclax kunne fortsættes i op til to år, såfremt patienterne ikke oplevede sygdomsprogression eller uacceptabel toksicitet. Intravenøs bendamustin 70 mg/m<sup>2</sup> blev administreret på dag 1 og 2 i 6 cykler. Rituximab blev i denne gruppe administreret efter det før omtalte regime. Alle cykler var på 28 dage. Median follow-up var 23,8 måneder [11]. En follow-up-artikel er udgivet i 2019 [53].

#### **RESONATE (NCT01578707)**

RESONATE er et internationalt, multicenter, open-label, randomiseret fase 3-studie, der inkluderer tidlige behandlede voksne patienter (> 18 år) med relapseret/refraktær CLL eller småcellet lymfocytært lymfom. Patienterne blev randomiseret 1:1 til ibrutinib (n=195) eller ofatumumab (n=196). Oral ibrutinib 420 mg blev administreret én gang dagligt indtil sygdomsprogression eller uacceptabel toksicitet. Intravenøs ofatumumab blev givet i op til 24 uger med en initial dosis på 300 mg i uge 1 efterfulgt af 2.000 mg ugentligt i syv uger samt 2.000 mg hver fjerde uge i 16 uger. Fire måneder efter den sidste patient blev randomiseret ind i studiet, muliggjorde en protokoljustering, at patienter, der modtog ofatumumab og oplevede sygdomsprogression, kunne skifte til ibrutinib. Median follow-up var 9,4 måneder [54]. Flere artikler, der vurderer langtidseffekten af ibrutinib, er publiceret igennem de senere år [11] [28] [29].

#### **RESONATE-2 (NCT01722487)**

RESONATE-2 er et internationalt, multicenter, open-label, randomiseret fase 3-studie, der inkluderer tidlige ubehandlede patienter ≥ 65 år med CLL eller småcellet lymfocytært lymfom. Patienterne blev randomiseret 1:1 til ibrutinib (n=136) eller chlorambucil (n=133). Oral ibrutinib 420 mg blev administreret én gang dagligt indtil sygdomsprogression eller udvikling af uacceptabel toksicitet. Oral chlorambucil blev givet i op til 12 cykler i doseringen 0,5 mg/kg på dag 1 og 15 i hver af de 28 dages cykler. Denne dosis kunne øges til maksimum 0,8 mg/kg. Behandlingen indstilles ved et uacceptabelt niveau af toksiner, sygdomsprogression eller manglende effekt. Overkrydsning var tilladt for patienter med sygdomsprogression. Median follow-up var 18,4 måneder [55]. Patienter med sygdomsprogression blev optaget i et separat *extension*-studie PCYC-1116/NCT01724346 [22] [23].

#### **Zelenetz (NCT01569295)**

Zelenetz-studiet er et internationalt, multicenter, dobbeltblindet, placebokontrolleret, randomiseret fase 3-studie, der inkluderer tidlige behandlede voksne patienter (> 18 år) med relaps CLL. Patienterne blev randomiseret 1:1 til at modtage idelalisib (n=207) eller placebo (n=209) i kombination med bendamustin + rituximab. Begge arme modtog intravenøs bendamustin 70 mg/m<sup>2</sup> på dag 1 og 2 i 6 cykler af 28 dage og intravenøs rituximab efter regimet: 375 mg/m<sup>2</sup> på dag 1 i første cyklus efterfulgt af 500 mg/m<sup>2</sup> på dag 1 i 2.-6. cyklus. Oral idelalisib 150 mg eller tilsvarende placebo blev givet to gange dagligt til sygdomsprogression eller uacceptabel toksicitet. Overkrydsning var ikke tilladt. Median follow-up var 14 måneder [43].





## 12.1 Bilag 2: Gennemgang af udvalgte baselinekarakteristika, som indgår i de forskellige analyser

**Tabel 40. Udvalgte baselinekarakteristika for ELEVATE-TN studiet, som indgår i den direkte sammenligning (acalabrutinib vs. obinutuzumab + chlorambucil) [8]**

Karakteristika	Acalabrutinib (n=179)	Obinutuzumab + chlorambucil (n=177)
Alder, median, år (IQR)	70,0 (66,0-75,0)	71,0 (67,0-76,0)
Kreatinin-clearance 30-69 ml/min.	4 (2,2)	7 (4)
CIRS-G > 6	21 (11,7)	15 (8,5)
ECOG PS		
0-1	165 (92,2)	167 (94,4)
2	14 (7,8)	10 (5,6)
Rai stadium		
0	0	1 (0,6)
I	48 (26,8)	50 (28,2)
II	44 (24,6)	48 (27,1)
III	50 (27,9)	40 (22,6)
IV	37 (20,7)	38 (21,5)
Høj risikofaktorer		
17p13 1 deletion	16 (8,9)	16 (9,0)
11q22 3 deletion	31 (17,3)	33 (18,6)
Ikke muteret IGHV	119 (66,5)	116 (65,5)
Muteret p53	19 (10,6)	21 (11,9)
Kompleks karyotype	31 (17,3)	32 (18,1)
Med 17p13 1 deletion	8 (4,5)	7 (4,0)
Uden 17p13 1 deletion	23 (12,8)	25 (14,1)
17p13 1 deletion og/eller muteret p53	23 (12,8)	25 (14,1)
17p13 1 deletion og muteret p53	12 (6,7)	12 (6,8)
CIRS-G score, n, median (IQR)	115, 6,0 (3,0-8,0)	118, 5,5 (4,0-8,0)
Kreatinin-clearance (ml/min.)		
Median (IQR)	75,0 (58,0-98,0)	70,0 (55,0-90,0)
< 60 ml/min., n (%)	48 (26,8)	56 (31,6)
Tid fra initial diagnose, måneder, median (IQR)	24,4 (7,0-70,3)	30,7 (9,4-64,2)

Data er angivet som n (%), medmindre andet er specificeret. CIRS-G = Cumulative Illness Rating Scale for Geriatrics, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene.



**Tabel 41. Udvalgte baselinekarakteristika for studiearmene, som indgår i MAIC-analysen for 1. linjebehandling**

Karakteristika	ELEVATE-TN [8]		RESONATE-2 [55]		iLLUMINATE [11]		CLL14 [38]		ALLIANCE [24]			CLL11 [33]						
	Acalabrutinib + obinutuzumab	Acalabrutinib	Obinutuzumab + chlorambucil	Ibrutinib	Chlorambucil	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	Bendamustin + rituximab	Ibrutinib	Ibrutinib + rituximab	Obinutuzumab + chlorambucil	Chlorambucil	Rituximab + chlorambucil	Chlorambucil	Obinutuzumab + chlorambucil	Rituximab + chlorambucil
Antal patienter	179	179	177	136	133	113	116	216	216	183	182	182	238	118	233	118	333	330
Alder, median, år (IQR)	70 (65-75)	70 (66-75)	71 (67-76)	73 (65-89)	72 (65-90)	70 (60-75)	72 (66-77)	72	71	70 (65-86)	71 (65-89)	71 (65-86)	74 (39-88)	72 (43-87)	73 (40-90)	72 (43-87)	74 (39-89)	73 (40-90)
Del17p-mutation	10	9	9	NR	NR	12	16	8,5	7,3	8	5	6	8	10	5	10	7	7
Del11q-mutation	17	17	19	21	19	12	19	18	20	18	19	21	16	15	19	14	16	17
Muteret p53	12	11	12	NR	NR	12	15	11	8	9	9	12	NR	NR	NR	NR	NR	NR
Ikke muteret IGHV	58	67	66	43	45	62	53	61	59	58	63	61	61	59	62	58	62	61
Binet stadium																		
A	NR	NR	NR	NR	NR	NR	NR	21	20	NR	NR	NR	23	20	21	20	22	22
B	NR	NR	NR	NR	NR	NR	NR	36	37	NR	NR	NR	41	42	43	42	43	41
C	NR	NR	NR	NR	NR	NR	NR	43	43	NR	NR	NR	36	37	36	37	35	37
ECOG PS																		
0	51	50	49	44	41	50	46	41	48	54	48	47	NR	NR	NR	NR	NR	NR
1	44	42	46	48	50	46	48	46	41	41	49	52	NR	NR	NR	NR	NR	NR
2	6	8	6	8	9	4	6	13	12	5	3	1	NR	NR	NR	NR	NR	NR
Rai stadium																		
0	2	0	1	4	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
I	30	27	28	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
II	20	25	27	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
III	27	28	23	III/IV 44	III/IV 47	III/IV 53	III/IV 51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
IV	21	21	22					NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CIRS-score, median (IQR)	6 (3-8)*	6 (3-8)*	5,5 (3-8)*	NR	NR	4 (2-7)	4 (2-7)	NR	NR	NR	NR	NR	8 (1-20)	8 (0-18)	8 (0-18)	8 (0-18)	8 (0-22)	8 (0-18)



Karakteristika	ELEVATE-TN [8]		RESONATE-2 [55]		ILLUMINATE [11]		CLL14 [38]		ALLIANCE [24]			CLL11 [33]						
	Acalabrutinib + obinutuzumab	Acalabrutinib	Obinutuzumab + chlorambucil	Ibrutinib	Chlorambucil	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	Bendamustin + rituximab	Ibrutinib	Ibrutinib + retuximab	Obinutuzumab + chlorambucil	Chlorambucil	Rituximab + chlorambucil	Chlorambucil	Obinutuzumab + chlorambucil	Rituximab + chlorambucil
Andel patienter med en CIRS-score < 6	17*	12*	9*	31	33	33	31	86	82	NR	NR	NR	75	78	72	78	78	75
Andel patienter med en median kreatinin-clearance < 70 ml/min.	25 <sup>i</sup>	27 <sup>i</sup>	32 <sup>i</sup>	44 <sup>i</sup>	50 <sup>i</sup>	23 <sup>i</sup>	33 <sup>i</sup>	60	55	NR	NR	NR	24	21	27	21	22	25

Data er angivet i %, medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene, \*Opgjort på CIRS-G = Cumulative Illness Rating Scale for Geriatrics, <sup>i</sup>Andel patienter med en median kreatinin-clearance < 60 ml/min.



**Table 42. Udvalgte baselinekarakteristika for studiearmene, som indgår i NMA-analysen for 1. linjebehandling**

Karakteristika	COMPLE- MENT1 [50]		RESONATE- 2 [55]		CAM-307 [32]		ILLUMI- NATE [11]		ALLIANCE [24]		CLL11 [33]		MaBLe [52]		ELEVATE-TN [8]		CLL14 [38]									
	Chlorambucil Chlorambucil + Ofatumumab	Ibrutinib	Chlorambucil	Alemtuzumab	Chlorambucil	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Bendamustin + rituximab	Ibrutinib	Ibrutinib + rituximab	Obinutuzumab + chlorambucil	Chlorambucil	Rituximab + chlorambucil	Chlorambucil	Obinutuzumab + chlorambucil	Rituximab + chlorambucil	Rituximab + bendamustin	Rituximab + chlorambucil	Acalabrutinib + obinutuzumab	Acalabrutinib	Obinutuzumab + chlorambucil	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab			
Antal patienter	226	221	136	133	149	148	113	116	183	182	182	238	118	233	118	333	330	121	120	179	179	177	216	216		
Alder, median, år (IQR)	70 (36- 91)	69 (35- 92)	73 (65- 89)	72 (65- 90)	59 (35- 86)	60 (36- 83)	70 (60- 75)	72 (66- 77)	70 (65- 86)	71 (65- 89)	71 (65- 86)	74 (39- 88)	72 (43- 87)	73 (40- 90)	72 (43- 87)	74 (39- 89)	73 (40- 90)	72 (41- 86)	72 (38- 91)	70 (65- 75)	70 (66- 75)	71 (67- 76)	72	71		
Del17p-mutation	8	5	NR	NR	7,7	7,2	12	16	8	5	6	8	10	5	10	7	7	8	3	10	9	9	8,5	7,3		
Del11q-mutation	11	19	21	19	16	22	12	19	18	19	21	16	15	19	14	16	17	20	16	17	17	19	18	20		
Muteret p53	NR	NR	NR	NR	NR	NR	12	15	9	9	12	NR	NR	NR	NR	NR	NR	NR	NR	12	11	12	11	8		
Ikke muteret IGHV	56	57	43	45	NR	NR	62	53	58	63	61	61	59	62	58	62	61	60	49	58	67	66	61	59		
Binet stadium																										
A	31	35	NR	NR	NR	NR	NR	NR	NR	NR	NR	23	20	21	20	22	22	5	7	NR	NR	NR	21	20		
B	38	33	NR	NR	NR	NR	NR	NR	NR	NR	NR	41	42	43	42	43	41	60	55	NR	NR	NR	36	37		
C	31	32	NR	NR	NR	NR	NR	NR	NR	NR	NR	36	37	36	37	35	37	31	36	NR	NR	NR	43	43		
ECOG PS																										
0	38	39	44	41	NR	NR	50	46	54	48	47	NR	NR	NR	NR	NR	NR	51	49	51	50	49	41	48		
1	54	53	48	50	NR	NR	46	48	41	49	52	NR	NR	NR	NR	NR	NR	41	43	44	42	46	46	41		
2	8	8	8	9	NR	NR	4	6	5	3	1	NR	NR	NR	NR	NR	NR	7	7	6	8	6	13	12		
Rai stadium																										
0	NR	NR	NR	NR	4	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2	0	1	NR	NR
I	NR	NR	NR	NR	I/II	I/II	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	30	27	28	NR	NR
II	NR	NR	NR	NR	62	65	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	20	25	27	NR	NR	
III	NR	NR	III/IV	III/IV	III/IV	III/IV	III/IV	III/IV	III/IV	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	27	28	23	NR	NR	
IV	NR	NR	44	47	34	33	53	51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	21	21	22	NR	NR	



Karakteristika	COMPLE- MENT1 [50]	RESONATE- 2 [55]	CAM-307 [32]	iLLUMI- NATE [11]	ALLIANCE [24]	CLL11 [33]	MaBLe [52]	ELEVATE-TN [8]	CLL14 [38]															
	Chlorambucil Chlorambucil + Ofatumumab	Ibrutinib	Chlorambucil	Alemtuzumab	Chlorambucil	Ibrutinib + obinituzumab	Chlorambucil + obinituzumab	Bendamustin + rituximab	Ibrutinib	Ibrutinib + rituximab	Obinituzumab + chlorambucil	Chlorambucil	Rituximab + chlorambucil	Chlorambucil	Obinituzumab + chlorambucil	Rituximab + chlorambucil	Rituximab + bendamustin	Rituximab + chlorambucil	Acalabrutinib + obinituzumab	Acalabrutinib	Obinituzumab + chlorambucil	Venetoclax + obinituzumab	Chlorambucil + obinituzumab	
CIRS-score, median (IQR)	8 (4- 19)	9 (4- 21)	NR	NR	NR	4 (2- 7)	4 (2- 7)	NR	NR	NR	8 (1- 20)	8 (0- 18)	8 (0- 18)	8 (0- 18)	8 (0- 22)	8 (0- 18)	NR	NR	6 (3- 8)*	6 (3- 8)*	5,5 (3- 8)*	NR	NR	
Andel patienter med en CIRS-score > 6	NR	NR	31	33	NR	NR	33	31	NR	NR	NR	75	78	72	78	78	75	NR	NR	17*	12*	9*	86	82
Andel patienter med en median kreatinin- clearance < 70 ml/min.	51	45	44 <sup>i</sup>	50 <sup>i</sup>	NR	NR	23 <sup>i</sup>	33 <sup>i</sup>	NR	NR	NR	24	21	27	21	22	25	NR	NR	25 <sup>i</sup>	27 <sup>i</sup>	32 <sup>i</sup>	60	55

Data er angivet i %, medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene. \*Opgjort på CIRS-G = Cumulative Illness Rating Scale for Geriatrics, <sup>i</sup>Andel patienter med en median creatinine clearance < 60 ml/min.



**Tabel 43. Udvalgte baselinekarakteristika for ELEVATE-TN, ALLIANCE, CLL10 og MaBLE, som indgår i narrativ sammenligning (acalabrutinib vs. bendamustin + rituximab)**

Karakteristika	ELEVATE-TN [8] Acalabrutinib (n=179)	ALLIANCE [24], Bendamustin + rituximab (n=183)	CLL10 [16], Bendamustin + rituximab (n=279)	MaBLE [52], Bendamustin + rituximab (n=121)
Alder, median, år (IQR)	70,0 (66,0-75,0)	70 (65-86)	61,0 (54,0-69,0)	72 (41-86)
Tid fra initial diagnose, måneder, median (IQR)	24,4 (7,0-70,3)	NR	24,6 (6,2-50,1)	NR
CIRS-score, median (IQR)	6,0 (3,0-8,0) <sup>i</sup>	NR	2,0 (0-3,0)	NR
Median kreatinin-clearance (IQR)	75,0 (58,0-98,0)	NR	86,4 (72,6-101,6)	NR
Binet stadium				
A	NR	NR	62 (22)	6 (5)
B	NR	NR	107 (38)	73 (60)
C	NR	NR	110 (39)	37 (31)
ECOG PS				
0		98 (54)	177 (64)	62 (51)
1	165 (92,2)*	75 (41)	98 (36)	50 (41)
2	14 (7,8)	10 (5)	1 (<1)	9 (7)
Rai stadium				
0	0	NR	11 (5)	NR
I	48 (26,8)	NR	32 (14)	NR
II	44 (24,6)	NR	84 (37)	NR
III	50 (27,9)	NR	34 (15)	NR
IV	37 (20,7)	NR	65 (29)	NR
Højrisikofaktorer				
Del17p-mutation	16 (8,9)	14 (8)	NR	10 (8)
Del11q-mutation	31 (17,3)	33 (18)	63 (23)	24 (20)
Ikke muteret IGHV	119 (66,5)	71 (58)	183 (68)	73 (60)
Muteret p53	19 (10,6)	16 (9)	NR	NR

Data er angivet som n (%), medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene, \* ECOG PS 0+1, <sup>i</sup>Opgjort på CIRS-G = Cumulative Illness Rating Scale for Geriatrics.

**Tabel 44. Udvalgte baselinekarakteristika for ELEVATE-TN-studiet (acalabrutinib + obinutuzumab vs. obinutuzumab + chlorambucil) [8]**

Karakteristika	Acalabrutinib + obinutuzumab (n=179)	Obinutuzumab + chlorambucil (n=177)
Alder, median, år (IQR)	70,0 (65,0-75,0)	71,0 (67,0-76,0)
Kreatinin-clearance 30-69 ml/min.	2 (1,1)	7 (4)
CIRS-G > 6	30 (16,8)	15 (8,5)
ECOG PS		
0-1	68 (38,0)	167 (94,4)
2	111 (62,0)	10 (5,6)
Rai stadium		
0	30 (1,7)	1 (0,6)
I	54 (30,2)	50 (28,2)
II	36 (20,1)	48 (27,1)



Karakteristika	Acalabrutinib + obinutuzumab (n=179)	Obinutuzumab + chloramabucil (n=177)
III	48 (26,8)	40 (22,6)
IV	38 (21,2)	38 (21,5)
Højrisikofaktorer		
17p13 1 deletion	17 (9,5)	16 (9,0)
11q22 3 deletion	31 (17,3)	33 (18,6)
Ikke muteret IGHV	103 (57,5)	116 (65,5)
Muteret p53	21 (11,7)	21 (11,9)
Kompleks karyotype	29 (16,2)	32 (18,1)
med 17p13 1 deletion	8 (4,5)	7 (4,0)
Uden 17p13 1 deletion	21 (11,7)	25 (14,1)
17p13 1 deletion og/eller muteret p53	25 (14,4)	25 (14,1)
17p13 1 deletion og muteret p53	13 (7,3)	12 (6,8)
CIRS-G-score, n, median (IQR)	117, 6,0 (3,0-8,0)	118, 5,5 (4,0-8,0)
Kreatinin-clearance (ml/min.)		
Median (IQR)	76,5 (59,0-92,5)	70,0 (55,0-90,0)
< 60 ml/min., n (%)	45 (25,1)	56 (31,6)
Tid fra initial diagnose, måned, median (IQR)	30,5 (9,4-70,7)	30,7 (9,4-64,2)

Data er angivet som n (%), medmindre andet er specificeret. CIRS-G = Cumulative Illness Rating Scale for Geriatrics, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene.

**Tabel 45. Udvalgte baselinekarakteristika for ELEVATE-TN, ALLIANCE, CLL10 og MaBLé, som indgår i narrativ sammenligning (acalabrutinib + obinutuzumab vs. bendamustin + rituximab)**

Karakteristika	ELEVATE-TN [8] Acalabrutinib + obinutuzumab (n=179)	ALLIANCE [24], Bendamustin + rituximab (n=183)	CLL10 [16], Bendamustin + rituximab (n=279)	MaBLé [52], Bendamustin + rituximab (n=121)
Alder, median, år (IQR)	70,0 (65,0-75,0)	70 (65-86)	61,0 (54,0- 69,0)	72 (41-86)
Tid fra initial diagnose, måneder, median (IQR)	30,5 (9,4-70,7)	NR	24,6 (6,2-50,1)	NR
CIRS-score, median (IQR)	6,0 (3,0-8,0) <sup>i</sup>	NR	2,0 (0-3,0)	NR
Median kreatinin- clearance (IQR)	76,5 (59,0-92,5)	NR	86,4 (72,6-101,6)	NR
Binet stadium				
A	NR	NR	62 (22)	6 (5)
B	NR	NR	107 (38)	73 (60)
C	NR	NR	110 (39)	37 (31)
ECOG PS				
0		98 (54)	177 (64)	62 (51)
1	68 (38,0)*	75 (41)	98 (36)	50 (41)
2	111 (62,0)	10 (5)	1 (< 1)	9 (7)
Rai stadium				
0	30 (1,7)	NR	11 (5)	NR
I	54 (30,2)	NR	32 (14)	NR
II	36 (20,1)	NR	84 (37)	NR
III	48 (26,8)	NR	34 (15)	NR
IV	38 (21,2)	NR	65 (29)	NR



Karakteristika	ELEVATE-TN [8] Acalabrutinib + obinutuzumab (n=179)	ALLIANCE [24], Bendamustin + rituximab (n=183)	CLL10 [16], Bendamustin + rituximab (n=279)	MaBLé [52], Bendamustin + rituximab (n=121)
Højrisikofaktorer				
Del17p mutation	17 (9,5)	14 (8)	NR	10 (8)
Del11q mutation	31 (17,3)	33 (18)	63 (23)	24 (20)
Ikke muteret IGHV	103 (57,5)	71 (58)	183 (68)	73 (60)
Muteret p53	21 (11,7)	16 (9)	NR	NR

Data er angivet som n (%), medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene, \*ECOG PS 0+1, <sup>i</sup>CIRS-G = Cumulative Illness Rating Scale for Geriatrics.

**Tabel 46. Udvalgte baselinekarakteristika for ELEVATE-RR-studiet (acalabrutinib vs. ibrutinib) [45]**

Karakteristika	Acalabrutinib (n=268)	Ibrutinib (n=265)
Alder, median, år (IQR)	66 (41-89)	65 (28-88)
ECOG PS		
0-1	247 (92,2)	243 (91,7)
2	20 (7,5)	22 (8,3)
Rai stadium 3 eller 4	131 (48,9)	134 (50,6)
Højrisikofaktorer		
17p13 1 deletion	121 (45,1)	120 (45,3)
11q22 3 deletion	167 (62,3)	175 (66,0)
Ikke muteret IGHV	220 (82,1)	237 (89,4)
Muteret p53	100 (37,3)	112 (42,3)
Kompleks karyotype	124 (46,3)	125 (47,2)
Antal tidligere behandlinger		
1-3	234 (87,3)	237 (89,4)
4 eller flere	33 (12,3)	28 (10,6)
Hyppigst anvendte tidligere behandlinger		
Alkylatorer	242 (90,3)	240 (90,6)
Anti-CD20 monoklonale antistoffer	227 (84,7)	229 (86,4)
Purinanaloger	172 (64,2)	158 (59,6)
Steroider	62 (23,1)	62 (23,4)
Kemoterapi*	39 (14,6)	37 (14,0)
Alemtuzumab	16 (6,0)	11 (4,2)
Lenalidomid (monoterapi og i kombination)	5 (1,9)	13 (4,9)

Data er angivet som n (%), medmindre andet er specificeret. ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene. \*Inkluderer doxorubicin, bleomycin, vinca/alkaloïder, etoposid og platinbaserede regimer.





**Tabel 47. Udvalgte baselinekarakteristika for ELEVATE-TN, RESONATE-2 og Ahn 2018, som indgår i den narrative sammenligning (acalabrutinib vs. ibrutinib)**

Karakteristika	ELEVATE-TN [8], Acalabrutinib (n=179)	RESONATE-2 [55], Ibrutinib (n=136)	Ahn [25], Ibrutinib (p53 kohorte, n=51)	Ahn [25], Ibrutinib, (ældre kohorte, n=35)
Alder, median, år (IQR)	70,0 (66,0-75,0)	73 (65-89)	62 (33-82)	69 (63-85)
Tid fra initial diagnose, måneder, median (IQR)	24,4 (7,0-70,3)	31 (1-241)	NR	NR
CIRS-score, median (IQR)	6,0 (3,0-8,0) <sup>i</sup>	NR	NR	NR
CIRS > 6	21 (11,7) <sup>i</sup>	42 (31)	NR	NR
Median kreatinin-clearance (IQR)	75,0 (58,0-98,0)	NR	NR	NR
Kreatinin-clearance < 60 ml/min.	48 (26,8)	60 (44)	NR	NR
ECOG PS				
0	165 (92,2) <sup>†</sup>	60 (44)	NR	NR
1		65 (48)	NR	NR
2	14 (7,8)	11 (8)	NR	NR
Rai stadium				
0	0	NR	NR	NR
I	48 (26,8)	NR	19 (37,3)*	9 (25,7)*
II	44 (24,6)	NR		
III	50 (27,9)			
IV	37 (20,7)	60 (44)*	32 (62,7)*	26 (74,3)*
Højrisikofaktorer				
Del17p-mutation	16 (8,9)	NR	47 (92,2)	3 (8,6)
Del11q-mutation	31 (17,3)	29 (21)	NR	NR
Ikke muteret IGHV	119 (66,5)	58 (43)	34 (66,7)	23 (65,7)
Muteret p53	19 (10,6)	NR	4 (7,8)	0 (0)

Data er angivet som n (%), medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene, \*Rai stadium 1+2 eller 3+4, <sup>i</sup>Opgjort på CIRS-G = Cumulative Illness Rating Scale for Geriatrics, <sup>†</sup>ECOG PS 0+1.

**Tabel 48. Udvalgte baselinekarakteristika for ELEVATE-TN, RESONATE-2 og Ahn 2018, som indgår i narrative sammenligning (acalabrutinib + obinutuzumab vs. ibrutinib)**

Karakteristika	ELEVATE-TN [8] Acalabrutinib + obinutuzumab (n=179)	RESONATE-2 [55], Ibrutinib (n=136)	Ahn [25] (p53 kohorte, n=51), ibrutinib	Ahn [25] (ældre kohorte, n=35), ibrutinib
Alder, median, år (IQR)	70,0 (65,0-75,0)	73 (65-89)	62 (33-82)	69 (63-85)
Tid fra initial diagnose, måneder, median (IQR)	30,5 (9,4-70,7)	31 (1-241)	NR	NR
CIRS-score, median (IQR)	6,0 (3,0-8,0) <sup>i</sup>	NR	NR	NR
CIRS > 6	30 (16,8) <sup>i</sup>	42 (31)	NR	NR
Median kreatinin-clearance (IQR)	76,5 (59,0-92,5)	NR	NR	NR
Kreatinin-clearance < 60 ml/min.	45 (25,1)	60 (44)	NR	NR



Karakteristika	ELEVATE-TN [8] Acalabrutinib + obinutuzumab (n=179)	RESONATE-2 [55], Ibrutinib (n=136)	Ahn [25] (p53 kohorte, n=51), ibrutinib	Ahn [25] (ældre kohorte, n=35), ibrutinib
ECOG PS				
0		60 (44)	NR	NR
1	68 (38,0) <sup>†</sup>	65 (48)	NR	NR
2	111 (62,0)	11 (8)	NR	NR
Rai stadium				
0	30 (1,7)	NR	NR	NR
I	54 (30,2)	NR	19 (37,3)*	9 (25,7)*
II	36 (20,1)	NR		
III	48 (26,8)	60 (44)*	32 (62,7)*	26 (74,3)*
IV	38 (21,2)			
Højrisikofaktorer				
Del17p-mutation	17 (9,5)	NR	47 (92,2)	3 (8,6)
Del11q-mutation	31 (17,3)	29 (21)	NR	NR
Ikke muteret IGHV	103 (57,5)	58 (43)	34 (66,7)	23 (65,7)
Muteret p53	21 (11,7)	NR	4 (7,8)	0 (0)

Data er angivet som n (%), medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene, \*Rai stadium 1+2 eller 3+4, <sup>†</sup>Opgjort på CIRS-G = Cumulative Illness Rating Scale for Geriatrics, <sup>‡</sup>ECOG PS 0+1.

**Tabel 49. Udvalgte baselinekarakteristika for studiearmene, som indgår i MAIC-analysen for 2. linjebehandling**

Karakteristika	ASCEND [49]		RESONATE [54] [29]		MURANO [56]	
	Acalabrutinib	Investigator's choice	Ibrutinib	Ofatumumab	Venetoclax + rituximab	Bendamustin + rituximab
Antal patienter	155	155	195	196	194	195
Alder, median, år (IQR)	68 (32- 89)	67 (34- 90)	67 (30- 86)	67 (37- 88)	65 (28- 83)	66 (22- 85)
Del17p-mutation	28 (18)	21 (14)	63 (32)	64 (33)	46 (27)	46 (27)
Del11q-mutation	39 (25)	44 (29)	63 (33)	59 (31)	NR	NR
Muteret p53	39 (26)	34 (22)	79 (51)	68 (46)	48 (25)	51 (28)
Ikke muteret IGHV	118 (77)	125 (82)	98 (73)	83 (63)	123 (68)	123 (68)
ECOG PS						
0	58 (37)	55 (35)	79 (41)	80 (41)	111 (57)	108 (56)
1	78 (50)	79 (51)	116 (59)	116 (59)	82 (68)	84 (43)
2	19 (12)	21 (14)	NR	NR	30 (23)	2 (1)
Rai stadium						
0	NR	NR	5 (3)	2 (1)		
I	NR	NR	51 (26)	42 (21)	88 (68)*	103 (74)*
II	NR	NR	30 (15)	39 (20)		
III			23 (12)	35 (18)	30 (23)*	18 (13)*
IV	65 (42)*	64 (41)*	86 (44)	78 (40)		
Andel patienter med en median kreatinin-clearance < 70 ml/min.	41 (26) <sup>i</sup>	37 (24) <sup>i</sup>	NR	NR	NR	NR

Data er angivet i n (%), medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene, \*Rai stadium 0+1+2 eller 3+4, <sup>i</sup>Andel af patienter med en median kreatinin-clearance < 60 ml/min.



**Tabel 50. Udvalgte baselinekarakteristika for studiearmene, som indgår i NMA-analysen for 2. linjebehandling**

Karakteristika	ASCEND [49]		RESONATE [54] [29]		MURANO [56]		Furman [51]		Jones [42]		HELIOS [37]		Huang [57]		Zelentz [43]	
	Acalabrutinib	Investigator's choice	Ibrutinib	Ofatumumab	Venetoclax + rituximab	Bendamustin + rituximab	Idelalisib + rituximab	Placebo + rituximab	Idelalisib + ofatumumab	Ofatumumab	Ibrutinib + B + R	Placebo + B + R	Ibrutinib	Rituximab	Idelalisib + B + R	Placebo + B + R
Antal patienter	155	155	195	196	194	195	110	110	174	87	289	289	106	54	207	209
Alder, median, år (IQR)	68 (32-89)	67 (34-90)	67 (30-86)	67 (37-88)	65 (28-83)	66 (22-85)	71 (48-90)	71 (47-92)	68 (61-74)	67 (62-74)	64 (31-86)	63 (36-83)	65 (39-87)	67 (21-86)	62 (56-69)	64 (56-70)
Del17p-mutation	28 (18)	21 (14)	63 (32)	64 (33)	46 (27)	46 (27)	42 % <sup>¥</sup>	45 % <sup>¥</sup>	70 (40) <sup>¥</sup>	33 (38) <sup>¥</sup>	NR	NR	23 (22)	13 (24)	38 (18)	40 (19)
Del11q-mutation	39 (25)	44 (29)	63 (33)	59 (31)	NR	NR	NR	NR	NR	NR	87 (30)	65 (22)	22 (21)	12 (22)	NR	NR
Muteret p53	39 (26)	34 (22)	79 (51)	68 (46)	48 (25)	51 (28)	42 % <sup>¥</sup>	45 % <sup>¥</sup>	70 (40) <sup>¥</sup>	33 (38) <sup>¥</sup>	NR	NR	NR	NR	69 (33) <sup>¥</sup>	68 (34) <sup>¥</sup>
Ikke muteret IGHV	118 (77)	125 (82)	98 (73)	83 (63)	123 (68)	123 (68)	83 %	85 %	137 (79)	68 (78)	210 (81)	208 (80)	63 (59)	35 (65)	173 (84)	173 (83)
Binet stadium																
A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	26 (10)	23 (9)	2 (2)	4 (8)	NR	NR
B	NR	NR	NR	NR	NR	NR	NR	NR	NR	51 (29)	29 (33)	132 (52)	119 (46)	25 (25)	10 (20)	NR
C	NR	NR	NR	NR	NR	NR	NR	NR	NR	107 (62)	45 (52)	98 (38)	116 (45)	73 (73)	37 (73)	NR
ECOG PS																
0	58 (37)	55 (35)	79 (41)	80 (41)	111 (57)	108 (56)	NR	NR	NR	NR	125 (43)	126 (44)	54 (51)	23 (43)	NR	NR
1	78 (50)	79 (51)	116 (59)	116 (59)	82 (68)	84 (43)	NR	NR	NR	NR	164 (57)	163 (56)	52 (49)	31 (57)	NR	NR
2	19 (12)	21 (14)	NR	NR	30 (23)	2 (1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rai stadium																
0	NR	NR	5 (3)	2 (1)			0 %	1 %	NR	NR			0	0	NR	NR
I	NR	NR	51 (26)	42 (21)	88 (68)*	103 (74)*	31 %*	26 %*	NR	NR	157 (61)*	139 (54)*	9 (9)	11 (22)	40 (19)	41 (20)
II	NR	NR	30 (15)	39 (20)					26 (15)	21 (24)			11 (11)	3 (6)	61 (30)	71 (34)
III			23 (12)	35 (18)			64 %*	65 %*	24 (14)	10 (12)			18 (18)	9 (18)	20 (10)	16 (8)
IV	65 (42)*	64 (41)*	86 (44)	78 (40)	30 (23)*	18 (13)*			93 (53)	39 (45)	99 (39)*	119 (46)*	61 (62)	28 (55)	82 (40)	69 (33)
CIRS-score, median (IQR)	NR	NR	NR	NR	NR	NR	NR	NR	4 (2-7)	4 (2-7)	NR	NR	NR	NR	NR	NR



Karakteristika	ASCEND [49]		RESONATE [54] [29]		MURANO [56]		Furman [51]		Jones [42]		HELIOS [37]		Huang [57]		Zelentez [43]	
	Acalabrutinib	Investigator's choice	Ibrutinib	Ofatumumab	Venetoclax + rituximab	Bendamustin + rituximab	Idelalisib + rituximab	Placebo + rituximab	Idelalisib + ofatumumab	Ofatumumab	Ibrutinib + B + R	Placebo + B + R	Ibrutinib	Rituximab	Idelalisib + B + R	Placebo + B + R
Andel patienter med en CIRS-score > 6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Andel patienter med en median kreatinin-clearance < 70 ml/min.	41 (26) <sup>i</sup>	37 (24) <sup>i</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Data er angivet i n (%), medmindre andet er specificeret. CIRS = Cumulative Illness Rating Scale, ECOG PS = Eastern Cooperative Oncology Group performance status, B+R = bendamustin + rituximab, IGHV = immunoglobulin heavy-chain variable gene, IQR = interquartile range, p53 = cellular tumour antigen p53 gene, \*Rai stadium 0+1+2 eller 1+2 eller 3+4, <sup>i</sup>Andel patienter med en median kreatinin-clearance < 60 ml/min., <sup>†</sup>17p-deletion eller p53-mutation.



## Bilag 3: Gennemgang Cochrane – risiko for bias

Vurdering af risiko for bias ved [Cochrane risk of bias tool 2.0](#).

**Tabel 51. Vurdering af risiko for bias Sharman et al., 2020, ELEVATE-TN, NCT02475681**

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	Lav	Randomiseringen blev gennemført vha. <i>interactive voice and web response system</i> med stratificering på udvalgte parametre: "Patients were randomly assigned (1:1:1) via a centralised interactive voice and web response system to receive acalabrutinib-obinutuzumab, acalabrutinib monotherapy, or obinutuzumab-chlorambucil. Patients were stratified based on the presence or absence of del(17)(p13-1), ECOG PS score (0-1 vs 2), and geographic region (North America, western Europe, or other)."
Effekt af tildeling til intervention	Forbehold	Studiet var open-label, og behandlingen var ublindt for studiepersonale og patienter. Når patienter ikke er blandede for interventionen, er der risiko for, at patienternes præferencer påvirker, i hvilken grad bivirkninger/uønskede hændelser rapporteres og tolereres inden eventuelt behandlingsophør. For disse effektmål er der derfor risiko for bias. For OS og PFS vurderes den manglende blinding ikke at have betydning.
Manglende data for effektmål	Lav	Effektmålene blev analyseret for intent-to-treat-populationen, mens sikkerhed blev analyseret for de patienter, der modtog mindst én dosis studiemedicin: "Efficacy was analysed in the intention-to-treat population according to the randomly assigned treatment group. Safety was analysed in all patients who received at least one dose of any study medication."
Risiko for bias ved indsamlingen af data	Lav	Behandlingen var blindet for den uafhængige komité, der analyserede resultaterne: "An independent data monitoring committee periodically reviewed safety data and efficacy results in the planned interim analysis. A masked independent review committee (IRC) assessed progression and response data. The study sponsor did not do any aggregated analyses by treatment group until after the IRC had been unmasked."
Risiko for bias ved udvælgelse af resultater, der rapporteres	Lav	Forud for studiet blev der lavet en plan for de udførte statistiske analyser. Denne er tilgængelig i det udgivne <i>supplementary appendix</i> og indeholder de nødvendige detaljer.
<b>Overordnet risiko for bias</b>	<b>Lav</b>	Data er indsamlet og analyseret efter en udførlig plan. Det vurderes derfor, at den samlede risiko for bias er lav.



**Tabel 52. Vurdering af risiko for bias Byrd et al., 2021, ELEVATE-RR, NCT-02477696**

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	Lav	Randomiseringen blev gennemført vha. <i>interactive web response system</i> med stratificering på udvalgte parametre og uden mulighed for cross over: <i>"An interactive web response system randomly assigned eligible patients in a 1:1 ratio to receive oral acalabrutinib 100 mg twice daily or ibrutinib 420 mg once daily (openlabel) until disease progression or unacceptable toxicity. Random assignment was stratified by del(17)(p13.1) status (yes or no), Eastern Cooperative Oncology Group performance status score (2 v 1 or less), and number of prior therapies (1-3 v 4 or more). Crossover between treatment groups was not permitted."</i>
Effekt af tildeling til intervention	Forbehold	Studiet var open-label, og behandlingen var ublindt for studiepersonale og patienter. Når patienter ikke er blinde for interventionen, er der risiko for, at patienternes præferencer påvirker, i hvilken grad bivirkninger/uønskede hændelser rapporteres og tolereres inden eventuelt behandlingsophør. For disse effektmål er der derfor risiko for bias. For OS og PFS vurderes den manglende blinding ikke at have betydning.
Manglende data for effektmål	Lav	<i>"Efficacy analyses were performed for the intent to-treat population (all randomly assigned patients). Safety analyses, including the safety secondary end points, were performed for the safety population (all patients who received at least one dose of study drug)."</i>
Risiko for bias ved indsamlingen af data	Lav	Behandlingen var blindet for den uafhængige komité, der analyserede resultaterne: <i>"An independent review committee (IRC) centrally assessed progression and response data in a blinded manner. An independent data monitoring committee periodically reviewed unblinded safety and efficacy data. The study team was blinded to data at the aggregate level from the start of the study until after the final data transfer from the IRC and finalization of the statistical analysis plan. The study sponsor performed aggregated analyses by treatment group after final results were received from the IRC."</i>
Risiko for bias ved udvælgelse af resultater, der rapporteres	Lav	Forud for studiet blev der lavet en plan for de udførte statistiske analyser. Denne er tilgængelig i det udgivne supplement og indeholder alle de nødvendige detaljer sammen med protokollen.
<b>Overordnet risiko for bias</b>	Lav	Data er indsamlet og analyseret efter en på forhånd angivet udførlig protokol. Det vurderes derfor, at den samlede risiko for bias er lav.

# Application for the assessment of Calquence (acalabrutinib) as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy.

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## 1 Basic information

Table 1. Contact information

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Table 2 Overview of the pharmaceutical

Proprietary name	Calquence
Generic name	Acalabrutinib
Marketing authorization holder in Denmark	AstraZeneca AB, SE-151 85 Södertälje Sverige
ATC code	L01XE51
Pharmacotherapeutic group	BTK inhibitor
Active substance(s)	Acalabrutinib is a protein kinase inhibitor which acts by inhibiting the Bruton tyrosine kinase (BTK), thus preventing signaling for B-cell survival and proliferation and resulting in blocking cellular adhesion, trafficking, and chemotaxis.
Pharmaceutical form(s)	Capsules (blisters). 100 mg x 2 times daily (every 12 <sup>th</sup> hour).
Mechanism of action	Acalabrutinib is a protein kinase inhibitor which acts by inhibiting the Bruton tyrosine kinase (BTK), thus preventing signaling for B-cell survival and proliferation and resulting in blocking cellular adhesion, trafficking, and chemotaxis.
Dosage regimen	100 mg x 2 times daily (every 12 <sup>th</sup> hour).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	<ul style="list-style-type: none"> <li>• Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).</li> <li>• Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.</li> </ul>
Other approved therapeutic indications	CLL is the first indication for Calquence in Denmark
Will dispensing be restricted to hospitals?	Yes. Label BEGR
Combination therapy and/or co-medication	Calquence mono and in combination with obinutuzimab
Packaging – types, sizes/number of units, and concentrations	10 x 6 capsules in one pack
Orphan drug designation	Yes. EMA is currently reviewing if the orphan designation can be maintained

## 2 Abbreviations

ACA	Acalabrutinib
AE	Adverse event
BCL	B-cell lymphoma
BCR	B-cell receptor
BID	Bis in die (twice a day)
BM	Bone marrow
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CrCl	Creatine clearance
CYP	Cytochrome P450
del	Deletion
DP	Disease progression
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
FN	Febrile neutropenia
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplantation
IB	Ibrutinib
IGHV	Immunoglobulin G heavy chain variable
IRC	Independent Review Committee
i.v.	Intravenous
KM	Kaplan-Meier
iwCLL	International workshop on chronic lymphocytic leukaemia
MAIC	Matching-adjusted indirect comparison
NCCN	National Comprehensive Cancer Network
NMA	Network meta-analysis
nPR	Nodular partial response
NR	Not reached

NYHA	New York Heart Association;
OR	Odds ratio
ORR	Overall survival rate
OS	Overall survival
PFS	Progression free survival
PS	Performance status
PO	Per os (orally)
PR	Partial response
PR-L	Partial response with lymphocytosis
R	Rituximab
RCT	Randomised controlled trial
RD	Rate difference
r/r	Relapsed/refractory
SAE	Serious adverse event
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
TLS	Tumour lysis syndrome
TP53	Tumour protein p53
VEN	Venetoclax

### 3 Summary

Chronic lymphatic leukemia (CLL) is a hematologic cancer type and originates in the bone marrow. From here, the malignant B lymphocytes will proliferate rapidly and accumulate in the lymph nodes, spleen and blood, overpopulating the system with immature and nonfunctional B cells, thereby weakening the immune system. The symptoms are therefore known to include fatigue, fever (unexplained), weight loss, anemia, bleeding, increased tendency to infection, enlarged lymph nodes and spleen [1, 2]. Patients with high-risk cytogenetics, such as del(17p), *TP53* mutation, del(11q), complex karyotype or unmutated *IGHV*, have a worse prognosis than patients without these genetic abnormalities.

Most CLL cases are associated with the loss or acquisition of genetic material [3]. The common cytogenetic changes are:

- deletion of chromosome 13q region (del[13q]) in approximately 55% of cases
- acquisition of chromosome 12 (trisomy 12) in a further 10–20% of cases

- deletion of chromosome 11q region (del[11q]) in about 10% of cases
- deletion of chromosome 17p region (del[17p]) in about 5–8% of cases.

These are of clinical significance, as some cytogenetic changes are associated with a particularly poor prognosis. In particular, del(17p) is associated with deletion or mutation of *TP53*.

In Denmark, approx. 450 new cases per year are registered, where the incidence is about 6-7 pr. 100,000 inhabitants per. year. Median age is 70 years at diagnosis, and twice as many men as women are diagnosed with Hematologic malignancy [2].

Clinically, CLL is usually detected by coincidence after a routine blood test, as it is often asymptomatic at the time of diagnosis. A clinical assessment will be performed, focusing on the disease stage and risk profile, which includes cytogenetic changes and immunoglobulin heavy-chain variable region (IGHV)-mutation-status. In addition, patient-specific factors, such as performance status, comorbidity (cumulative illness rating scale (CIRS)), age and preferences are examined. These have an influence on treatment- strategy and choices, due to the impact on the patient's prognosis. The diagnosis is made by persistent lymphocytosis for > 3 months (> 5 billion monoclonal B cells per liter of blood) [2].

For treatment purposes, the patient population is divided according to deletion 17p/t53 mutation. The patient group without the mutation are candidates for first-line chemo immunotherapy, which include either chlorambucil or bendamustine in combination with CD20 antibody, or fluradabine and cyclophosphamide in combination with CD20 antibody. The patient group with the HR or TP53/del17p mutation is treated with a protein kinase inhibitor, ibrutinib.

In 2<sup>nd</sup> line, either ibrutinib or venetoclax in combination with rituxmab are used in patients who have previously received at least one treatment [4]

The below treatment (figure 1 and 2) diagram is based on recommended drugs/indications by KRIS/Medicinrådet and national guidelines. Combined with the protocol from Fagudvalget/Medicinrådet we find the following treatments/products as relevant comparator for Acalabrutinib(ACA) mono or in combination with obinutuzumab:

1<sup>st</sup> line:

- Chemotherapy + CD20(rituximab) in patients without 17p/t53 (data from ELEVATE study)
- Ibrutinib in patients with 17p/tp53 mutation (indirect comparison)
- Venetoclax + obinutuzumab (recommended by Medicinrådet November 2020)

R/R:

- Chemotherapy ( + CD20 antibody(rituximab)
- Ibrutinib
- Venetoclax + rituximab

We have agreed with Fagudvalget that chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR) is not a relevant comparator for acalabrutinib in 1<sup>st</sup> line CLL. Patients included in the ELEVATE trial are not comparable to FCR study population. Acalabrutinib in 1<sup>st</sup> is investigated in patients above 65 years or below 65 years but with CIRS > 6. According to Danish treatment

protocols patients with CIRS >6 independent of age will be treated with Chlorambucil + Obinutuzumab(ELEVATE comparator) or Bendamustine + Rituximab (>65 with CIRS<6).

FCR is according to guidelines recommended for the younger, "fit" population and even further sub grouped to patients that are IGHV mutated and this does not correspond to the acalabrutinib segment.

For questions in 1<sup>st</sup> line high-risk patients and R/R, Medicinraadet has stated in the protocol that the comparator should be "Danish standard treatment", in this case either Venetoclax + O/R or ibrutinib. As Calquence and Ibrutinib have the same mode of action (ATC L01XE; protein kinase inhibitors), the same approved indications, treatment until progression and the fact that ibrutinib is clear market leader in Denmark, we consider Ibrutinib to be the most relevant comparator to be able to answer the clinical questions in 1<sup>st</sup> line high risk and R/R. We are also aware of a head to head study ELEVATE RR that will compare acalabrutinib with ibrutinib and will be published in near future which underlines ibrutinib most relevant comparator in R/R.

The indication for acalabrutinib is broad:

- Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

Based on figure 1 and 2 it is estimated that the below number of patients are in scope for acalabrutinib treatment:

- Acalabrutinib monotherapy or in combination with obinutuzumab is expected to be introduced as a 1<sup>st</sup> line treatment for patients in all ages, >6 CIRS, and without 17p/t53-mutation, who are currently candidates to receive chlorambucil in combination with obinutuzumab. (**approx. 90 patients**)
- Acalabrutinib monotherapy or in combination with obinutuzumab is expected to be introduced as 1<sup>st</sup> line treatment for patients with 17p/t53-mutation, who are currently candidates to receive ibrutinib. (**between 10-25 patients**)
- Acalabrutinib monotherapy is expected to be introduced as R/R treatment for patients with and without 17p/t53-mutation, , that previously have received at least one treatment and has experienced relapse/refractory. These are currently candidates to receive ibrutinib or venetoclax + rituximab or idelalisib or bendamustin in combination with rituximab. (**150 patients**)

Figure 1. Treatment overview according to RADS 2016, KRIS 2017, Medicinrådet 2020

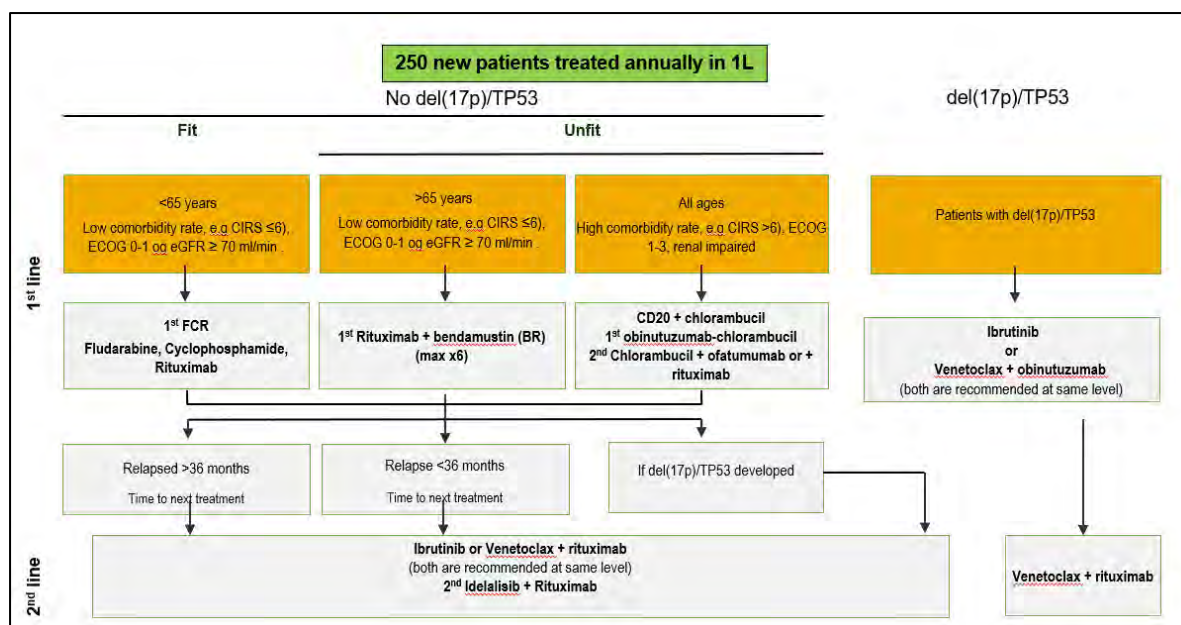
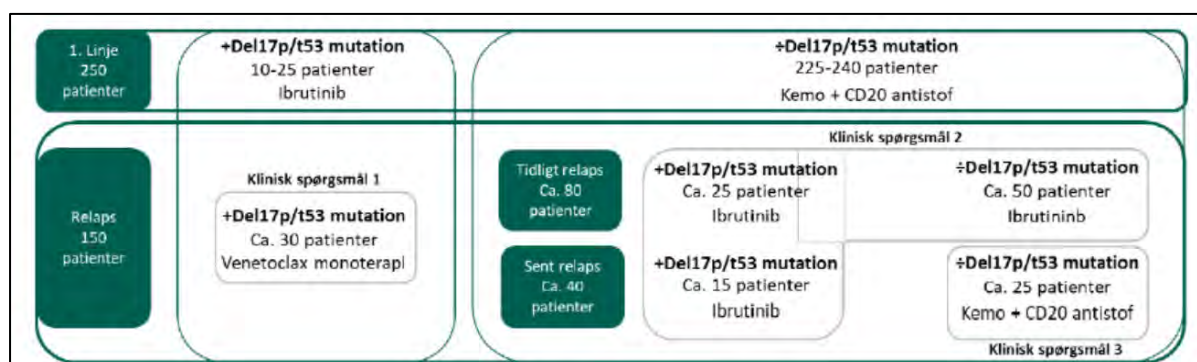


Figure 2. Patient numbers according to Fagudvalget (taken from Venetoclax protocol 2<sup>nd</sup> line CLL)



In 1<sup>st</sup> line acalabrutinib +/- obinutuzumab is investigated in the ELEVATE study and in ACSEND for the R/R population

Acalabrutinib received CHMP July 23<sup>rd</sup> and EC approval October 26<sup>th</sup> 2020.

Overall conclusion based on the five questions from Medicinraadet.

### 1<sup>st</sup> line CLL

The key 1<sup>st</sup> line study in CLL is ELEVATE-TN. Based on the study results acalabrutinib with or without obinutuzumab significantly improved progression-free survival over obinutuzumab plus chlorambucil with an acceptable side-effect profile. NMA and MAIC indirect comparison were conducted to compare to other approved therapies also including obinutuzumab plus chlorambucil (see later for details about these ITC's).

The indirect comparison vs bendamustine plus rituximab showed the same conclusion.



Several treatment options are available and recommended in Denmark but is depending on the mutation status. A key factor that affects choice of treatment is the presence of cytogenetic mutations, specifically deletion of chromosome 17p region (del(17p)), which is associated with deletion or mutation of the tumour protein 53 gene (*TP53*). Patients with these cytogenetic changes have a particularly poor prognosis and do not respond well to chemoimmunotherapy [3]. ELEVATE-TN included 14% with 17p/TP53 mutations. For the narrative and indirect comparisons we estimated that the questions relevant for the patient group without mutations can be answered based on the ITT population from ELEVATE while some studies do have subgroup analyses for the del17 or del17/TP53 patients.

- Indirect comparison vs bendamustine plus rituximab in question 1 and 2 showed low Hazard Ratios for the PFS comparisons
- For question 3 and 4 ibrutinib was chosen as comparator due to availability of data from the indirect comparison and also because it is market leader in Denmark, belong to the same BTK class a acalabrutinb and has treatment to progression as with acalabrutinib.
- The indirect and narrative comparisons showed that acalabrutinib PFS trended in favor of acalabrutinib monotherapy versus ibrutinib based regimens, albeit not significant but with an improved safety profile.
- Safety and HQoL data are not available for all the subgroups and data from ITT are used. Overall survival data are in general immature and firm conclusion cannot be made for ITT population and subgroups.

## R/R CLL

Acalabrutinib ASCEND study showed that acalabrutinib significantly improved PFS compared with idelalisib + rituximab or bendamustine + rituximab and has an acceptable safety profile in patients with R/R CLL. NMA and MAIC indirect comparison were conducted to compare to other approved therapies(see later for details about these ITC's). Ibrutinib was chosen as comparator in R/R CLL as it is widely use in Denmark and supported by guidelines, but most importantly because the first direct comparison of a more- vs less-selective BTK inhibitor in a phase III R/R setting was published in July 2021(ELEVATE RR, NCT02477696) [5]. The primary endpoint was PFS and the study was designed for non-inferiority but with the hypothesis that the greater selectivity of acalabrutinib might improve tolerance vs. ibrutinib of continuous therapy.

- The ELEVATE RR study in patients with R/R CLL met its primary endpoint, demonstrating non-inferior PFS for adults with previously treated, high-risk CLL compared to ibrutinib, as well as comparable results on response rate and overall survival. Compared with ibrutinib, acalabrutinib was associated with a lower incidence of grade  $\geq 3$  TEAEs, as well as a lower incidence of serious adverse events (STAEs) and TEAEs that led to treatment discontinuation. Fewer cardiovascular adverse events was seen in the acalabrutinib arm [5].

## 1.line and R/R overall

In general acalabrutinib(+/- obinutuzumab) both in 1<sup>st</sup> line and R/R CLL should be considered as an alternative to current clinical standards.

In addition as shown in both in the head-to-head study ELEVATE RR and the ITCs , acalabrutinib may provide a better tolerated alternative to ibrutinib, owing to its improved side effect profile, without compromising efficacy.

## 4 Literature search

Literature search in **PubMed** was performed 10.12.2020.

Table 2. Search relevant for Literature in **PubMed**. Provided by Medicinraadet

#	Søgetermer	Kommentar	#	Søgetermer	Kommentar
1	Leukemia, Lymphocytic, Chronic, B-Cell[mh]	Søgetermer for indikationen	15	acalabrutinib[nm] OR acalabrutinib[tiab] OR ACP-196[tiab] OR Calquence*[tiab]	Søgetermer for intervention og komparatorer
2	CLL[tiab]		16	venetoclax[nm] OR venetoclax[tiab] OR Venclyxto*[tiab] OR Venclexta*[tiab]	
3	chronic lymphocytic leukemia[tiab] OR chronic lymphocytic leukaemia[tiab]		17	obinutuzumab[nm] OR obinutuzumab[tiab] OR Gazyva*[tiab] or afutuzumab[tiab]	
4	chronic lymphatic leukemia[tiab] OR chronic lymphatic leukaemia[tiab]		18	Chlorambucil[mh] OR chlorambucil[tiab] OR amboclorin*[tiab] OR chloraminophene[tiab] OR chlorbutin*[tiab] OR Leukeran*[tiab]	
5	chronic lymphoblastic leukemia[tiab] OR chronic lymphoblastic leukaemia[tiab]		19	Bendamustine Hydrochloride[mh] OR bendamustin*[tiab] OR Levact*[tiab] OR Treanda*[tiab]	
6	chronic b-cell leukemia[tiab] OR chronic b-cell leukaemia[tiab]		20	Rituximab[mh] OR rituximab[tiab] OR Rituxan*[tiab] OR Mabthera*[tiab]	
7	SLL[tiab] OR small lymphocytic lymphoma[tiab] OR small cell lymphoma[tiab]		21	fludarabine[nm] OR fludarabine[tiab] OR Fludara*[tiab]	
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7		22	Cyclophosphamide[mh] OR cyclophosphamide[tiab] OR cyclophosphan*[tiab] OR cytophosphan*[tiab] OR Cytosan*[tiab] OR Endoxan*[tiab] OR Neosar*[tiab]	
9	newly diagnosed[tiab] OR treatment-naïve[tiab] OR treatment-naïve[tiab]	Søgetermer for tidligere ubehandlede patienter	23	R-FC[tiab] OR RFC[tiab]	
10	1L[tiab] OR firstline[tiab] OR first-line[tiab] OR frontline[tiab] OR front-line[tiab] OR primary treatment[tiab] OR primary therapy[tiab] OR untreated[tiab] OR initial therapy[tiab]		24	PCI 32765[nm] OR ibrutinib[tiab] OR imbruvica*[tiab] OR PCI-32765[tiab] OR PCI32765[tiab]	
11	Recurrence[mh] OR Neoplasm Recurrence, Local[mh] OR 2L[ti] OR secondline[ti] OR second-line[ti] OR relapse*[ti] OR refractory[ti] OR recurren*[ti] OR previously treated[ti]	Søgetermer for 2.-linjebehandling til eksklusion i spg 1-4	25	#15 OR (#17 AND #18) OR (#19 AND #20) OR (#23 OR (#20 AND #21 AND #22)) OR #24	Intervention og komparatorer spg 1-4
12	Recurrence[mh] OR Neoplasm Recurrence, Local[mh] OR 2L[tiab] OR secondline[tiab] OR second-line[tiab] OR relapse*[tiab] OR refractory[tiab] OR recurren*[tiab] OR previously treated[tiab]	Søgetermer 2.-linjebehandling til anvendelse i spg 5	26	#15 OR #24 OR (#20 AND #16)	Intervention og komparatorer spg 5
13	(#8 AND (#9 OR #10)) NOT #11	Population klinisk spg 1-4			
14	(#8 AND #12)	Population klinisk spg 5			

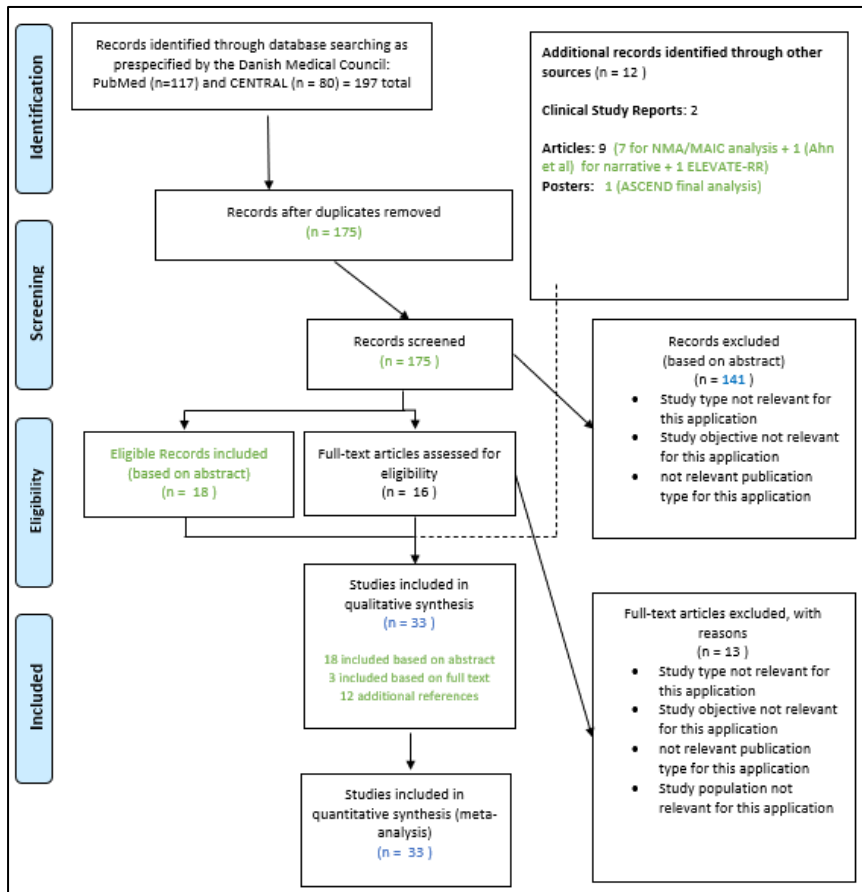
#	Søgetermer	Kommentar
27	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	Søgetermer for ikke relevante publikationstyper og dyrestudier (der ekskluderes)
28	animals[mh] NOT humans[mh]	
29	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	
30	#27 OR #28 OR #29	
31	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]	Filter til identifikation af RCT'er
32	(#13 AND #25 AND #31)	Kombination af population, intervention og komparatorer til spg 1-4.
33	(#14 AND #26 AND #31)	Kombination af population, intervention og komparatorer til spg 5.
34	(#32 OR #33) NOT #30	Endelig søgning
Feltkoder: mh = MeSH Term nm = Supplementary Concept/Substance tiab = title/abstract, inkl. forfatterkeywords pt = publication type		

Literature search in **Central** was performed 10.12.2020.

Table 3. Search relevant for Literature in **CENTRAL (Cochrane Library)**. Provided by Medicinraadet

#	Søgetermer	Kommentar	#	Søgetermer	Kommentar
#1	[mh "Leukemia, Lymphocytic, Chronic, B-Cell"]	Søgetermer for indikationen	#12	(cyclophosphamide or cyclophosphan* or cytophosphan* or Cytosan* or Endoxan* or Neosar*)ti,ab,kw	
#2	[CLL or SL]ti,ab		#13	(R-FC or RFC)ti,ab	
#3	(chronic next (lymphocytic or lymphatic or lymphoblastic or b-cell or small) next leuk*emia)ti,ab,kw		#14	(ibrutinib or imbruvica* or "PCI 32765" or PCI32765)ti,ab,kw	
#4	#1 or #2 or #3		#15	#5 or (#7 and #8) or (#9 and #10) or (#13 or (#10 and #11 and #12)) or #14 or (#6 and #10)	Kombination af intervention og komparatorer
#5	(acalabrutinib or ACP-196 or Calquence*)ti,ab,kw	Søgetermer for intervention og komparatorer	#16	("conference abstract" or review)pt	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
#6	(venetoclax or Venclyxto* or Venclexta* or "ABT 199" or ABT199 or "GDC 0199" or GDC0199 or "RG 7601" or RG7601)ti,ab,kw		#17	(clinicaltrials.gov or trialsearch):so	
#7	(obinutuzumab or Gazyva* or afutuzumab or "GA 101" or GA101 or "RO 5072759" or RO5072759)ti,ab,kw		#18	NCT*.au	
#8	(chlorambucil or chlorambucil or amboclorin or chloraminophene or chlorbutin or Leukeran*)ti,ab,kw		#19	#16 or #17 or #18	
#9	(bendamustin* or Levact* or Treanda*)ti,ab,kw		#20	(#4 and #15) not #19	
#10	(rituximab or Rituxan* or Mabthers*)ti,ab,kw		#21	#20 not pubmed.an	Endelig søgning
#11	(fludarabine or Fludara*)ti,ab,kw		Feltkoder: ti: title ab: abstract kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type		

Figur 3. PRISMA diagramme



See separate document (Literature search) for included and excluded publications

## 4.1 Relevant studies

Table 4. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
<p>Sharman JP. et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukaemia: a randomised, controlled, phase 3 trial. <i>Lancet</i> 2020;395:1278-1291. [6]</p> <p>2) Davids MS, Waweru C, Le Nouveau P, Padhiar A, Singh G, Abhyankar S, Leblond V., Comparative Efficacy of Acalabrutinib in Frontline Treatment of Chronic Lymphocytic Leukemia: a Systematic Review and Network Meta-analysis. <i>Clin Ther.</i> 2020 Oct 5:S0149-2918(20)30423-9. [7]</p> <p>3) ELEVATE-TN clinical study report[8]</p>	<p><b>ELEVATE-TN</b></p> <p>A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination With Chlorambucil, Acalabrutinib (ACP-196) in Combination With Obinutuzumab, and Acalabrutinib Monotherapy in Subjects With Previously Untreated CLL</p>	NCT02475681	<p>Actual Study Start: September 2015</p> <p>Actual Primary Completion Date: February 2019</p> <p>Estimated Study Completion Date: July 2021</p>	<p><b>Clinical Question 1-4</b></p> <p>Overall survival, progression free survival, Discontinuations, AE grade 3 or more</p> <p>1) Network-meta analysis, MAIC and literature search</p> <p>2) Network-meta analysis and literature search</p>
<p>Ghia P, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. <i>J Clin Oncol.</i> May. 2020 [9]</p> <p>2) Paolo Ghia, Andrzej Pluta, Malgorzata Wach, et al., Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final results, <i>Journal of Clinical Oncology</i> 38, no. 15_suppl (May 20, 2020) 8015-8015 [10]</p> <p>3)ASCEND Clinical Study report [11]</p>	<p><b>ASCEND</b></p> <p>A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects With R/R Chronic Lymphocytic Leukemia</p>	NCT02970318	<p>Actual Study Start Date: February 28, 2017</p> <p>Actual Primary Completion Date: January 15, 2019</p> <p>Estimated Study Completion Date: March 2020</p> <p>2) Final analysis at 22 months</p> <p>3)Clinical study report</p>	<p><b>Clinical Question 5</b></p> <p>Overall survival, progression free survival, Discontinuations, AE grade 3 or more</p> <p>1) Network-meta analysis, MAIC and literature search</p> <p>2) Added literature</p>
<p>1) Jan A Burger , Alessandra Tedeschi, Paul M Barr et al., Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia, <i>NEJM.</i> 2015 Dec 17;373(25):2425-37 [12]</p>	<p><b>RESONATE-2</b></p> <p>1)Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine</p>	<p>1)NCT01722487</p> <p>2)NCT01724346</p>	<p>1) Study Start Date: March 2013</p> <p>Actual Primary Completion Date: May 2015</p>	<p><b>Clinical Question 1-4</b></p> <p>Overall survival, progression free survival, Discontinuations,</p>

<p>2) Barr PM et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: Haematologica 2018;103:1502-1510. [13]</p> <p>3) Jan A. Burger, Paul M. Barr et al., Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study, Leukemia volume 34, pages787–798(2020)[14]</p>	<p>Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma</p> <p>2) An Open-label Extension Study in Patients 65 Years or Older With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib Versus Chlorambucil)</p>		<p>Actual Study Completion Date: May 2015</p> <p>2) Actual Study Start Date: August 28, 2012</p> <p>Estimated Primary Completion Date: April 30, 2023</p> <p>Estimated Study Completion Date: April 30, 2023</p> <p>3) 60 month follow-up</p>	<p>AE grade 3 or more</p> <p>1) Network-meta analysis, MAIC and literature search</p> <p>2) Network-meta analysis, MAIC and literature search</p> <p>3) literature search</p>
<p>Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, Bartlett NL, Brander DM, Barr PM, Rogers KA, Parikh SA, Coutre S, Hurria A, Brown JR, Lozanski G, Blachly JS, Ozer HG, Major-Elechi B, Fruth B, Nattam S, Larson RA, Erba H, Litzow M, Owen C, Kuzma C, Abramson JS, Little RF, Smith SE, Stone RM, Mandrekar SJ, Byrd JC. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018 Dec 27;379(26):2517-2528. [15]</p>	<p><b>Alliance</b></p> <p>A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients (&gt;= 65 Years of Age) With Chronic Lymphocytic Leukemia (CLL)</p>	<p>NCT01886872</p>	<p>Actual Study Start Date: December 9, 2013</p> <p>Actual Primary Completion Date: August 7, 2018</p>	<p><b>Clinical Question 5</b></p> <p>Overall survival, progression free survival, Discontinuations, AE grade 3 or more</p> <p>Network-meta analysis, MAIC and literature search</p>
<p>1) Ahn IE, Farooqui MZH, Tian X, Valdez J, Sun C, Soto S, Lotter J, Housel S, Stetler-Stevenson M, Yuan CM, Maric I, Calvo KR, Nierman P, Hughes TE, Saba NS, Marti GE, Pittaluga S, Herman SEM, Niemann CU, Pedersen LB, Geisler CH, Childs R, Aue G, Wiestner A. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 2018 May 24;131(21):2357-2366. [16]</p> <p>2) Farooqui MZ, Valdez J, Martyr S, Aue G, Saba N, Niemann CU, Herman SE, Tian X, Marti G, Soto S, Hughes TE, Jones J, Lipsky A, Pittaluga S, Stetler-Stevenson M, Yuan C, Lee YS, Pedersen LB, Geisler CH, Calvo KR, Arthur DC, Maric I, Childs R, Young NS, Wiestner A. Ibrutinib for previously</p>	<p>PCI-32765 for Special Cases of Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma</p> <p>A Phase II Study of PCI-32765 for Patients With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Need Therapy and Are</p>	<p>NCT01500733</p>	<p>1) 5 year follow up</p> <p>2)Between Dec 22, 2011, and Jan 2, 2014, patients enrolled. Median follow up of 24months</p>	<p><b>Clinical Question 1-4</b></p> <p>Overall survival, progression free survival, Discontinuations, AE grade 3 or more</p> <p>To see if PCI-32765 is a safe and effective treatment for CLL/SLL in older people and people with 17p deletion</p>

untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. <i>Lancet Oncol.</i> 2015 Feb;16(2):169-76. [17]	Older Than 65 or Have a 17p Deletion			1) literature search 2) Added literature
<p>1) John C. Byrd, Jennifer R. Brown, Susan O'Brien et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia, <i>N Engl J Med</i> 2014; 371:213-223 [18]</p> <p>2) Brown JR, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre SE, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. <i>Leukemia.</i> 2018;32(1):83-91 [19]</p> <p>3) John C. Byrd, Peter Hillmen, Susan O'Brien et al., Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab, <i>Blood</i> (2019) 133 (19): 2031–2042 [20]</p> <p>4) Talha Munir, Jennifer R. Brown, Susan O'Brien, Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma, <i>American Journal of Hematology</i>, Volume94, Issue12, December 2019, Pages 1353-1363 [21]</p>	<p><b>RESONATE</b></p> <p>A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma</p>	NCT01578707	<p>Actual Study Start Date: June 2012</p> <p>Actual Primary Completion Date: November 2013</p> <p>Actual Study Completion Date: October 25, 2018</p> <p>2) median follow up 19 months</p> <p>3) median follow up of 44months</p> <p>4) final analysis median 65.3 months</p>	<p><b>Clinical Question 5</b></p> <p>Overall survival, progression free survival, Discontinuations, AE grade 3 or more</p> <p>1) literature search</p> <p>2) Network-meta analysis, MAIC</p> <p>3-4) literature search</p>
Hillmen P, Robak T, Janssens A, Babu KG, Kloczko J, Grosicki S, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. <i>Lancet (London, England).</i> 2015;385(9980):1873-83. [22]	COMPLEMENT-1	NCT00748189	<p>Actual Study Start Date: Dec 22 2008</p> <p>Actual Primary Completion Date: March 20 2013</p> <p>Actual Study Completion Date: May 17 2018</p>	<p><b>Clinical Question 5</b></p> <p>Overall survival, progression free survival, Discontinuations, AE grade 3 or more</p> <p>Network-meta analysis</p>
Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. <i>Journal of clinical oncology : official journal of the American Society of Clinical Oncology.</i> 2007;25(35):5616-23. [23]	CAM307	<a href="#">NCT00046683</a>	<p>Actual Study Start Date: July 2001</p> <p>Actual Study Completion Date: June 2006</p>	<p><b>Clinical Question 5</b></p> <p>Network-meta analysis</p>

Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. The New England journal of medicine. 2014;370(12):1101-10. [24]	<b>CLL-11</b>	<a href="#">NCT01010061</a>	Actual Study Start:December 21 2009  Actual Primary Completion:July 1 2012  Actual Study Completion:August 23 2017	<b>Clinical questions 1+2</b>  Network-meta analysis, MAIC
Tedeschi A, Greil R, Demirkan F, Robak T, Moreno C, Barr PM, et al. A cross-trial comparison of single-agent ibrutinib versus chlorambucil- obinutuzumab in previously untreated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. Haematologica. 2020;105(4):e164-e8. [25]	<b>Tedeschi</b>	NCT02264574 (illuminate)  NCT01722487. (RESONATE-2)		<b>Clinical questions 1+2</b>  Network-meta analysis
Eichhorst B, et al First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016. [26]  2) Kutsch N, Bahlo J, Robrecht S, Franklin J, Zhang C, Maurer C, et al. Long Term Follow-up Data and Health-Related Quality of Life in Frontline Therapy of Fit Patients Treated With FCR Versus BR (CLL10 Trial of the GCLLSG). HemaSphere. 2020;4(1):e336. [27]	<b>CLL-10-Phase III Trial of Combined Immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Bendamustine and Rituximab (BR) in Patients With Previously Untreated Chronic Lymphocytic Leukaemia</b>	NCT00769522	Actual Study Start:October 2, 2008  Actual Primary Completion:July 2011  Actual Study Completion:January 2018  2) 5-median follow up 58.2 months	<b>Clinical Question 1+2</b>  1-2) literature search
Michallet AS, et al Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: Primary analysis of the randomized, open-label mable study. Haematologica. 2018;103(4):698–706 [28]	<b>MABLE-A Randomized Study to Assess the Effect on Response Rate of MabThera (Rituximab) Added to a Standard Chemotherapy, Bendamustine or Chlorambucil, in Patients With Chronic Lymphocytic Leukemia</b>	NCT01056510	Study Start Date :March 2010Actual  Primary Completion Date :March 2014  Actual Study Completion Date :March 2014	<b>Clinical Question 1+2</b>  Network-meta analysis and literature search
Moreno C. et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic	iLLUMINATE  A Randomized, Multi-center, Open-label, Phase 3 Study of the	NCT02264574	Actual Study Start Date: October 6, 2014  Actual Primary	<b>Clinical Question 1-4</b> Overall survival, progression free survival,



leukaemia: Lancet Oncol 2019;20:43-56. [29]	Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Subjects With Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma		Completion Date: March 26, 2018  Actual Study Completion Date: September 3, 2019	Discontinuations, AE grade 3 or more  Network-meta analysis, MAIC
<u>1</u> ) Asher Chanan-Khan et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. The Lancet, VOLUME 17, ISSUE 2, P200-211, FEBRUARY 01, 2016 PRINT, 1-10, DOI: 10.1080/10428194.2020.1795159 [30]	HELIOS-Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination With Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	NCT01611090	Actual Study Start Date: September 19, 2012  Actual Primary Completion Date: January 23, 2019  Actual Study Completion Date: January 23, 2019  2) updated results at median follow-up 34.8 months  3) Final 5-year findings	Clinical Question 5 Overall survival, progression free survival, Discontinuations, AE grade 3 or more  Network-meta analysis
1) Fischer K. et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med 2019;380:2225-2236. [31]	CLL14  A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare The Efficacy and Safety of A Combined Regimen of Obinutuzumab and Venetoclax (GDC-0199/ABT-199) Versus Obinutuzumab and Chlorambucil in Previously Untreated Patients With CLL and Coexisting Medical Conditions	NCT02242942	Actual Study Start Date: December 31, 2014  Actual Primary Completion Date: August 17, 2018  Estimated Study Completion Date: August 31, 2025	Network-meta analysis, MAIC
Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. The	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study	NCT01539512	Actual Study Start Date: April 2012	Clinical question 5

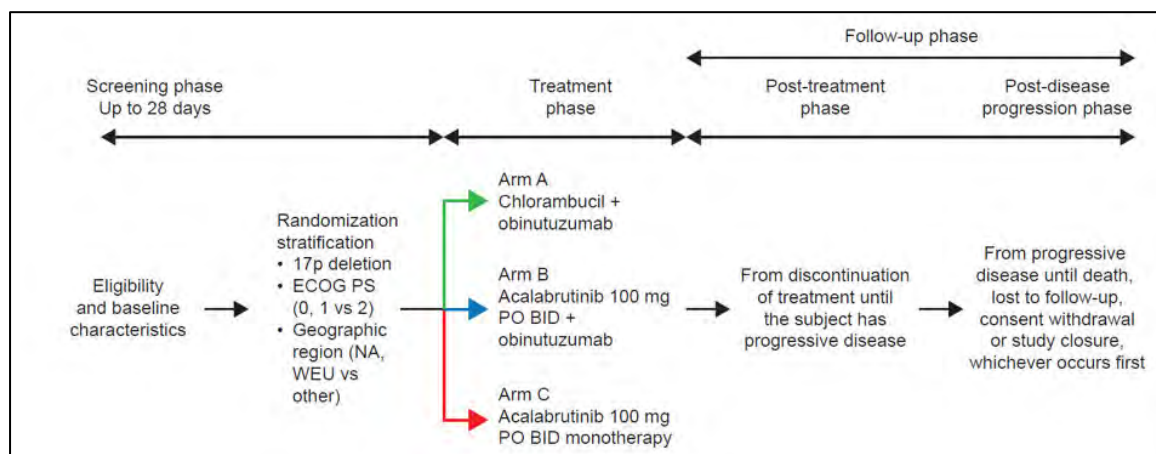
New England journal of Medicine. 2014;370(11):997-1007. [34]	Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia		Actual Primary Completion Date: October 2013 Estimated Study Completion Date: April 2014	Network-meta analysis
Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, phase 3 trial. The Lancet Haematology. 2017;4(3):e114-e26. [35]	A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia	NCT01659021	Actual Study Start Date: Dec 4 2012 Actual Primary Completion Date: August 15 2018 Estimated Study Completion Date: August 15 2018	Clinical question 5 Network-meta analysis
Huang X, Qiu L, Jin J, Zhou D, Chen X, Hou M, et al. Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study. Cancer medicine. 2018 [36]	A Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 (Ibrutinib) Versus Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	NCT01973387	Actual Study Start Date: October 28 2013 Actual Primary Completion Date: December 1 2015 Estimated Study Completion Date: August 11 2017	Clinical question 5 Network-meta analysis
Zelenetz AD, Barrientos JC, Brown JR, Coiffier B, Delgado J, Egyed M, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, 20binutuzum, double-blind, placebo-controlled trial. The Lancet Oncology. 2017;18(3):297-311. [37]	Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia	NCT01569295	Actual Study Start Date: June 15 2012 Actual Primary Completion Date: June 10 2019 Estimated Study Completion Date: June 10 2019	Clinical question 5 Network-meta analysis
Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. DOI: 10.1200/JCO.21.01210 Journal of Clinical Oncology. Published online July 26, 2021 [5]	ELEVATE RR Phase 3, randomized, multicenter, open-label, noninferiority study study in previously treated subjects with high risk CLL.		Study enrollment between Oct 2015 and Nov. 2017.	Clinical question 5 and also as supplement for the naïve comparison of AEs and SAEs in 1-4

## 4.2 Main characteristics of included studies

### ELEVATE-TN:

The efficacy and safety of **acalabrutinib with or without Obinutuzumab** versus **chlorambucil plus Obinutuzumab (CO)** was investigated in the ELEVATE-TN randomized controlled trial (figure 4). A total of 535 **treatment-naïve CLL** patients considered unsuitable for fludarabine-based treatment based on their age ( $\geq 65$  years) or comorbidities (Cumulative Illness Rating Scale-Geriatric score  $> 6$  or renal dysfunction [CrCl 30–69 mL/min]), were randomized to acalabrutinib plus obinutuzumab ( $n = 179$ , primary analysis), acalabrutinib monotherapy ( $n = 179$ ) or CO ( $n = 177$ ) [8, 38]. The primary endpoint was progression-free survival (PFS) for acalabrutinib plus Obinutuzumab versus chlorambucil plus obinutuzumab, as assessed by IRC using the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria[39]. The key secondary endpoint was PFS for acalabrutinib monotherapy versus chlorambucil plus obinutuzumab, as assessed by IRC. The primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS), with overall survival (OS) and overall response rate (ORR) as secondary endpoints. Median age at baseline was 70 years, 61.3% of patients were men and 14% had del 17p/TP53 mutations.

FIGURE 4. ELEVATE-TN STUDY DESIGN



Source. AstraZeneca data on file

Compared with CO, acalabrutinib plus obinutuzumab reduced the risk of disease progression or death by 90% (HR, 0.10; 95% CI, 0.06–0.17;  $p < 0.0001$ ), and acalabrutinib monotherapy by 80% (HR, 0.20; 95% CI, 0.13–0.30;  $p < 0.0001$ ), at a median follow-up of 28.3 months [6]. When comparing acalabrutinib monotherapy with acalabrutinib plus obinutuzumab in a *post hoc* analysis, the PFS HR was found to be 0.49 (95% CI: 0.26–0.95) in favour of acalabrutinib plus obinutuzumab. The OS data were not mature and median OS was not reached in any treatment arm; however, the OS trend favored acalabrutinib plus obinutuzumab (HR: 0.47; 95% CI: 0.21–1.06;  $p = 0.0577$ ) and acalabrutinib monotherapy (HR: 0.60; 95% CI: 0.28–1.27;  $p = 0.1556$ ), compared with CO. ELEVATE-TN is therefore the first and only trial to date, to show an added benefit over monotherapy of combining an anti-

CD20 antibody with a BTK inhibitor. PFS benefits associated with acalabrutinib plus obinutuzumab therapy or acalabrutinib monotherapy compared with CO were also seen across patient subgroups (age, race, sex, geographic region, chromosomal abnormalities, baseline disease status; acalabrutinib + obinutuzumab: HR, 0.02–0.22; acalabrutinib monotherapy, HR, 0.03–0.76). Proportionally more patients in the acalabrutinib arms had an overall response to treatment than did those on CO (ORR: acalabrutinib + obinutuzumab, 93.9%; acalabrutinib monotherapy, 85.5%; CO, 78.5%), the difference reaching significance with acalabrutinib plus obinutuzumab ( $p < 0.0001$ ) [6].

Patient-reported outcomes showed modest improvements from baseline in fatigue and in global health status/HRQoL, which occurred significantly faster with acalabrutinib monotherapy ( $p = 0.0316$ ) and trended towards being faster with acalabrutinib plus obinutuzumab ( $p = 0.0527$ ), compared with CO. These improvements in fatigue and HRQoL did not wane over time and no significant differences were seen between treatment arms, despite the much longer duration of treatment with acalabrutinib compared with CO, which is administered over 6 monthly cycles [8].

Similar numbers of patients experienced treatment-emergent adverse events (TEAEs) of any grade in each treatment arm: acalabrutinib plus obinutuzumab, 171 (96.1%); acalabrutinib monotherapy, 170 (95.0%); CO, 167 (98.8%). However, more acalabrutinib AEs were grade 1-2 events compared to AEs associated with CO. In the acalabrutinib plus obinutuzumab and acalabrutinib monotherapy groups versus the CO group, headache (39.9%, 36.9% vs 11.8%) and diarrhoea (38.8%, 34.6% vs 21.3%) were more frequent, but nausea was less common (20.2%, 22.3% vs 31.4%). Discontinuation because of AEs was less common with acalabrutinib plus obinutuzumab (10.7%) and acalabrutinib monotherapy (9.5%) than with CO (14.2%). Pneumonia was the most common serious adverse event with acalabrutinib, and tumour lysis syndrome the most common with CO. There were 13 deaths (7.7%) in the CO arm, 12 (6.7%) in the acalabrutinib monotherapy arm, and 8 (4.5%) in the acalabrutinib plus obinutuzumab arm. Most AEs were observed during the first 6 months of treatment and the rate of discontinuation due to AEs was similar between the acalabrutinib monotherapy and acalabrutinib plus obinutuzumab arms (9.5% and 11.8%, respectively), as were the rates of cardiac, bleeding and infection events [6].

Table 5. Dosing regimen in ELEVATE

Treatment	Dosing regimen
<b>Arm A: chlorambucil + obinutuzumab</b>	<ul style="list-style-type: none"> <li>Oral chlorambucil 0.5 mg/kg on days 1 and 15 of cycles<sup>a</sup> 1–6</li> <li>IV obinutuzumab over 6 cycles: 100 mg on day 1 of cycle 1, 900 mg on day 2 of cycle 1, 1000 mg on days 8 and 15 of cycle 1 and 1000 mg on day 1 of cycles 2–6</li> </ul>
<b>Arm B: acalabrutinib + obinutuzumab</b>	<ul style="list-style-type: none"> <li>Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity</li> <li>IV obinutuzumab over 6 cycles,<sup>a</sup> 100 mg starting day 1 of cycle 2, 900 mg on day 2 of cycle 2, 1000 mg on days 8 and 15 of cycle 2, and 1000 mg on day 1 of cycles 3–7</li> </ul>
<b>Arm C: acalabrutinib monotherapy</b>	<ul style="list-style-type: none"> <li>Oral acalabrutinib 100 mg twice daily on day 1 of cycle<sup>a</sup> 1 until disease progression or unacceptable toxicity</li> </ul>
<b>Crossover from arm A</b>	<ul style="list-style-type: none"> <li>Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity</li> </ul>

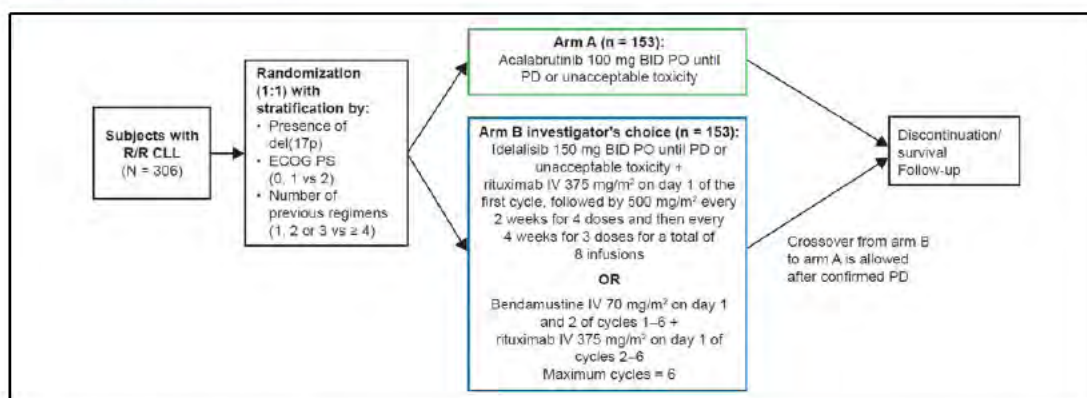
Table 6. Definition of endpoints in ELEVATE

Endpoint	Definition
<b>Primary endpoint and key secondary endpoint</b>	
<b>PFS (IRC)</b>	The time from the date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first
<b>Secondary endpoints</b>	
<b>ORR (IRC)</b>	The proportion of patients achieving a best overall response (assessed by IRC) of CR, Cri, nPR or PR at or before initiation of subsequent anti-cancer therapy
<b>TTNT</b>	The time from date of randomization to date of start of non-protocol-specified subsequent anti-cancer treatment for CLL or death due to any cause, whichever occurred first
<b>OS</b>	The time from date of randomization to death due to any cause
<b>Safety endpoints</b>	
<b>AEs</b>	AEs and SAEs as coded using the MedDRA reporting system (version 21.1) and graded according to the NCI CTCAE (version 4.03)
<b>Selected exploratory endpoints</b>	
<b>PFS (investigator)</b>	The time from randomization until disease progression (assessed by the investigator per IWCLL 2008 criteria) or death from any cause, whichever occurred first
<b>ORR (investigator)</b>	The proportion of patients achieving a best overall response (assessed by the investigator) of CR, Cri, nPR or PR at or before initiation of subsequent anti-cancer therapy
<b>ORR + PRL (investigator)</b>	The proportion of patients achieving a best overall response (assessed by the investigator) of CR, Cri, nPR, PR or PRL at or before initiation of subsequent anti-cancer therapy
<b>Medical resource use</b>	Number of hospitalizations, emergency department visits, blood product transfusions and haematopoietic growth factor treatments, per patient per year
<b>FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D</b>	Change from baseline in FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D scores

**ASCEND:**

The ASCEND RCT (figure 5) compared the efficacy and safety of acalabrutinib monotherapy to the investigators' choice of Idelalisib plus rituximab (IR) or bendamustine plus rituximab (BR) [9]. There were no restrictions on patient eligibility based on age or comorbidities. The primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS), with overall survival (OS) and overall response rate (ORR) as key secondary endpoints. A total of 310 patients were randomized to receive acalabrutinib (n = 155) versus IR/BR (n = 155). IR was the investigators' preferred choice with 119 patients randomized to IR compared to 36 patients to BR. Median age at baseline was 67 years, 67.1% of patients were men, 11% had del 17p/TP53 mutations and more than half had received two or more previous therapies [9].

FIGURE 5. ASCEND STUDY DESIGN



Source. AstraZeneca data on file

Compared with IR/BR, acalabrutinib reduced the risk of disease progression or death by 69% (HR, 0.31; 95% CI, 0.20–0.49;  $p < 0.0001$ ) at a median follow-up of 16.1 months. PFS benefits associated with acalabrutinib compared with IR/BR were also seen across patient subgroups (age, chromosomal abnormalities, baseline disease status; HR, 0.20–0.84). Median OS was not reached in either treatment arm during the analysis period; however, the OS trend favoured acalabrutinib, with a HR of 0.84 (95% CI: 0.42–1.66;  $p = 0.6089$ ). Proportionally more patients on acalabrutinib than on IR/BR had an overall response to treatment (ORR, 81.3% vs 75.5%, respectively), but the difference was not significant [9]. Patient-reported outcomes showed modest improvements from baseline in fatigue and in global health status/HRQoL [11].

When looking at AEs of any grade, headache (22.1%) was most common with acalabrutinib, diarrhoea (46.6%) and neutropenia (44.9%) were most common with IR, and neutropenia (34.3%), fatigue (22.9%), infusion-related reaction (22.9%) and nausea (20.0%) were most common with BR. Patients receiving acalabrutinib experienced fewer serious Aes (SAEs), grade  $\geq 3$  Aes and Aes leading to discontinuation, compared with those receiving IR. The most common SAE with acalabrutinib was pneumonia (5.2%) and was diarrhoea with IR (13.6%). Atrial fibrillation and grade  $\geq 3$  hypertension and bleeding occurred infrequently in patients receiving acalabrutinib and no occurrences of intracranial haemorrhage were reported. Aes led to fewer treatment discontinuations in the acalabrutinib group (10.4%) compared with the IR (52.5%) and BR (17.1%) groups. There were 15 deaths (9.7%) with acalabrutinib and 18 (11.8%) in the IR/BR arm, one of which was deemed treatment related [9].

TABLE 7. DOSING AND TREATMENT SCHEDULE ASCEND

Treatment	Dosing regimen
<b>Arm A: acalabrutinib</b>	Oral acalabrutinib 100 mg twice daily
<b>Arm B: idelalisib + rituximab</b>	Oral idelalisib 150 mg twice daily + rituximab 375 mg/m <sup>2</sup> IV on day 1, followed by 500 mg/m <sup>2</sup> IV every 2 weeks for 4 doses, then every 4 weeks for 3 doses, for a total of 8 infusions
<b>Arm B: bendamustine + rituximab</b>	Bendamustine 70 mg/m <sup>2</sup> on days 1 and 2 of each 28-day cycle for a maximum of 6 cycles, + rituximab 375 mg/m <sup>2</sup> IV on day 1 of the first cycle and 500 mg/m <sup>2</sup> IV on day 1 of cycles 2–6
<b>Crossover from arm B</b>	Oral acalabrutinib 100 mg twice daily

## RESONATE 2 [12, 14]

*This study is included in the NMA, MAIC and narrative analysis of 1L CLL NCT01722487.*

Resonate 2 evaluated the effect of ibrutinib in older patients with **CLL or small lymphocytic lymphoma (SLL)**. Patients were randomly assigned, in a 1:1 ratio, to receive either oral **ibrutinib** (at a dose of 420 mg once daily) until disease progression or development of an unacceptable level of toxic effects or up to 12 cycles of **chlorambucil** (at a dose of 0.5 mg per kilogram of body weight on days 1 and 15 of each 28-day cycle, which was increased to a maximum of 0.8 mg per kilogram). The primary endpoint was PFS, as assessed by the independent review committee. Key secondary endpoints included OS and overall response [12]

Ibrutinib resulted in significantly longer progression-free survival than did chlorambucil (median, not reached vs. 18.9 months), with a risk of progression or death that was 84% lower with ibrutinib than that with chlorambucil (hazard ratio, 0.16;  $P < 0.001$ ). Ibrutinib significantly prolonged overall survival; the estimated survival rate at 24 months was 98% with ibrutinib versus 85% with chlorambucil, with a relative risk of death that was 84% lower in the ibrutinib group than in the chlorambucil group (hazard ratio, 0.16;  $P = 0.001$ ). median follow-up 18.4 months. In the ibrutinib group, diarrhea was the most frequent adverse event (in 42% of the patients, including grade 3 diarrhea in 4%). Other adverse events that occurred in 20% or more of the patients in the ibrutinib group were fatigue, nausea, and cough. In the chlorambucil group, nausea, fatigue, neutropenia, anemia, and vomiting were observed in 20% or more of the patients; all these events occurred at a higher frequency in the chlorambucil group than in the ibrutinib group. Discontinuation of treatment owing to adverse events occurred less frequently in the ibrutinib group than in the chlorambucil group (in 9% vs. 23% of the patients) [12].

### Long term efficacy results.

With a median (range) follow-up of 60 months, PFS and OS benefits for ibrutinib versus chlorambucil were sustained (PFS estimates at 5 years: 70% vs 12%; HR [95% CI]: 0.146 [0.098–0.218]; OS estimates at 5 years: 83% vs 68%; HR [95% CI]: 0.450 [0.266–0.761]).

## Alliance [15]

*This study is included in the NMA, MAIC and narrative analysis of 1L CLL*

NCT01886872.

Patients 65 years of age or older who had **untreated CLL** were randomly assigned, in a 1:1:1 ratio, to receive **bendamustine plus rituximab, ibrutinib, or ibrutinib plus rituximab**. Treatment was administered in 28-day cycles. Bendamustine-plus-rituximab therapy consisted of six cycles of bendamustine (administered at a dose of 90 mg per square meter of body-surface area on days 1 and 2 of each cycle) plus rituximab (administered at a dose of 375 mg per square meter on the day before day 1 of cycle 1 and then at a dose of 500 mg per square meter on day 1 of cycles 2 through 6). Ibrutinib was administered at a dose of 420 mg daily until the patient had unacceptable toxic effects or disease progression. The primary endpoint was progression-free survival.

A total of 183 patients were assigned to receive bendamustine plus rituximab, 182 to receive ibrutinib, and 182 to receive ibrutinib plus rituximab. Median PFS was reached only with bendamustine plus rituximab. The estimated percentage of patients with PFS at 2 years was 74%

with bendamustine plus rituximab and 87% for ibrutinib alone (HR=0.39; 95% CI (0.26- 0.58); P<0.001) and 88% with ibrutinib plus rituximab (88%; HR=0.38; 95% CI, (0.25-0.59); P<0.001). There was no significant difference between the ibrutinib + rituximab group and the ibrutinib group with regard to PFS (HR= 1.00; 95% CI (0.62-1.62); P=0.49). With a median follow-up of 38 months, there was no significant difference among the three treatment groups with regard to OS. The rate of grade 3 or more hematologic adverse events was higher with bendamustine plus rituximab (61%) than with ibrutinib or ibrutinib plus rituximab (41% and 39%, respectively), whereas the rate of grade 3, 4, or 5 nonhematologic adverse events was lower with bendamustine plus rituximab (63%) than with the ibrutinib-containing regimens (74% with each regimen).

[Ahn et al \[16\]](#)

*This study is included in the narrative analysis of 1L 17pdel/Tp53 mutated population*

NCT01500733

The safety and efficacy of **ibrutinib** (420 mg) in chronic lymphocytic leukemia (CLL) were evaluated in a phase 2 study; 51 patients had **TP53 aberration** (TP53 cohort) and 35 were enrolled because of **age 65 years or older** (elderly cohort). Both cohorts included patients with **treatment-naïve (TN)** and **relapsed/refractory (RR)** CLL. With the median follow-up of 4.8 years, 49 (57.0%) of 86 patients remain on study. Treatment was discontinued for progressive disease in 20 (23.3%) patients and for adverse events in 5 (5.8%). Atrial fibrillation occurred in 18 (20.9%) patients for a rate of 6.4 per 100 patient-years. No serious bleeding occurred. The overall response rate at 6 months, the primary study endpoint, was 95.8% for the TP53 cohort (95% confidence interval, 85.7%-99.5%) and 93.9% for the elderly cohort (95% confidence interval, 79.8%-99.3%). Depth of response improved with time: at best response, 14 (29.2%) of 48 patients in the TP53 cohort and 9 (27.3%) of 33 in the elderly cohort achieved a complete response. In the TP53 cohort, the estimated 5-year progression-free survival (PFS) was 74.4% in TN-CLL compared with 19.4% in RR-CLL ( $P = .0002$ ), and overall survival (OS) was 85.3% vs 53.7%, respectively ( $P = .023$ ). In the elderly cohort, the estimated 5-year PFS and OS in RR-CLL were 64.8% and 71.6%, respectively [16].

[RESONATE \[18\]](#)

*This study is included in the NMA, MAIC and narrative analysis of R/R CLL*

NCT01578707

RESONATE is a randomized, multicenter, open-label, phase 3 study that evaluate the efficacy and safety of **ibrutinib** compared with **ofatumumab** in previously treated patients with **relapsed or refractory CLL/SLL** (NCT01578707). Patients were enrolled between June 2012 to April 2013. Patients were randomly assigned 1:1 to receive either oral ibrutinib 420 mg once daily (until disease progression or unacceptable toxicity) or intravenous ofatumumab for up to 24 weeks at an initial dose of 300 mg at week one, followed by a dose of 2000 mg weekly for seven weeks and then every four weeks for 16 weeks. Stratification was by purine analog refractory status (defined as no response to or relapse within 12 months of last dose of purine analog) and presence or absence of del(17p). Patients were allowed to cross over from the ofatumumab arm and receive ibrutinib. Baseline characteristics of patients randomized to ibrutinib (n = 195) or ofatumumab (n = 196) are shown in table A2. Similar proportions of patients in the ibrutinib and ofatumumab arms had high-risk features, including del(17p) (32% and 33%, respectively), mutated *TP53* (51% and 46%,



respectively), del(11q) (33% and 31%, respectively), unmutated *IGHV* (73% and 63%, respectively), and complex karyotype (25% and 22%, respectively). The majority of patients in both the ibrutinib and ofatumumab arms (86% and 79%, respectively) comprised the high-risk population, defined as having any of the following: del(17p), *TP53* mutation, del(11q), and/or unmutated *IGHV* status [18].

At a median follow-up of 9.4 months, ibrutinib significantly improved progression-free survival; the median duration was not reached in the ibrutinib group (with a rate of progression-free survival of 88% at 6 months), as compared with a median of 8.1 months in the ofatumumab group (hazard ratio for progression or death in the ibrutinib group, 0.22;  $P < 0.001$ ) [18]. Ibrutinib also significantly improved overall survival (hazard ratio for death, 0.43;  $P = 0.005$ ). At 12 months, the overall survival rate was 90% in the ibrutinib group and 81% in the ofatumumab group. The overall response rate was significantly higher in the ibrutinib group than in the ofatumumab group (42.6% vs. 4.1%,  $P < 0.001$ ) [19]. The most frequent nonhematologic adverse events that occurred in at least 20% of the patients were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. Overall, 57% of the patients in the ibrutinib group and 47% of the patients in the ofatumumab group had at least one adverse event of grade 3 or higher. Adverse events of grade 3 or higher that occurred more frequently in the ibrutinib group than in the ofatumumab group included diarrhea (4% vs. 2%) and atrial fibrillation (3% vs. 0%)

The final analysis was performed upon study closure. Median follow-up on the study of patients initially assigned to ibrutinib was 65.3 months (range: 0.3–71.6), and median duration of ibrutinib therapy was 41 months (range: 0.2–71.1), with 41% of patients receiving more than four years of therapy. Among patients initially assigned to ibrutinib, 43/195 (22%) remained on therapy until study closure. The most common reasons for ibrutinib discontinuation prior to study closure were PD (72/195, 37%) and AEs (32/195, 16%) [21].

Long term data was published in *Blood* 2019 May 9;133(19):2031-2042 and *Am J Hematol.* 2019 Dec; 94(12):1353-1363 [20]. PFS HR was 0.133; 95% CI (0.099-0.178) and for OS HR=0.591(0.378-0.926) including patients who crossed over. Before crossover HR was 0.426 (0.220-0.823). Overall response to ibrutinib increased over time, with 91% of patients attaining a response. The PFS benefit with ibrutinib was independent of most baseline risk factors, although patients with  $\geq 2$  prior therapies had shorter PFS than those with  $< 2$  prior therapies, and the presence of *TP53* or *SF3B1* mutations showed a trend toward shorter PFS vs without these factors. Median duration of ibrutinib was 41 months, with 46% remaining on treatment at a median follow-up of 44 months. Grade  $\geq 3$  adverse events generally decreased over time, causing only a small proportion of patients to cease therapy [20]

#### [COMPLEMENT-1 \[22\]](#)

*This study is included in the NMA analysis of 1L CLL*

NCT00748189

This is a randomised, open-label, phase 3 trial in **treatment-naive patients with CLL**. The study included patients who had active disease needing treatment, but in whom fludarabine-based treatment was not possible. Patients (1:1) were randomised to receive oral **chlorambucil** (10 mg/m<sup>2</sup>) on days 1-7 of a 28 day treatment course or to receive **chlorambucil** by this schedule **plus intravenous ofatumumab** (cycle 1: 300 mg on day 1 and 1000 mg on day 8; subsequent cycles: 1000 mg on day 1) for three to 12 cycles. Randomisation was stratified, in a block size of two, by age ( $< 65$  years vs  $\geq 65$  years), disease stage (Binet A vs Binet B vs Binet C), and ECOG performance status score (0–1 vs 2).

447 patients, median age 69 years were randomized between Dec 22, 2008 and May 26, 2011. 221 patients to chlorambucil plus ofatumumab and 226 patients to chlorambucil alone. The primary endpoint was PFS. Secondary endpoints included OS, time to progression, ORR, complete response rate, time to response, duration of response, time to next therapy, safety assessments and quality of life. Median PFS was 22.4 months (95% CI 19.0-25.2) in the group assigned to chlorambucil plus ofatumumab compared with 13.1 months (10.6-13.8) in the group assigned to chlorambucil only HR=0.57, (95% CI 0.45-0.72; p<0.0001). With a median follow-up time of 28.9 months, OS was not reached in either treatment group, with 34 (15%) deaths in group assigned to chlorambucil plus ofatumumab (n=221) and 40 (18%) deaths in the group assigned to chlorambucil (n=226), HR 0.91 (95% CI 0.57–1.43), p=0.666.

Grade 3 or more adverse events were more common in the chlorambucil plus ofatumumab group 109 (50%) patients; vs 98 (43%) given chlorambucil alone, with neutropenia being the most common event 56 (26%) vs 32 (14%).

Grade 3 or more infections were seen at same frequency in both groups. Grade 3 or more infusion-related adverse events were reported in 22 (10%) patients given chlorambucil plus ofatumumab.

Five (2%) patients died during treatment in each group.

### [CAM307 \[23\]](#)

*This study is included in the NMA analysis of 1L CLL*

NCT00046683

CAM307 was an international, multicenter, randomized, open-label phase III trial comparing **alemtuzumab** with **chlorambucil** in previously **untreated** patients requiring treatment for **CLL**. The primary end point of CAM307 was PFS. Secondary end points included response rates, time to alternative treatment, OS, and safety. From December 2001 to July 2004, 297 patients were enrolled and randomly assigned to alemtuzumab (n = 149) or chlorambucil (n = 148) treatment.

Alemtuzumab was escalated daily (3, 10, and 30 mg) until tolerated at an intravenous (IV) dose of 30 mg over 2 hours. Subsequently, patients received alemtuzumab 30 mg three times a week for no more than 12 weeks, including the dose-escalation phase. Patients in the chlorambucil arm received 40 mg/m<sup>2</sup> PO q 28 days for no more than 12 cycles with allopurinol PO days -1 to 8 for the first three cycles. Alemtuzumab showed superior PFS, with a 42% reduction in risk of progression or death (HR = 0.58; P = 0.0001), and a median time to alternative treatment of 23.3 versus 14.7 months for chlorambucil (HR = 0.54; P = 0.0001). The ORR was 83% with alemtuzumab (24% CR) versus 55% with chlorambucil (2% CR). Differences in ORR and CR were statistically significant (P < .0001). Elimination of minimal residual disease occurred in 11 of 36 complete responders to alemtuzumab versus none to chlorambucil.

Sixteen patients (11%) treated with alemtuzumab and 26 patients (18%) treated with chlorambucil had grade 3 to 4 anemia. Sixty patients (41%) receiving alemtuzumab and 36 patients (25%) receiving chlorambucil had grade 3 to 4 neutropenia (P = .0041). Eighteen patients (12%) receiving alemtuzumab and 17 patients (12%) receiving chlorambucil had grade 3 to 4 thrombocytopenia.

### [CLL-11\[24\]](#)

*This study is included in the NMA and MAIC analysis of 1L CLL*

#### NCT01010061

This is an open-label, randomized three-arm study. Between April 2010 and July 2012, 781 Previously untreated patients were enrolled and randomly assigned on a 1:2:2 basis to chlorambucil alone, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil. After 118 patients had been assigned to the chlorambucil-alone group, this group was closed on the basis of predefined criteria, and randomization to the two antibody groups was performed on a 1:1 basis. Randomization was stratified according to geographic region and Binet stage. Patients assigned to the chlorambucil-alone group in whom progressive disease developed during treatment or within 6 months after the end of treatment were allowed to cross over to the obinutuzumab–chlorambucil group.

Patients received chlorambucil alone, obinutuzumab–chlorambucil, or rituximab–chlorambucil in six 28-day cycles. Chlorambucil was administered orally at a dose of 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle. Obinutuzumab was administered intravenously at a dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6. Rituximab was administered intravenously at a dose of 375 mg per square meter of body-surface area on day 1 of cycle 1 and 500 mg per square meter on day 1 of cycles 2 through 6.

The primary end point was PFS (investigator). Key secondary end points were PFS as assessed by an independent review committee, response rates and the rate of negative testing for minimal residual disease after the end of treatment, event-free survival, the time to new treatment, OS, adverse events and patient-reported outcomes.

Treatment with obinutuzumab–chlorambucil or rituximab–chlorambucil, compared with chlorambucil alone, was associated with significant improvement in the median PFS (26.7 months with obinutuzumab–chlorambucil vs. 11.1 months with chlorambucil alone; HR= 0.18; 95% CI, (0.13- 0.24); P<0.001; and 16.3 months with rituximab–chlorambucil vs. 11.1 months with chlorambucil alone; HR= 0.44; 95% CI, 0.34- 0.57; P<0.001). This benefit was consistent in all analyzed subgroups, except in patients with del17p.

Grade 3 to 5 adverse events were reported in 72% of patients in the obinutuzumab arm and 60% of patients in the rituximab arm. Grade 5 adverse event rates were 7% and 10%, respectively.

### [Tedeschi \[25\]](#)

*This study is included in the NMA analysis of 1L CLL*

#### [NCT01578707](#) and [NCT02264574](#)

This is a prespecified cross-trial analysis of the RESONATE-2 and iLLUMINATE studies in first-line CLL that compares outcomes with single-agent ibrutinib against chlorambucil-obinutuzumab.

This cross-trial analysis included all patients in the ibrutinib arm from RESONATE-2 and patients without del17p from iLLUMINATE, given the exclusion of patients with del(17p) from RESONATE-2.

The primary analysis was PFS (investigator-assessed) of patients treated with single-agent ibrutinib in RESONATE-2 versus PFS of patients treated with chlorambucil-obinutuzumab in iLLUMINATE. Secondary analyses included investigator-assessed PFS in genomic high-risk patients. The safety

analysis included evaluation of adverse events collected for the time-matched analysis (first 6 months of study treatment) and for the entire follow-up.

For patients included in the analysis, the median follow-up was 48.8 months for the ibrutinib arm of RESONATE-2 and 31.3 months for both arms in ILLUMINATE. In total, 136 patients treated with single-agent ibrutinib and 98 patients treated with the chlorambucil-obinutuzumab combination were included. The baseline characteristics of the patients were well balanced. The median age of the patients was 73 years for both groups. The proportions of patients with high-risk genomic features were similar in the ibrutinib and chlorambucil-obinutuzumab groups (55% and 58%, respectively), as were the proportions with *TP53* mutations (10% and 5%), del(11q) (22% and 22%), and/or unmutated IGHV (59% and 50%). The PFS was significantly longer among patients treated with single-agent ibrutinib compared with those given chlorambucil-obinutuzumab (median not reached vs. 22.2 months), resulting in an 83% reduction in risk of progression or death with ibrutinib [HR=0.184;(0.111-0.306); *P*<0.0001]. The 30-month PFS rates were 85% with ibrutinib and 40% with chlorambucil-obinutuzumab.

The PFS benefit with ibrutinib vs. chlorambucil-obinutuzumab was more pronounced among patients with high-risk features (median not reached vs. 18.3 months), with a 93% reduction in risk of progression or death [HR=0.072; 95% (0.034-0.152); *P*<0.0001]. 30 months PFS rates for high-risk patients were 89% vs. 19%, respectively. The PFS benefit with single-agent ibrutinib compared with chlorambucil-obinutuzumab was consistent across all subgroups examined. Rates of grade ≥3 adverse events were lower with single-agent ibrutinib than with chlorambucil-obinutuzumab during the first 6 months of treatment (50% and 71%). Grade ≥3 adverse events occurred in 81% and 71% of ibrutinib and chlorambucil-obinutuzumab-treated patients, respectively. Rates of grade ≥3 pneumonia (12% and 4%), hypertension (7% and 4%), and hyponatremia (5% and 1%) were higher with ibrutinib than with chlorambucil-obinutuzumab. Grade ≥3 hematologic adverse events occurred at a higher rate with chlorambucil-obinutuzumab than with ibrutinib, including neutropenia (48% and 15%) and thrombocytopenia (10% and 7%).

#### [CLL-10 \[26, 27\]](#)

*This study is included in the narrative analysis of 1L CLL*

NCT 00769522.

This is an open-label, phase 3, non-inferiority study in previously untreated fit patients aged 33–81 years with **advanced CLL**.

688 CLL pts were based on immunophenotype, genomic aberrations by FISH, *IGHV* sequencing, comorbidity burden and renal function. 564 CLL pts with CIRS score ≤ 6, creatinine clearance > 70 ml/min and without del(17p) were enrolled between October 2008 and June 2011. Patients were randomly assigned to receive 6 courses of either **FCR** (N= 284; F 25mg/m<sup>2</sup> i.v. d1–3, C 250 mg/m<sup>2</sup> i.v. d1–3, R 375 mg/m<sup>2</sup> i.v. d 0 at first cycle and 500 mg/m<sup>2</sup> d1 all subsequent courses; q 28 days) or **Bendamustine plus rituximab** (N=280; B 90mg/m<sup>2</sup> i.v. d1+2, R 375 mg/m<sup>2</sup> i.v. d 0 at first cycle and 500 mg/m<sup>2</sup> d1 all subsequent courses; q 28 days).

Of the patient pool randomized, 22 % were Binet A, 38 % Binet B and 40 % Binet C. The median age was 62 years (range 33 to 82), median CIRS score 2 (range 0-6). There were significantly more patients with unmutated *IGHV* in the BR arm (68%) in comparison to the FCR arm (55%; *p*=0.003).

After a median observation time of 37.1 months median PFS was 41.7 months (95% CI 34.9–45.3) with bendamustine plus rituximab and 55.2 months (95% CI not evaluable) with FCR, HR=1.643, 90.4% (CI 1.308–2.064).

Severe, CTCAE grade 3 and 4, adverse events occurred more frequently in the FCR group compared with the bendamustine plus rituximab group. Severe neutropenia and infections were more frequently observed with FCR 235 (84%) vs. 164 (59%), and 109 (39%) vs 69 (25%), respectively. The increased frequency of infectious complications with fludarabine, cyclophosphamide, and rituximab was more pronounced in patients older than 65 years.

## MABLE [28]

*This study is included in the NMA and narrative analysis of 1L CLL*

NCT01056510

MABLE-A (Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia): Primary analysis of the randomized, open-label MABLE study. Michallet AS, et al. *Haematologica*. 2018;103(4):698–706) is a Randomized, open-label Study to Assess the Effect on Response Rate of MabThera (Rituximab) Added to a Standard Chemotherapy, Bendamustine or Chlorambucil, in Patients With CLL (NCT NCT01056510) [28]

Bendamustine :90mg/m<sup>2</sup> (first-line) or 70mg/m<sup>2</sup> (second-line) iv, days 1 and 2 every 4 weeks, cycles 1-6

Rituximab:375mg/m<sup>2</sup> iv day 1 of cycle 1, followed by 500mg/m<sup>2</sup> iv every 4 weeks cycles 2-6  
Chlorambucil:10mg/m<sup>2</sup> po days 1-7 every 4 weeks, for up to 12 cycles

MABLE investigated the efficacy and safety of **rituximab plus bendamustine** or **rituximab plus chlorambucil** in **fludarabine-ineligible patients with CLL**. Patients received rituximab plus bendamustine or rituximab plus chlorambucil every four weeks for six cycles. Rituximab plus chlorambucil-treated patients without a complete response after Cycle 6 received chlorambucil monotherapy for at least six additional cycles or until complete response. The primary endpoint was complete response rate (confirmed by bone marrow biopsy) after Cycle 6 in first-line patients. Secondary endpoints included PFS, OS, minimal residual disease, and safety. Overall, 357 patients were randomized (rituximab plus bendamustine, n=178; rituximab plus chlorambucil, n=179; intent-to-treat population), including 241 first-line patients (n=121 and n=120, respectively); 355 patients received treatment (n=177 and n=178, respectively; safety population). In first-line patients, complete response rate after Cycle 6 ; rituximab plus bendamustine, 24%; rituximab plus chlorambucil, 9%;  $P=0.002$  and median PFS; rituximab plus bendamustine, 40 months; rituximab plus chlorambucil, 30 months;  $P=0.003$  were higher with rituximab plus bendamustine than rituximab plus chlorambucil. Overall response rate and OS were not different. In first-line patients with a complete response, minimal residual disease-negativity was higher with rituximab plus bendamustine than rituximab plus chlorambucil (66% vs 36%). Overall adverse event incidence was similar (rituximab plus bendamustine, 98%; rituximab plus chlorambucil, 97%). Follow-up time 23,5 months [28].

## ILLUMINATE [29]

*This study is included in the NMA and MAIC analysis of 1L CLL*

NCT02264574

The iLLUMINATE trial is a phase 3, open-label, multicenter trial that was designed to test the efficacy of **ibrutinib with obinutuzumab** versus **chlorambucil with obinutuzumab** in **treatment-naïve** patients with CLL/SLL. [29]

Eligibility criteria included treatment-naïve CLL/SLL, ≥65 years or <65 years with coexisting conditions (Cumulative Illness Rating Scale score >6, creatinine clearance <70 mL/min, and/or del(17p) or TP53 mutation).

Intervention:

6 cycles of 420 mg ibrutinib once daily, combined with obinutuzumab 1000 mg on days 1/2, 8, and 15 of cycle 1, and day 1 of subsequent 28-day cycles.

Comparator: 6 cycles of chlorambucil (0.5 mg/kg on days 1 and 15 of each 28-day cycle) combined with obinutuzumab, in the same dose and frequency as above.

PFS was the primary endpoint and secondary endpoints included PFS in a high-risk population—del(17p)/TP53 mutation, del(11q), and/or unmutated IGHV—rate of undetectable minimal residual disease, overall response rate (ORR), overall survival (OS), and safety.

The trial allowed crossover of patients with confirmed progression in the chlorambucil—obinutuzumab arm to single-agent ibrutinib. [29]

The trial enrolled 229 patients, 113 of whom were randomized to the ibrutinib-obinutuzumab arm and 116 to the chlorambucil-obinutuzumab arm. Median age was 71 years (range, 40-87) and 65% of patients had the above listed high-risk genomic features. [29]

With a median follow-up of 31.3 months, patients who were treated with ibrutinib—obinutuzumab had a significantly better PFS(ICR) compared with the comparator arm (median not reached [NR] vs 19.0 months; hazard ratio [HR], 0.231; 95% CI, 0.145-0.367;  $P < .0001$ ). At 30 months, the PFS rates were 79% with ibrutinib—obinutuzumab and 31% with chlorambucil—obinutuzumab. Investigator (INV)-assessed PFS showed a similar trend for ibrutinib—obinutuzumab versus chlorambucil—obinutuzumab (median PFS NR vs 21.9 months; HR, 0.260; 95% CI, 0.163 to 0.415;  $P < .0001$ ).

Improvements in PFS receiving ibrutinib—obinutuzumab were independent of their genomic status compared with the comparator arm (median NR vs 14.7 months; HR, 0.154; 95% CI, 0.087-0.270;  $P < .0001$ ). [29]

30-month OS rates: 86% in the ibrutinib—obinutuzumab arm and 85% in the chlorambucil-obinutuzumab arm, with 40% of patients randomized to chlorambucil—obinutuzumab receiving single-agent ibrutinib as second-line therapy. Over a median follow-up of 31.3 months, 4% of patients in the ibrutinib—obinutuzumab arm and 44% in the chlorambucil—obinutuzumab arm initiated subsequent therapy. [29]

The most frequent (≥3%) serious adverse events (AEs) among patients in the ibrutinib—obinutuzumab arm were pneumonia (5%), atrial fibrillation (4%), febrile neutropenia (4%), and pyrexia (4%). The more common serious AEs in the chlorambucil—obinutuzumab were infusion-related reactions (IRRs; 7%), febrile neutropenia (6%), pneumonia (4%), tumor lysis syndrome (4%), and pyrexia (3%). AEs leading to discontinuation of ibrutinib or chlorambucil occurred in 18 (16%) and 11 patients (9%), respectively, and AEs leading to discontinuation of obinutuzumab occurred in 10 patients (9%) in the ibrutinib—obinutuzumab arm and 15 (13%) in the chlorambucil—obinutuzumab arm. [29]

## HELIOS [30]

*This study is included in the NMA analysis of R/R CLL*

NCT01611090

The HELIOS trial was an international, double-blind, placebo-controlled, phase 3 study in adult patients who had active CLL or small lymphocytic lymphoma with measurable lymph node disease (>1.5 cm) by CT scan, and had **relapsed or refractory** disease. Patients with del(17p) were excluded because of known poor response to bendamustine plus rituximab. Patients who had received previous treatment with ibrutinib or other BTK inhibitors, refractory disease or relapse within 24 months with a previous bendamustine-containing regimen, or haemopoietic stem-cell transplant were also excluded [30].

Patients were randomized 1:1 to receive **bendamustine plus rituximab** given in cycles of 4 weeks' duration (bendamustine: 70 mg/m<sup>2</sup>) intravenously on days 2-3 in cycle 1, and days 1-2 in cycles 2-6; rituximab: 375 mg/m<sup>2</sup>) on day 1 of cycle 1, and 500 mg/m<sup>2</sup>) on day 1 of cycles 2-6 for a maximum of six cycles) with either **ibrutinib** (420 mg daily orally) or **placebo** until disease progression or unacceptable toxicity.

The primary endpoint was IRC-assessed PFS. Crossover to ibrutinib was permitted for patients in the placebo group with IRC-confirmed disease progression. Analysis was by intention-to-treat and is continuing for further long-term follow-up. The trial is registered with ClinicalTrials.gov, number NCT01611090.

Between Sept 19, 2012, and Jan 21, 2014, 578 eligible patients were randomly assigned to ibrutinib or placebo in combination with bendamustine plus rituximab (289 in each group). The primary endpoint was met at the preplanned interim analysis (March 10, 2015). At a median follow-up of 17 months (IQR 13·7-20·7), progression-free survival was significantly improved in the ibrutinib group compared with the placebo group (not reached in the ibrutinib group (95% CI not evaluable) vs 13·3 months (11·3-13·9) in the placebo group (hazard ratio [HR] 0·203, 95% CI 0·150-0·276; p<0·0001). IRC-assessed progression-free survival at 18 months was 79% (95% CI 73-83) in the ibrutinib group and 24% (18-31) in the placebo group (HR 0·203, 95% CI 0·150-0·276; p<0·0001). The most frequent all-grade adverse events were neutropenia and nausea. 222 (77%) of 287 patients in the ibrutinib group and 212 (74%) of 287 patients in the placebo group reported grade 3-4 events; the most common grade 3-4 adverse events in both groups were neutropenia (154 [54%] in the ibrutinib group vs 145 [51%] in the placebo group) and thrombocytopenia (43 [15%] in each group). A safety profile similar to that previously reported with ibrutinib and bendamustine plus rituximab individually was noted [30].

## CLL14 [31]

*This study is included in the NMA and MAIC analysis of 1L CLL*

NCT02242942.

This is an open-label, phase 3 trial, investigating fixed-duration treatment with **venetoclax plus obinutuzumab** vs **chlorambucil plus obinutuzumab** in patients with previously **untreated CLL**. The treatment duration in both groups consisted of 12 cycles lasting 28 days each; no crossover was allowed. Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6. Chlorambucil was administered orally at

0.5 mg per kilogram of body weight on days 1 and 15 of each cycle until completion of 12 cycles. The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a 5-week dose escalation, thereafter continuing at 400 mg daily until completion of cycle 12.

Patients with a score of greater than 6 on the CIRS scale or a calculated creatinine clearance of less than 70 ml per minute were randomly assigned to receive **venetoclax plus obinutuzumab** or **chlorambucil plus obinutuzumab**. The primary end point was PFS (investigator-assessed). Key secondary end points were PFS as assessed by an independent review committee, and overall survival. Other secondary end points included the duration of response, event-free survival, and time to new antileukemic treatment.

In total, 432 patients, median age, 72 years; median CIRS score = 8; median creatinine clearance, 66.4 ml per minute, underwent randomization. 216 patients were assigned to each group. After a median follow-up of 28.1 months, 30 patients had disease progression or death in the venetoclax–obinutuzumab group and 77 in the chlorambucil–obinutuzumab group (HR=0.35; 95% CI, (0.23-0.53); P<0.001). The Kaplan–Meier estimate of the percentage of patients with progression-free survival at 24 months was significantly higher in the venetoclax–obinutuzumab group compared to the chlorambucil–obinutuzumab group: 88.2% (95% CI, (83.7-92.6) as compared with 64.1% (95% CI, 57.4-70.8). This benefit was also observed in patients with *TP53* deletion, mutation, or both and in patients with unmutated *IGHV* genes.

Grade 3 or 4 neutropenia occurred in 52.8% of patients in the venetoclax–obinutuzumab group and in 48.1% of patients in the chlorambucil–obinutuzumab group, and grade 3 or 4 infections occurred in 17.5% and 15.0%, respectively. All-cause mortality was 9.3% in the venetoclax–obinutuzumab group and 7.9% in the chlorambucil–obinutuzumab group. These differences were not significant.

#### [Furman 2014 \[34\]](#)

*This study is included in the NMA analysis of R/R CLL*

NCT01539512

This is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study, evaluating the efficacy and safety of **idelalisib, in combination with rituximab** versus **rituximab plus placebo** with **relapsed** chronic lymphocytic leukemia (CLL). All patients were assigned to receive rituximab intravenously (at a dose of 375 mg per square meter of body-surface area), followed by 500 mg per square meter every 2 weeks for 4 doses and then every 4 weeks for 3 doses, for a total of 8 infusions. Patients were stratified according to the presence of 17p deletion, other *TP53* mutations or the lack of *IGHV*. The patients were then randomly assigned to receive rituximab with either oral idelalisib (at a dose of 150 mg) (idelalisib group) or placebo (placebo group) twice a day. 220 patients with relapsed CLL were randomized. The primary end point was progression-free survival. At the first prespecified interim analysis, the study was stopped early on the recommendation of the data and safety monitoring board.

The median PFS was 5.5 months in the placebo group and was not reached in the idelalisib group (HR=0.15; P<0.001). Patients receiving idelalisib versus those receiving placebo had improved rates of ORR (81% vs. 13%; odds ratio, 29.92; P<0.001) and OS at 12 months (92% vs. 80%; HR=0.28; P=0.02). In the idelalisib group, the five most common adverse events were pyrexia, fatigue, nausea, chills, and diarrhea. In the placebo group, the adverse events were similar to those in the idelalisib group, with the most common being infusion-related reactions, fatigue, cough, nausea, and dyspnea. Serious adverse events occurred in 40% of the patients receiving idelalisib and rituximab and in 35% of those receiving placebo and rituximab. The most frequent serious adverse events in the two groups were pneumonia, pyrexia, and febrile neutropenia. Adverse events leading to study-



drug discontinuation were 9 patients (8%) in the idelalisib group and 11 patients (10%) in the placebo group [34]

#### Jones 2017 [35]

*This study is included in the NMA analysis of R/R CLL*

NCT01659021

This study is an open-label, randomised, controlled phase 3 trial, enrolling patients with relapsed CLL progressing less than 24 months from last therapy. Patients refractory to ofatumumab were excluded. Patients were stratified by relapsed versus refractory disease, presence or absence of del(17p) and or TP53 mutation and IGHV mutation. Patients were randomized 2:1 ratio to receive either idelalisib plus ofatumumab (oral idelalisib 150 mg twice daily continuously plus ofatumumab 300 mg intravenously in week 1, then 1000 mg intravenously weekly for 7 weeks, and every 4 weeks for 16 weeks) or ofatumumab alone (ofatumumab dosing as per the combination group, except 2000 mg was substituted for the 1000 mg dose). The primary endpoint was PFS assessed by an independent review committee in the intention-to-treat population. The primary data cutoff was January 2015 followed by an updated analysis with data cutoff in September 2015. Enrollment was between Dec 17, 2012, and March 31, 2014 and 261 patients were randomized. At the primary analysis, median PFS was 16.3 months (95% CI 13.6-17.8) in the idelalisib plus ofatumumab group and 8.0 months (5.7-8.2) in the ofatumumab group (HR 0.27, 95% CI 0.19-0.39,  $p < 0.0001$ ). The most frequent grade 3 or more adverse events in the idelalisib plus ofatumumab group were neutropenia 59 (34%) patients vs 14 (16%) in the ofatumumab group, diarrhoea 34 (20%) vs 1 (1%), and pneumonia 25 (14%) vs 7 (8%). The most frequent grade 3 or more adverse events in the ofatumumab group were neutropenia 14 (16%), pneumonia 7 (8%), and thrombocytopenia 6 (7%) vs 19 (11%) in the idelalisib plus ofatumumab group. Serious infections were more common in the idelalisib plus ofatumumab group and included pneumonia 23 (13%) patients in the idelalisib plus ofatumumab group vs nine [10%] in the ofatumumab group, sepsis 11 (6%) vs 1 (1%), and *Pneumocystis jirovecii* pneumonia eight (5%) vs 1 (1%). 22 treatment-related deaths occurred in the idelalisib plus ofatumumab group (the most common being sepsis, septic shock, viral sepsis, and pneumonia). Six treatment-related deaths occurred in the ofatumumab group (the most common being progressive multifocal leukoencephalopathy and pneumonia) [35].

#### Huang 2018 [36]

*This study is included in the NMA analysis of R/R CLL*

NCT01973387

In this study **ibrutinib** was compared with **rituximab** in a randomized, open-label phase 3 study design with **relapsed/refractory CLL/SLL**. Patients were randomly assigned 2:1 to receive 420 mg oral ibrutinib once daily or intravenous rituximab. Randomization was stratified by purine analog refractory status and the presence of del17p. Patients were assigned to a treatment group between 26 December 2013 and 15 September 2015. Rituximab was administered at 375 mg/m<sup>2</sup> on day 1 and 500 mg/m<sup>2</sup> on day 15 of cycle 1; 500 mg/m<sup>2</sup> on days 1 and 15 for cycle 2; and 500 mg/m<sup>2</sup> on day 1 of cycles 3–6. 106 patients were randomized to ibrutinib and 54 to rituximab. The primary endpoint was investigator-assessed progression-free survival (PFS); key secondary endpoints were ORR, OS,

and safety. Rituximab-treated patients could crossover to receive ibrutinib after confirmed PD. At data cutoff, median treatment duration was 16.4 months for ibrutinib and 4.6 months for rituximab. Ibrutinib significantly improved PFS (hazard ratio [HR] = 0.180, 95% confidence interval [CI]: 0.105-0.308). ORR was significantly higher ( $P < 0.0001$ ) with ibrutinib (53.8%) than with rituximab (7.4%). At a median follow-up of 17.8 months, ibrutinib improved OS compared with rituximab (HR = 0.446; 95% CI: 0.221-0.900;  $P = 0.0206$ ). Overall incidence of adverse events (AEs) was similar between treatments and was not exposure-adjusted. With ibrutinib, most common AEs were diarrhea and platelet count decreased; with rituximab, most common AEs were neutrophil count decreased and platelet count decreased. Grade  $\geq 3$  AEs were reported in 82.7% of ibrutinib-treated patients and 59.6% of rituximab-treated patients. Ibrutinib improved PFS, ORR, and OS compared with rituximab and displayed a manageable safety profile in Asian patients with relapsed/refractory CLL/SLL [36]

### Zelenets AD [37]

*This study is included in the NMA analysis of R/R CLL*

NCT01569295.

This is an international, multicentre, double-blind, placebo-controlled trial, that included patients with **relapsed or refractory CLL**. Patients were randomly assigned (1:1) to receive **bendamustine plus rituximab** for a maximum of six cycles (bendamustine: 70 mg/m<sup>2</sup> intravenously on days 1 and 2 for six 28-day cycles; rituximab: 375 mg/m<sup>2</sup> on day 1 of cycle 1, and 500 mg/m<sup>2</sup> on day 1 of cycles 2-6) in addition to either twice-daily oral **idelalisib** (150 mg) or **placebo** until disease progression or intolerable study drug-related toxicity. Randomization was stratified by high-risk features (IGHV, del[17p], or TP53 mutation) and refractory versus relapsed disease. The primary endpoint was PFS assessed by an independent review committee in the ITT population [37].

Between June 26, 2012, and Aug 21, 2014, 416 patients were enrolled and randomly assigned to the idelalisib (n=207) and placebo (n=209) groups. At a median follow-up of 14 months (IQR 7-18), median PFS was 20.8 months (95% CI 16.6-26.4) in the idelalisib group and 11.1 months (8.9-11.1) in the placebo group (hazard ratio [HR] 0.33, 95% CI 0.25-0.44;  $p < 0.0001$ ). The most frequent grade 3 or worse adverse events in the idelalisib group were neutropenia 124 (60%) and febrile neutropenia 48 (23%), whereas in the placebo group they were neutropenia 99 (47%) and thrombocytopenia 27 (13%). An increased risk of infection was reported in the idelalisib group compared with the placebo group (grade  $\geq 3$  infections and infestations: 80 (39%) vs 52 (25%). Serious adverse events, including febrile neutropenia, pneumonia, and pyrexia, were more common in the idelalisib group 140 (68%) than in the placebo group 92 (44%). Treatment-emergent adverse events leading to death occurred in 23 (11%) patients in the idelalisib group and 15 (7%) in the placebo group, including six deaths from infections in the idelalisib group and three from infections in the placebo group [37].

Table 8. Overview of the ELEVATE-RR study

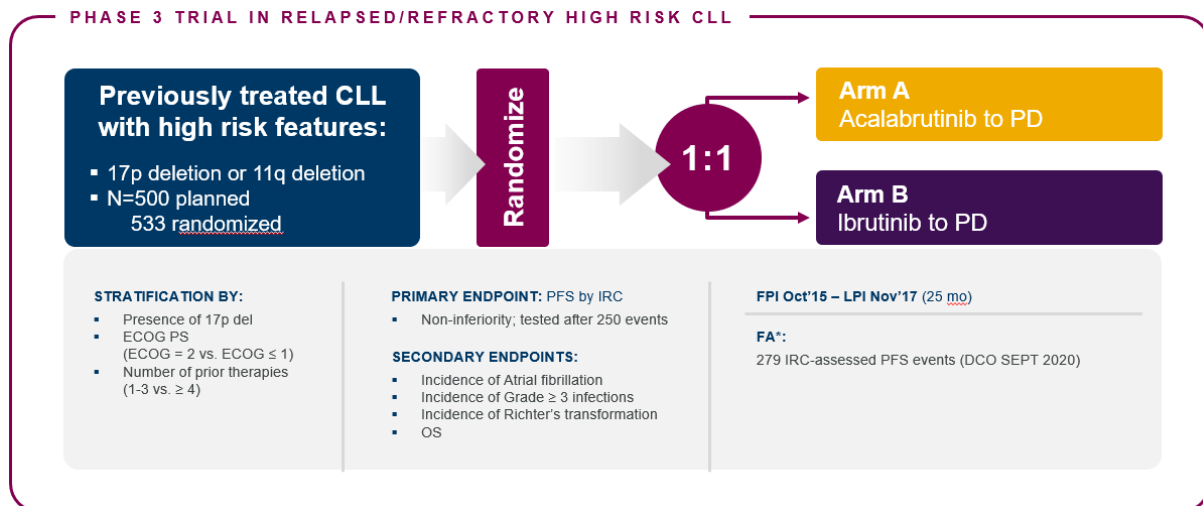
Sample size (n)	533 patients
Study design	Randomised, multicentre, open-label Phase III non-inferiority trial. Patients were randomised (1:1) into two arms
Patient population	Patients with previously treated CLL with high-risk features (presence of 17p deletion and/or 11q deletion).
Intervention(s)	Calquence (100mg orally twice daily) until disease progression
Comparator(s)	Ibrutinib (420mg orally once daily) until disease progression or unacceptable toxicity
Follow-up period	Median follow-up of 41 months
Is the study used in the health economic model?	Yes
Primary endpoints reported	PFS by IRC
Other outcomes reported	Incidence of adverse events (AE) – any grade Incidence of Atrial Fibrillation (AF) Incidence of grade $\geq 3$ infection Incidence of Richter's transformation Overall Survival (OS)

### Design, Interventions and Dosing

ELEVATE-RR (ACE-CL-006) is a randomised, multicentre, open-label Phase III non-inferiority trial of acalabrutinib versus ibrutinib in patients with previously treated CLL with high-risk features (presence of 17p deletion and/or 11q deletion). In the trial, 533 patients were randomised (1:1) into two arms. Patients in the first arm received acalabrutinib (100mg orally twice daily) until disease progression or unacceptable toxicity. Patients in the second arm received ibrutinib (420mg orally once daily) until disease progression or unacceptable toxicity.

Key inclusion criteria included patients with previously treated CLL, with high risk features 17p deletion or 11q deletion. Diagnosis of CD20+ CLL,  $\geq 1$  prior systemic therapy for CLL, active disease that met  $\geq 1$  of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria for requiring treatment [39]. A schematic of the study design is shown below in figure 6.

**Figure 6.** ELEVATE-RR study design



### Study Population

Baseline patient characteristics were generally balanced between the two treatment groups, as shown in the appended results of ELEVATE-RR. At baseline, about half (54%) of patients were ≥65 years of age (16% ≥75 years), 93%/92% had an ECOG score of 0 or 1 in the acalabrutinib and the ibrutinib arm respectively, 48%/51% had tumour bulk ≥5cm and 49%/50% had Rai stage III or IV disease, 46% of the patients had 17p deletion, and 62/66% had an 11q deletion.

Patients were stratified by presence of 17p deletion, ECOG performance status (ECOG 2 versus ECOG ≤ 1) and number of prior therapies (1 to 3 versus ≥4). The median time from diagnosis to randomization was 84.8 months in the acalabrutinib arm and 73.0 months in the ibrutinib arm, and median time from prior treatment to randomization was 19 months in both arms. Both arms had a median of 2 prior lines of therapy (range 1-9 in the acalabrutinib arm and 1-12 in ibrutinib arm), with 89% of 1-3 prior lines of therapy in the acalabrutinib arm 89% and 90% in the ibrutinib arm.

### Study Endpoints

The primary endpoint for the trial was PFS assessed by an independent review committee (non-inferiority; tested after 250 events). Secondary endpoints included incidence of atrial fibrillation, incidence of treatment-emergent Grade 3 or higher infections, incidence of Richter's transformation (a condition in which CLL changes into an aggressive form of lymphoma) and overall survival.

After a median follow-up of 41 months, acalabrutinib was demonstrated to be non-inferior to ibrutinib in high-risk patients with previously treated CLL, with a median PFS as assessed by the independent review committee (IRC) of 38.4 months in both arms (HR 1.00; 95% CI 0.79 to 1.27). Results were generally comparable across all evaluated subgroups, including age, race, sex, ECOG status, geographic region, presence of chromosomal abnormalities (17p deletion), number of prior therapies, tumor load and disease stage (Rai), as well as on investigator-assessed PFS (HR 0.90; 95% CI 0.69 to 1.16).

The trial met a key secondary endpoint for safety, showing patients treated with acalabrutinib had statistically significantly lower incidence of atrial fibrillation compared to patients treated with ibrutinib (9.4% vs. 16.0%, respectively, p = 0.0228). Compared with ibrutinib, acalabrutinib was

associated with a lower incidence of grade  $\geq 3$  TEAEs, as well as a lower incidence (not significant) of serious adverse events (SAEs) and TEAEs that led to treatment discontinuation.

### NMA and MAIC

In all the studies listed above it is stated if they are part of the NMA/MAIC in 1<sup>st</sup> or R/R CLL.

NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., odds ratio, relative risk, or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers.

MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison.

The studies included in the NMAs were selected based on a systematic literature review. The identification of potential prognostic factors and treatment effect modifiers was done through a review of the literature and survival analyses from the ASCEND/ELEVATE trials. NMAs and MAICs were conducted for PFS, OS, and ORR, in line with recommendations in the NICE guidelines (Phillippo et al., 2018).

The NMA has been published by Davids et al. As the ITCs were completed in 2019 and therefore it is relevant to investigate if updates of long term results has been published and can affect the outcome and also more important if new studies within has been published and are not included.

The SLR for the NMA and MAIC was carried out in August 2019 and the SLR for this application was performed 10.12.2020. Long term updates have been published for the below 5 studies since the NMA and MAIC. In the table we have included updated results from the 5 studies and compared against the data used in the NMA/MAIC. Ibrutinib was evaluated to be the most relevant comparator in both 1<sup>st</sup> and RR (section 8 and 9). The RESONATE 2 update by Burger reveals no change in HR for PFS and OS (highlighted in table 9). The other study updates also show minor changes vs primary publication and investigate interventions that are not comparators for acalabrutinib(+O) in 1<sup>st</sup> line CLL. In RR the ASCEND and RESONATE study updates (table 9) confirm the high risk reductions in PFS and immature OS data.

- RESONATE 5 years follow up 2020
- CLL14 follow-up results 2020
- RESONATE 2 long term follow up 2019
- Helios 5 years follow up 2020
- ASCEND follow up (poster) 2020

Overall the naïve comparison for the 5 study updates in the tables below confirms the data used in the NMA/MAIC and do not change the overall conclusion vs the targets set by Medicinrådet. This has also been confirmed by Catherine Waweru who is co-author on the publication of the NMA

Table 9. Trials in the ITC's comparing acalabrutinib vs comparators in patients with 1<sup>st</sup> incl. updates not included in ITC SLR

Author, year	Line	Trial name	Sample size	Intervention	Comparator	Median follow-up	PFS	OS
Hillmen 2015 [22] NMA	1L CLL	COMPLEMENT 1	447	Ofatumumab + chlorambucil	Chlorambucil	28.9 m		
Barr 2018 [13] NMA and MAIC	1L CLL	RESONATE-2	269	Ibrutinib	Chlorambucil	29 m	NR vs 15 m; HR= 0.12 (0.07; 0.20) p<0.0001 PFS at 24m 89% vs 34%	HR= 0.43 (0.21; 0.86) p=0.0145
Burger et al. 2020 [14] Published after NMA/MAIC	1L CLL	RESONATE-2	269	Ibrutinib	Chlorambucil	60 m	PFS estimates at 5 years: 70% vs 12%; HR=0.146 (0.098; 0.218). TP53, 11q del, and/or unmutated IGHV): HR= 0.083 (0.047, 0.145)	OS estimates at 5 years: 83% vs 68%; HR=0.450 (0.266; 0.761) TP53, 11q del, and/or unmutated IGHV): HR [95% CI]: 0.366 [0.181–0.736]
Hillmen 2007[23] NMA	1L CLL	CAM307	297	Alemtuzumab	Chlorambucil	NR		
Moreno 2019[29] NMA and MAIC	1L CLL	iLLUMINATE	229	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab	31.3 m		
Woyach 2018[15] NMA and MAIC	1L CLL	Alliance (A041202)	547	Ibrutinib	Ibrutinib + rituximab, bendamustine + rituximab	38 m		
Michallet 2018[28] NMA	1L and 2L CLL <sup>a</sup>	MaBLE	241	Bendamustine + rituximab	Chlorambucil + rituximab	~ 23.4 months		
Goede 2014[24] NMA and MAIC	1L CLL	CLL11	781	Chlorambucil	Rituximab + chlorambucil, obinutuzumab + chlorambucil	30 months		
Sharman 2020[6] NMA and MAIC	1L CLL	ELEVATE-TN	535	Acalabrutinib Acalabrutinib + obinutuzumab	Chlorambucil + obinutuzumab	~ 29 m		
Fischer 2019[31] NMA and MAIC	1L CLL	CLL14	432	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	28.1 m	HR=0.35 (0.23; 0.53) P<0.001 PFS at 2 years 88.2% (	Median OS not reached 24 months, 91.8% (88.1 to 95.5) vs.

							83.7; 92.6) vs. 64.1% (57.4;70.8)	93.3% (90.0; 96.7), HR=1.24; 90.64; 2.40) P=0.52
<i>Al Sawaf et al. CLL14 follow-up results 2020[41] Published after NMA</i>	1L CLL	CLL14	432	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	39.6 m	NR vs. 35.6 m HR= 0.31 (0.22-0.44); p<0.0001 3 year PFS 81.9% (76.5; 87.3) vs. 49.5% (42.4; 56.6)	HR=1.03 (0.60; 1.75) p=0.92
Tedeschi 2019[25] NMA	1L CLL	RESONATE-2 and iLLUMINATE		Ibrutinib arm of RESONATE-2	Chlorambucil + obinutuzumab arm from iLLUMINATE	Ibrutinib arm from RESONATE-2: 48.8 m iLLUMINATE study: 31.3 months		

Table 10. Trials in the ITC's comparing acalabrutinib with comparators in patients with R/R CLL incl. updates not included in ITC SLR

Author, year	Population	Trial name	Sample size	Intervention	Comparator	Median follow-up	PFS	OS
Furman 2014[34]	R/R CLL	NR	220	IR	Rituximab + placebo	NR		
Jones 2017[35]	R/R CLL	NR	261	Idelalisib + ofatumumab	Ofatumumab	16.1 m		
Brown 2018[19]	R/R CLL	RESONATE	391	Ibrutinib	Ofatumumab	19 m	NR vs 8.1 m HR=0.106(0.075; 0.151) p=0.0001. PFS at 18 m 76 % vs. 8 %	86 % vs. 77%
Talha Munir et al, 2019[21]  Published after NMA/MAIC		RESONATE					44.1 m vs 8.1m HR= 0.148 (0.113-0.196) P<.001	OS was 67.7 m(61.0 ; NE) in the ibrutinib arm and 65.1 months HR= 0.810 ( 0.602-1.091) Not including crossover
Ghia 2020[9]	R/R CLL	ASCEND	310	Acalabrutinib	IR/BR	16 m	NR vs 16.8 m HR=0.31 (0.20; 0.49]; p < 0.0001). 12m PFS 88% (81; 92)	HR, 0.84; (0.42; 1.66) OS at 12m 94% (89%; 97%) vs 91% ( 85%; 94%)

							vs. 68%( 59; 75)  del(17p) and TP53 mutations: PFS (HRs, 0.21 and 0.24.  With versus without unmutated IgVH (HRs, 0.32 and 0.32	
Ghia P, ASCEND final results.[10]  Published after NMA/MAIC	R/R CLL	ASCEND	310	Acalabrutinib	IR/BR	22 m	NR vs 16.8 m, HR = 0.27, p < 0.0001  18 m rates 82 % vs 48 %  del(17p) and TP53 mutations: PFS (HRs, 0.11 and 0.29.  With versus without unmutated IgVH (HRs, 0.28 and 0.30	OS rate at 18 m 88% vs. 88%
Chanan-Khan 2016[30]	R/R CLL	HELIOS	578	Ibrutinib + BR	Placebo + BR	17m	NR vs 13.3 m (11.3–13.9) HR= 0.203 (0.150–0.276) p<0.0001  18 months was 79% (73–83) vs 24% (18–31) HR= 0.203, (0.150–0.276) p<0.0001	NR vs NR  HR=0.628(0.385; 1.024) p=0.0598
Published after MAIC Fraser et al 2020[42]		HELIOS				63.7m	65.1m vs 14.3m HR= 0.229 (0.183; 0.286); p < 0.0001	NR vs NR  HR=0.611 (0.455–0.822); p = 0.0010
Huang 2018[36]	R/R CLL	NR	160	Ibrutinib	Rituximab	NR		



<b>Zelenetz 2017[37]</b>	R/R CLL	NR	416	Idelalisib + BR	BR + placebo	14 m		
<b>Seymour 2018[32] Kater 2019 (included in MAIC)[33]</b>	R/R CLL	MURANO	389	Venetoclax + rituximab	BR	23.8 months (NMA) 36 months (MAIC)		

## 5 Clinical question Acalabrutinib vs. O + C and B + R in 1<sup>st</sup> line CLL without p17/del53 .

### 5.1 PFS and PFS rate at 3 years or latest

#### 5.1.1 Presentation of relevant studies PFS and PFS rate at 3 years

##### Obininutuzumab-chlorambucil

###### ELEVATE:

The study is a direct comparison vs. obininutuzumab-chlorambucil and subgroups results are available for the population without p17/del53. PFS rate at 3 years is only available for the ITT population. The combination is also covered by the NMA and MAIC indirect comparison.

##### Bendamustine + rituximab:

Indirect treatment comparisons using network meta-analysis (NMA) and matching-adjusted indirect comparison (MAIC) were performed to compare the efficacy and safety of acalabrutinib monotherapy and acalabrutinib plus obinutuzumab versus other regimens recommended for the first-line treatment of patients with CLL. Both analyses were based on data from ELEVATE-TN for acalabrutinib monotherapy and acalabrutinib plus obinutuzumab, and a systematic review was performed to identify randomized controlled trials (RCTs) in first-line CLL for relevant comparators. The data has been published by David et al [7, 43, 44].

##### Narrative vs. Bendamustine + Rituximab

Naïve comparisons are used for evaluating different outcomes and support data from the ITC's. Below is a table showing patient characteristics of relevant studies used in narrative comparison of acalabrutinib ( + obinutuzuamb) vs. Bendamustine + Rituximab.

Table 11. Study characteristics

Study characteristics	ELEVATE-TN [6]	CLL-10 [26]	ALLIANCE [15]	MABLE [28]
<b>Eligibility</b>	>65y <65y with CIRS-score > 6 del17p/Tp53	previously untreated fit patients aged 33– 81 years No del 17p patients	>65y No CIRS score	>18 years FCR ineligible patients
<b>Age (median in years)</b>	A: 70 (65-75) AO:70 (66-75)	61 (54-69)	70 (65-86)	72 (41-86)
<b>ECOG %</b>				
0		64	54	51
1	A: 94,4 AO: 92*	36	41	41
2	A: 5,6 AO: 7.8	<1	5	1
<b>CIRS score (median)</b>	A: 6 (3-8) AO: 6 (3-8) #	2 (0-3)	NR	NR
<b>Binet stage %</b>			NR	**
A	NR	22		5
B		38		60
C		39		31
<b>Rai stage (%)</b>				NR
0	A: 1.7 AO: 0	5	I/II: 46 (intermediate)	
I	A: 30,2 AO: 26,8	14		
II	A: 20,1 AO: 24,6	37		
III	A: 26,8 AO: 27,9	15	III/IV: 54 (High)	
IV	A: 21,2 AO: 20,7	29		
<b>IGHV mutated %</b>	A: 42,5 AO: 34,5	32	42	34
<b>IGHV unmutated %</b>	A: 57,5 AO: 66,5	68	58	60
<b>Del17p mutation %</b>	A: 9,5 AO: 8,9	NR	8	8
<b>Tp53 %</b>	A; 11,7 AO: 10,6	NR	9	NR

\* ECOG 0-1, NR= not reported, \*\* 4 with missing data, # CIRS not required for all patients

#### Rationale for study selection for narrative comparisons

The ELEVATE-TN study [6] is an open label Ph III, multi center randomized study in previously untreated CLL patients that included patients above 65 years, which according to Danish clinical practice would receive either BR (>65 years and CIRS-score < 6) or Clb+O (any age, CIRS-score > 6). CIRS was however not measured in ELEVATE-TN for patients above 65 years (Table 8). ELEVATE-TN also included patients below 65 years but with a CIRS-score above 6, a group who according to Danish clinical practice would receive chlorambucil+ obinutuzimab. As demonstrated in table 8, the study allowed patients with del17p (acalabrutinib: 9,5% and acalabrutinib + obinutuzimab: 8.9%) or mutated TP53 (Acalabrutinib: 11,7% and Acalabrutinib + obinutuzimab: 10,6%), these patients would in Danish clinical practice would receive ibrutinib (venetoclax + obinutuzimab was recently approved also).

Three studies with bendamustine + rituximab as 1<sup>st</sup> line treatment were chosen for the narrative comparison:

- The CLL-10 study is an open label Ph III, multi center randomized study in previously untreated CLL patients. The inclusion criteria allowed for patients between 33-81 years of age (Table 8) that according to Danish clinical practice would either receive FCR (<65 years and fit e.g. CIRS <6) or bendamustine + rituximab (>65 years and CIRS-score < 6). The patient population is partially comparable to the population in ELEVATE-TN, in that both

studies contain a patient population that in Danish clinical practice would receive BR. However, patients in CLL-10 deviates from ELEVATE-TN in that patients are younger with median age (61) than in the ELEVATE-TN study (median age of 70) and more fit with a lower CIRS score (median 2 vs median 6 in ELEVATE-TN) and the CLL-10 study also excluded del 17p patients. Thus, patients in CLL-10 have a more favourable prognosis than the patients in the ELEVATE-TN study. The percentage of patients with unmutated IGHV (table 8), which is an unfavorable feature are however similar between the studies (68% in CLL-10 vs A: 57,5 and AO: 66,5% in ELEVATE-TN). We, evaluate the studies to be partially comparable for a narrative analysis.

- The ALLIANCE study is an open label Ph III, multi center randomized study in previously untreated CLL patients that included patients above 65 years (no CIRS required) and allowed 17pdel/Tp53 mutated patients (table 10). The patient population constitutes patients that would be treated with BR in Danish clinical practice (above 65 and CIRS score <6) or Clb+O (any age and CIRS score >6) as well patients that would receive ibrutinib/VO (17p del/Tp53 mutated).

The median age in the Alliance and ELEVATE-TN studies was 70 years, ECOG status was similar between the studies and percentage of patients with unmutated IGHV, del17p and TP53 mutation was also similar (table 8). We thus evaluate the patient population included in ALLIANCE study to be sufficiently comparable for a narrative comparison.

- The MABLE study is an open label Ph III, multi center randomized study that included FCR ineligible patients that according to Danish clinical practice would receive B + R, C+O or ibrutinib. The median age in the MABLE study (72 years) is similar to the median age in the ELEVATE-TN study (70 years). ECOG status, percentage of patients with unmutated IGHV and del 17p are similar between the studies (Table 8). Of note is that the MABLE study included approximately 32,5% patients with previous therapy. We, evaluate the studies to be partially comparable for a narrative analysis.

For detailed patient characteristics and design of the studies please see above in section 4.2 or visit tables A2.

#### NMA:

A systematic literature review (SLR) was conducted to identify RCTs previously conducted in first-line and R/R CLL up to 19 August 2019 [7, 44]. The population, intervention, comparators, outcomes, study design (PICOS) criteria for study selection are summarized in table 12. Following completion of the SLR, 66 of the identified studies included a first-line population, 56 included a R/R population and 19 had mixed-line populations.

TABLE 12. SUMMARY OF THE PICOS CRITERIA FOR FIRST-LINE CLL

Eligibility criteria	
<b>Population</b>	Treatment-naïve patients with CLL (aged ≥ 18 years) considered ineligible for fludarabine-based chemotherapy
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• Acalabrutinib monotherapy</li> <li>• Acalabrutinib + obinutuzumab</li> </ul>
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Alemtuzumab</li> <li>• Ibrutinib</li> <li>• Ibrutinib + obinutuzumab</li> <li>• Chlorambucil + rituximab</li> <li>• Chlorambucil + ofatumumab</li> <li>• Chlorambucil + obinutuzumab</li> <li>• Bendamustine + rituximab</li> <li>• Venetoclax + obinutuzumab</li> </ul>
<b>Outcomes</b>	PFS and OS
<b>Study design</b>	RCTs

Source: NMA report.[44]

Among the trials identified through the SLR, nine were considered relevant for inclusion in the NMA for first-line CLL. Table 13 provides an overview of these studies.

Table 13. Trials included in the NMA. Acalabrutinib and acalabrutinib + obinutuzumab vs. selected comparators in 1<sup>st</sup> CLL

Author, year	Population	Trial name	Sample size	Phase	Intervention	Comparator	Median follow-up
Hillmen 2015 [19]	1L CLL	COMPLEMENT 1	447	3	Ofatumumab + chlorambucil	Chlorambucil	28.9 months
Barr 2018 [10]	1L CLL	RESONATE-2	269	3	Ibrutinib	Chlorambucil	29 months
Hillmen 2007 [20]	1L CLL	CAM307	297	3	Alemtuzumab	Chlorambucil	NR
Moreno 2019 [26]	1L CLL	ILLUMINATE	229	3	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab	31.3 months
Woyach 2018 [12]	1L CLL	Alliance (A041202)	547	3	Ibrutinib	Ibrutinib + rituximab, bendamustine + rituximab	38 months
Michallet 2018 [25]	1L and 2L CLL <sup>a</sup>	MaBLE	241	3b	Bendamustine + rituximab	Chlorambucil + rituximab	~ 23.4 months
Goede 2014 [21]	1L CLL	CLL11	781	3	Chlorambucil	Rituximab + chlorambucil, obinutuzumab + chlorambucil	30 months
Sharman 2020 [5]	1L CLL	ELEVATE-TN	535	3	Acalabrutinib Acalabrutinib + obinutuzumab	Chlorambucil + obinutuzumab	~ 29 months
Fischer 2019 [28]	1L CLL	CLL14	432	3	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	28.1 months
Tedeschi 2019 [22] <sup>b</sup>	1L CLL	RESONATE-2 and ILLUMINATE		3 cross-trial comparison	Ibrutinib arm of RESONATE-2	Chlorambucil + obinutuzumab arm from ILLUMINATE	Ibrutinib arm from RESONATE-2: 48.8 months ILLUMINATE study: 31.3 months

<sup>a</sup> Patients with 2L CLL were excluded after a protocol amendment. <sup>b</sup> Identified separately from the SLR. Source: NMA report [44]

Two networks were generated from the identified studies . One network included only RCTs (network 1) and a second network (network 2) was added to provide a more direct comparison between acalabrutinib and ibrutinib by including a cross-trial comparison of ibrutinib (RESONATE-2) and chlorambucil plus obinutuzumab (iLLUMINATE) [25]. Network 1 used IRC-assessed PFS and OS (investigator-assessed PFS and OS were used if IRC-assessed results were unavailable) and network 2 used investigator-assessed PFS and OS (IRC-assessed PFS and OS were used if investigator-assessed results were unavailable). The NMA is published by Davids et al. [7].

The NMA can be submitted on request to Medicinrådet.

#### MAIC:

Six of the studies identified in the SLR conducted for the NMA were also included in the MAIC: RESONATE-2, iLLUMINATE, Alliance (A041202), CLL11, ELEVATE-TN and CLL14 [6, 8, 13, 15, 24, 29, 31, 43].

The MAIC approach used individual patient-level trial data from the acalabrutinib trial ELEVATE-TN, and adjusted the trial population to match average baseline characteristics reported for the comparator trials: RESONATE-2 (ibrutinib vs chlorambucil), iLLUMINATE (ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab), CLL14 (venetoclax + obinutuzumab vs chlorambucil + obinutuzumab), Alliance (A041202) (BR vs ibrutinib [alone or + rituximab]) and CLL11 (rituximab + chlorambucil vs obinutuzumab + chlorambucil and additionally, each of these vs chlorambucil). Individual patients in ELEVATE-TN were assigned weights, such that weighted mean baseline characteristics in ELEVATE-TN exactly matched all of those reported for patients in the comparator trials, and each individual patient's weight was equal to their estimated odds (relative propensity) of being in the comparator trials relative to ELEVATE-TN. Weights were obtained from a logistic regression model. These weights were used to calculate the ESS achieved after weighting patients, and also to recalculate clinical outcomes from ELEVATE-TN. Matching parameters were selected based on whether they were reported in the published comparator trial and in consultation with two clinical experts [43, 45].

The following baseline characteristics were considered for matching:

- age over 75 years
- sex
- presence of bulky disease ( $\geq 5$  cm)
- presence of del(17p) mutation
- presence of *TP53* mutation
- presence of del(11q) mutation
- ECOG Performance Status
- beta-2 microglobulin at baseline ( $> 3.5$  mg/L)
- Rai stage or Binet stage
- complex karyotype
- *IGHV* mutation status

- creatinine clearance below 60 mL/min or 70 mL/min or 67 mL/min or 62 mL/min
- CIRS-Geriatric score of 6 or higher, or 9 or higher.

The MAIC in 1<sup>st</sup> line CLL is expected to be published in near future.

### 5.1.2 Results per study Acalabrutinib vs. O+C and B+R 1<sup>st</sup> line CLL without p17/del53 PFS/PFS rate

#### NMA

The NMA include data from the subpopulation without 17p deletion. When considering patients without a 17p deletion, only a few studies reported results for the outcomes of interest. The RESONATE-2 study reports results for patients only without a 17p deletion as this was an inclusion criterion in the trial. However, RESONATE-2 could not be included in this network as the CLL-11 trial, used to link chlorambucil to chlorambucil + obinutuzumab in the base case network, did not report results for this subgroup. Therefore, RESONATE-2 was disconnected.

In terms of data from the publications, only the ILLUMINATE trial was used to compare acalabrutinib monotherapy and in combination with obinutuzumab to ibrutinib in combination with obinutuzumab. The corresponding data inputs are reported in table 14. For this subgroup, the population sizes were 197 patients for ILLUMINATE and of 478 patients for ELEVATE.

Table 14. Data inputs for the PFS NMA in first line on patients without a 17p deletion

Study name	Sample size	Treatments	HR [CI]
ILLUMINATE	197	Ibrutinib+Obinu vs. Chlorambucil+Obinu	0.25 [0.16,0.42]
ELEVATE	478	Acalabrutinib+Obinu vs. Chlorambucil+Obinu	0.10 [0.06,0.19]
		Acalabrutinib vs. Chlorambucil+Obinu	0.20 [0.12,0.32]

As shown in table 15 through the results of the NMA, acalabrutinib, monotherapy, was associated with a lower risk of progression, compared to chlorambucil in combination with obinutuzumab (HR [95%CrI] = 0.20 [0.12,0.32] and ibrutinib plus obinutuzumab (HR [95%CrI] = 0.80 [0.40,1.58]).

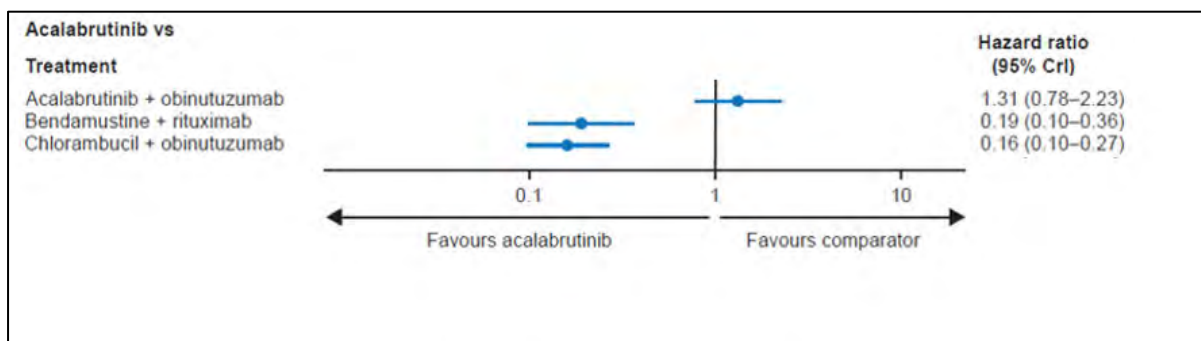
Table 15. Results from the PFS NMA in first line for patients without a 17p deletion

Row vs. Column HR [95%CrI]	Chlor+Obinu	Ibru+Obinu	Acala+Obinu	Acala
<b>Chlor+Obinu</b>	-	4.00 [2.43,6.64]	9.81 [5.35,18.08]	5.03 [3.13,8.06]
<b>Ibru+Obinu</b>	0.25 [0.15,0.41]	-	2.45 [1.11,5.39]	1.26 [0.63,2.49]
<b>Acala+Obinu</b>	<b>0.10</b> [0.06,0.19]	<b>0.41</b> [0.19,0.90]	-	<b>0.51</b> [0.30,0.89]
<b>Acala</b>	<b>0.20</b> [0.12,0.32]	<b>0.80</b> [0.40,1.58]	<b>1.95</b> [1.13,3.37]	-

Source [7, 44]

Below is the result from the NMA ITT population (figure 7). The HR=0.19 vs bendamustine + rituximab and 0.16 vs. obinutuzumab + chlorambucil with upper CI limit below 1.0.

Figure 7. Forest plot of the PFS NMA including a cross-trial comparison in first line (acalabrutinib mono vs. comparators)

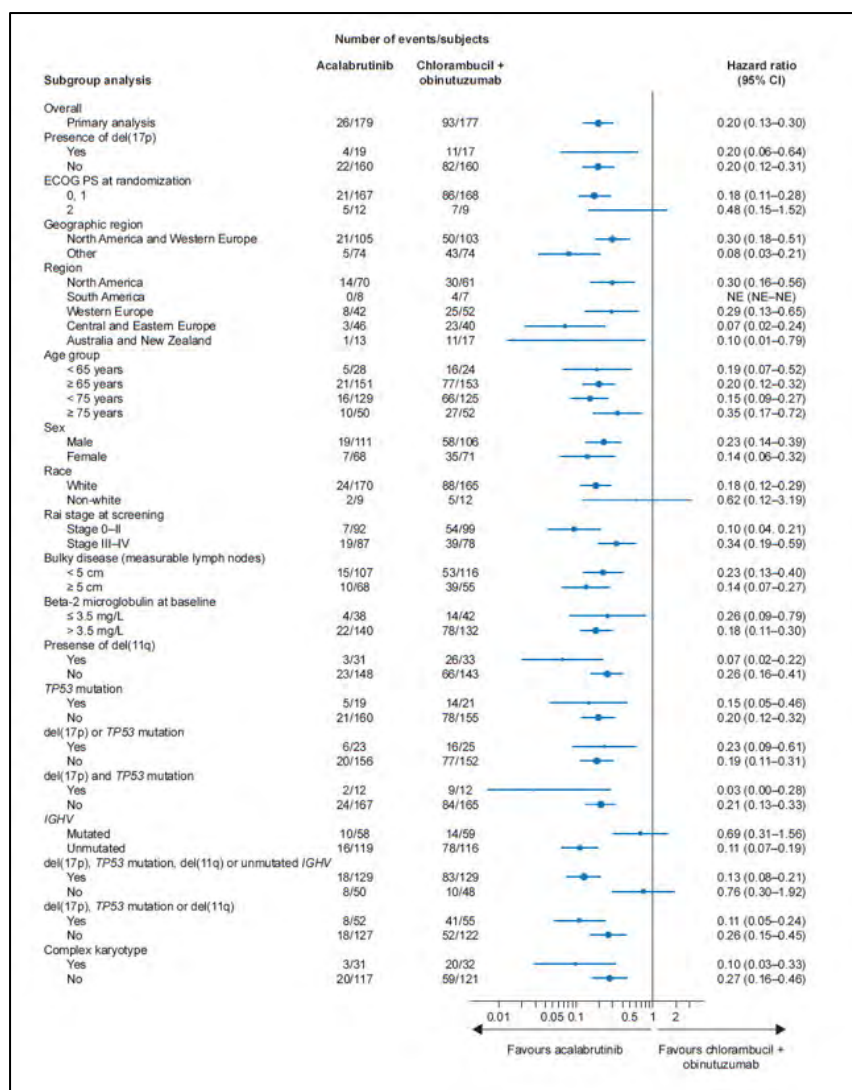


Source Davids et al and NMA report [7, 44]

### ELEVATE-TN

In the subgroup without p17/del53 the results is shown below in figure 8. Comparing acalabrutinib monotherapy with obinutuzumab + chlorambucil resulted in HR=0.19(0.11; 0.31). Data from this subgroup has a median follow-up of 28 months.

FIGURE 8. KEY SECONDARY ANALYSIS (ACALABRUTINIB MONOTHERAPY VS CHLORAMBUCIL + OBINUTUZUMAB): PFS SUBGROUP ANALYSIS (IRC ASSESSMENT). ELEVATE



Source: ELEVATE-TN clinical study report

### 5.1.3 Comparative analysis Acalabrutinib vs. C + O 1<sup>st</sup> line CLL without p17/del53. PFS/PFS rate

PFS rate at 3 years is not available for the subpopulation without p17/del53. As more than 85% of the study population did not have the mutations, the below rate from the overall population should be an indicator for the PFS rate in the group without p17/del53. The ELEVATE-TN trial also met its key secondary endpoint, with acalabrutinib monotherapy demonstrating a statistically significant and clinically meaningful improvement in IRC-assessed PFS, compared with chlorambucil plus obinutuzumab, after a median follow-up of 28 months. Treatment with acalabrutinib monotherapy resulted in an 80% reduction in the relative risk of disease progression or death vs chlorambucil plus obinutuzumab (HR: 0.20; 95% CI: 0.13–0.30;  $p < 0.0001$ ) [8]. Median PFS for acalabrutinib monotherapy was not reached.

The KM estimate of the proportion of subjects (ITT) is shown in table 16.



TABLE 16. ELEVATE ITT PRIMARY AND KEY SECONDARY PFS ANALYSIS (IRC ASSESSMENT)

	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 177)
<b>Death</b>	6 (3.4)	11 (6.2)
<b>Disease progression</b>	20 (11.2)	82 (46.3)
<b>6-month PFS</b>	95.9 (91.6–98.0)	97.0 (92.9–98.7)
<b>12-month PFS</b>	92.9 (87.8–95.9)	84.6 (78.0–89.3)
<b>18-month PFS</b>	90.5 (84.9–94.1)	65.6 (57.7–72.4)
<b>24-month PFS</b>	87.3 (80.9–91.7)	46.7 (38.5–54.6)
<b>30-month PFS</b>	81.9 (73.3–88.0)	34.2 (25.3–43.2)
<b>36-month PFS</b>	63.9 (29.4–84.9)	31.3 (21.8–41.3)

<sup>a</sup>Assessed by IRC. Source: ELEVATE-TN clinical study report, Table 14.[8]

In the patient group (ELEVATE-TN) without p17/del53 the 20 out of 156 (12.8%) patients in the acalabrutinib arm had progressed vs. 77 out of 152 (50.7%) patients in the control arm resulting in a 37,9% difference or HR= 0.19 (0.11-0.31). The NMA showed similar effect (for the group without del17p) HR=0.20(0.12; 0.31) for the acalabrutinib monotherapy arm vs. chlorambucil plus obinutuzumab. PFS at 3 years in the ITT population showed a difference of 32,6 % which is believed to be valid for the group of patients without mutations.

Medicinerådet has set a target of 10 % difference at 36 month. We conclude that the target is met vs. the combination of chlorambucil plus obinutuzumab.

#### 5.1.4 Comparative analysis Acalabrutinib vs. B + R 1<sup>st</sup> line CLL without p17/del53 PFS/PFS rate

##### MAIC

Results are not available for the subgroup without P17/del53. Based on the MAIC (table 17) acalabrutinib monotherapy is superior in the ITT population with HR = 0.38 (0.20-0.72) p < 0.001.

TABLE 17. RESULTS FROM THE MAIC FOR ACALABRUTINIB MONO COMPARED WITH BENDAMUSTINE + RITUXIMAB

Column vs row Median HR (95% CI)	MAIC	
	Acalabrutinib monotherapy	
	PFS	OS
<b>Bendamustine + rituximab</b>	<b>0.38</b> <b>(0.20–0.72)</b> <b>p &lt; 0.001</b>	<b>1.18</b> <b>(0.51–2.71)</b> <b>p = 0.70</b>

Source MAIC AstraZeneca[43]

## NMA

Acalabrutinib is not evaluated vs. bendamustine + rituximab in the population without del17/p53. Results from overall population/ITT are shown in table 18.

TABLE 18. SUBGROUP ANALYSES FOR NMA OF PFS COMPARING MONOTHERAPY VS. BENDAMUSTINE + RITUXIMAB AND IBRUTINIB

Column vs row, HR (95% CI)	Overall population		Del(17p)		Without del(17p)		IGHV mutations		Without IGHV mutations	
	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab
<b>Bendamustine + rituximab</b>	<b>0.15</b> <b>(0.08–0.27)</b>	<b>0.08</b> <b>(0.04–0.16)</b>	NE	NE	NE	NE	0.31 <i>(0.06–1.57)</i>	<b>0.09</b> <b>(0.01–0.54)</b>	0.10 <i>(0.03–0.32)</i>	<b>0.08</b> <b>(0.02–0.25)</b>
Ibrutinib	0.35 <b>(0.18–0.66)</b>	0.19 <i>(0.09–0.38)</i>	NE	NE	NE	NE	0.47 <i>(0.12–1.82)</i>	0.14 <b>(0.03–0.64)</b>	0.33 <i>(0.12–0.88)</i>	<b>0.24</b> <b>(0.09–0.69)</b>
Acalabrutinib	NA	0.53 <b>(0.32–0.87)</b>	NA	0.54 <i>(0.19–2.11)</i>	NA	<b>0.51</b> <b>(0.30–0.89)</b>	NA	0.29 <b>(0.11–0.75)</b>	NA	0.75 <i>(0.41–1.37)</i>
Acalabrutinib + obinutuzumab	<b>1.88</b> <b>(1.14–3.10)</b>	NA	1.56 <i>(0.47–5.14)</i>	NA	<b>1.95</b> <b>(1.13–3.37)</b>	NA	<b>3.43</b> <b>(1.33–8.90)</b>	NA	1.33 <i>(0.73–2.45)</i>	NA

**Bold** indicates HR values that are statistically significant. Shaded cells indicate HR values that differ in statistical significance, or where the HR differs by  $\geq 0.2$  for a subgroup and the overall population. Source NMA report[44]

Acalabrutinib monotherapy vs. bendamustine plus rituximab is not evaluated in the population without del(17p)/del53 and also not as PFS rate at 3 years. In the overall population in the NMA the HR = 0.15 (0.08–0.27). In the MAIC the HR in the overall population of acalabrutinib vs. bendamustine plus rituximab was 0.38 (0.20–0.72)  $p < 0.001$ . Due to the low number of mutations in the included studies data from the overall population are expected to be representative for the populations without mutations. Data for PFS rate at 3 years vs. bendamustine + rituximab are not available and cannot fully answer the question from Medicinrådet however the PFS results as such are significantly in favour of acalabrutinib monotherapy based on the indirect comparison in the overall populations.

AS PFS rates vs. bendamustine + rituximab are not answered by the ITC's we have based on the studies mentioned in table 12 and data shown in table 21 studies also performed a narrative comparison vs. Bendamustine + Rituximab.

- In the ELEVATE-TN study, the 2-year PFS rate was 87% and the estimated 3-year PFS rate was 63,9% (Table 13)[8] (Table 21), for acalabrutinib monotherapy and the median PFS was not reached at 28.1 months follow-up [6], (Table 22).

- In the CLL-10 study, The 2 and 3-year estimated PFS rates were 79% and **56%** (read of KM curve) respectively and the median PFS was 42,3months at a median follow up of 58 months [26, 27] (Table 22).
- In the Alliance study, the percentage of patients with progression-free survival at 2 years was 74% with bendamustine plus rituximab and the estimated 3-year PFS was **61%** (read of KM curve) the median PFS was 43months [15] (Table 22).
- In the MABLE study with a median follow-up of 23,5 months the estimated 2 year PFS (read on KM-curve) was 79% and the median PFS for bendamustin-rituximab was 39,6 months [28] (Table 22).

The 10% target set by Medicinraadet was met based on the 2-year PFS rate compared to the Alliance study, but not with CLL-10 and MABLE. The 3-year PFS rate does not meet the target.

## 5.2 Acalabrutinib vs. C + O and B + R 1<sup>st</sup> line CLL without p17/del53. OS/OS rate

### 5.2.1 Presentation of relevant studies OS/OS rate

See section 5.2 for more details of studies included in the NMA and MAIC. For the naïve comparison MABLE, CLL-10 and Alliance was compared against ELEVATE.

#### NMA

The data inputs from the studies included in the NMA OS network are presented in table 19.

Table 19. OS data inputs for the first line population

Study name	Treatments	HR [CI]
ALLIANCE	Ibrutinib vs. BendamustineR	0.86 [0.47,1.55]
	IbrutinibR vs. BendamustineR	0.91 [0.51,1.63]
MaBLe	BendamustineR vs. ChlorambucilR	0.98 [0.51,1.88]
RESONATE-2	Ibrutinib vs. Chlorambucil	0.43 [0.21,0.86]
CLL11	ChlorambucilR vs. Chlorambucil	0.66 [0.39,1.11]
	Chlorambucil+Obinu vs. Chlorambucil	0.41 [0.23,0.74]
ILLUMINATE	Ibrutinib+Obinu vs. Chlorambucil+Obinu	0.92 [0.48,1.77]
ELEVATE	Acalabrutinib+Obinu vs. Chlorambucil+Obinu	0.47 [0.21,1.06]
	Acalabrutinib vs. Chlorambucil+Obinu	0.60 [0.28,1.27]
CLL14	Venetoclax+Obinu vs. Chlorambucil+Obinu	1.24 [0.64,2.40]
COMPLEMENT1	Chlorambucil+Ofa vs. Chlorambucil	0.91 [0.57,1.43]

Source NMA report[44]

## 5.2.2 Result per study Acalabrutinib vs. C + O and B+ R OS/OS rate

### Chlorambucil + Obinutuzumab ITT population ELEVATE

The OS data are not mature and median OS was not reached in any treatment arm; however, the OS trend favoured acalabrutinib monotherapy (HR: 0.60; 95% CI: 0.28–1.27;  $p = 0.1556$ ), compared with chlorambucil plus obinutuzumab. After a median follow-up of 28.3 months, 11 patients (6.1%) receiving acalabrutinib monotherapy and 17 patients (9.6%) receiving chlorambucil plus obinutuzumab had died [8].

The KM-estimated OS at 12 months was 98.3% (95% CI: 94.8–99.4) for acalabrutinib monotherapy and 96.5% (95% CI: 92.4–98.4) for chlorambucil plus obinutuzumab. At 36 months, the corresponding OS was 93.5% (95% CI: 88.6–96.3) and 88.1% (95% CI: 80.7–92.8), respectively [8].

Of note, patients who crossed over from chlorambucil plus obinutuzumab to acalabrutinib monotherapy were included in the analysis of OS in the chlorambucil plus obinutuzumab arm; this may have affected the results.

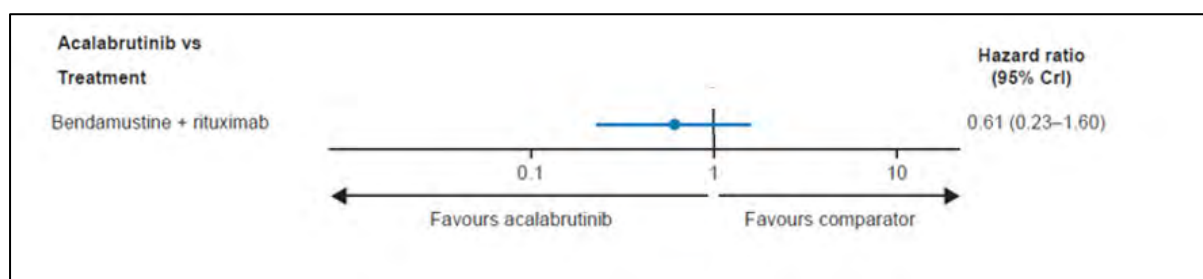
### Bendamustine plus Rituximab

Comparisons of OS are likely to be less robust than comparisons of PFS: in most studies the OS data were immature, reflected by the fact that the duration of follow-up was insufficient for median OS to be achieved. In addition, the trials of acalabrutinib and ibrutinib and the CLL11 trial allowed cross-over of patients, whereas other studies did not. Consequently, although statistically significant reductions in the risk of death (i.e. HR for OS) were noted for some of the comparisons (acalabrutinib monotherapy and acalabrutinib plus obinutuzumab vs chlorambucil monotherapy, chlorambucil plus rituximab or chlorambucil plus ofatumumab, and acalabrutinib monotherapy vs alemtuzumab), in most comparisons, a risk reduction was observed for acalabrutinib monotherapy and acalabrutinib plus obinutuzumab, but the difference was not statistically significant.

### NMA

Below is the OS Forest plot from the NMA for the comparison vs other treatments.

Figure 9. Forest plot of the OS NMA including a cross-trial comparison in first line (acalabrutinib vs. B + R )



Source NMA report[44]

## MAIC

The results of the MAIC are consistent with those of the NMA, suggesting that acalabrutinib, as monotherapy, compares at least favorably with the main standards of care for the treatment of previously untreated patients with CLL, as summarized in table 20 [43, 44].

Results for OS were variable and this variation could be explained by immature OS data and in some trials, the ability of progressed patients in the comparator arm to cross over to the treatment arm.

TABLE 20. SUMMARY OF RESULTS FROM THE MAIC FOR ACALABRUTINIB MONO COMPARED WITH OTHER REGIMENS. OS

Column vs row Median HR (95% CI)	MAIC
	Acalabrutinib Mono
	OS
<b>Chlorambucil + rituximab</b>	<b>0.17</b> <b>(0.07–0.43)</b> <b><i>p</i> &lt; 0.001</b>
<b>Bendamustine + rituximab</b>	<b>1.18</b> <b>(0.51–2.71)</b> <b><i>p</i> = 0.70</b>
<b>Ibrutinib</b>	<b>0.73</b> <b>(0.27–2.02)</b> <b><i>p</i> = 0.55</b>
<b>Ibrutinib + obinutuzumab</b>	<b>0.16</b> <b>(0.05–0.47)</b> <b><i>p</i> = 0.001</b>

Source: MAIC report[43]

### 5.2.3 Comparative analysis/conclusion Acalabrutinib vs C+O OS/OS rate

OS and OS at 3 year results are not available for the subgroup without P17/del53. The OS data in the overall population are not mature and median OS was not reached in any treatment arm; however, the OS trend favored acalabrutinib monotherapy (HR: 0.60; 95% CI: 0.28–1.27; *p* = 0.1556), compared with chlorambucil plus obinutuzumab. At 36 months, the corresponding OS in the ITT population was 93.5% (95% CI: 88.6–96.3) and 88.1% (95% CI: 80.7–92.8), respectively equal to a difference of 5.4 % point. The target set by Medicinraadet was 5 %.

### 5.2.4 Comparative analysis Acalabrutinib vs. B + R. OS/OS rate

#### MAIC and NMA

OS results are not available for the subgroup without P17/del53. The indirect comparison based on the overall population showed that in the MAIC HR was 1.18 (0.51–2.71) *p* = 0.70 and in the NMA the HR was 0.61(0.23; 1.60) so the OS trend favored acalabrutinib. OS data at 3 years is not available for the indirect comparison and the target cannot be meet.

AS OS rates vs. bendamustine + rituximab are not answered by the ITC's we have based on studies mentioned in table 8 and results in table 19 also performed a narrative comparison vs. Bendamustine + Rituximab.

### Narrative

- In the ELEVATE-TN study, the estimated 3 year OS (read of KM) was **93,5%** [8] and the 2 year OS-rate was 95% for acalabrutinib monotherapy [6] (table 22).
- In the CLL-10 study, the 3-year OS rate for the bendamustin-rituximab arm was **92%** [26]
- In the Alliance study, the estimated 3 year OS (read of KM curve) was **88%** and OS at 2 years was 95% with bendamustine plus rituximab [15] (table 22).
- The MABLE study with a median follow-up of 23,5months reported an estimated **2 year OS** (read on KM-curve) of **89%** [28] (table 22).

The 5% target set by Medicinrådet can be met vs. Alliance with 3-year OS and MABLE with 2 year OS (3 year OS not available for MABLE) but cannot be met with CLL-10 (3-year OS).

Overall the conclusion from the naïve comparison is mixed and cannot confirm a 5 % OS benefit for acalabrutinib vs. bendamustine plus rituximab

## 5.3 Acalabrutinib vs. C + O and B + R AEs Grade $\geq 3$

### 5.3.1 Relevant studies 1<sup>st</sup> line CLL AEs Grade $\geq 3$

See section 5.2 for more details of studies included in the NMA and MAIC. For the naïve comparison MABLA, CLL-10 and Alliance was compared against ELEVATE-TN.

### 5.3.2 Result per study AEs Grade $\geq 3$ Acalabrutinib vs. C + O and B + R.

#### Definition of TEAE and SAE

In the ELEVATE-TN study, treatment-emergent adverse events (TEAEs) were defined as any event with an onset date on or after the date of the first dose of study drug, or any ongoing event that worsened in severity after the first dose of study drug, and before 30 days after the date of the last dose of study drug or the date of first starting new anti-cancer therapy. Thus, all AEs and SAEs discussed in this application are TEAEs unless otherwise specified.

An Serious Adverse Event (SAE) was defined as any untoward medical occurrence that, at any dose, resulted in death, was life threatening, required hospitalization of more than 24 hours or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect. An event that did not meet these criteria was considered an SAE when, based upon appropriate medical judgement, the event may have jeopardized the patient or may have required intervention to prevent one of the other outcomes listed above [8]

AE Grade  $\geq 3$  and SAEs are not available for the specific population without p17/del53. The level of AEs and SAE's are however not expected to be different from the ITT population. AE Grade  $\geq 3$  occurred in 49.7 % in the acalabrutinib arm vs. 69.8 in the chlorambucil plus obinutuzumab arm. SAEs in the ITT population, most of which were grade  $\geq 3$ , occurred in 31.8% and 21.9% of patients who received acalabrutinib monotherapy and chlorambucil plus obinutuzumab. Among patients treated with acalabrutinib mono, the most common SAE was pneumonia, which affected five patients (2.8%) receiving acalabrutinib monotherapy. The most common SAE in patients treated with chlorambucil plus obinutuzumab was tumour lysis syndrome, which occurred in eight patients (4.7%) (table 21) [8].

TABLE 21. SUMMARY OF SAEs AND GRADE 3 OR MORE AEs (SAFETY POPULATION)

Event	Number of patients(n)	
	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 169)
<b>Any grade AE</b>	170 (95.0)	167 (98.8)
<b>Grade 1</b>	14 (7.8)	4 (2.4)
<b>Grade 2</b>	67 (37.4)	45 (26.6)
<b>Grade <math>\geq 3</math></b>	89 (49.7)	118 (69.8)

Event	Number (%) of patients	
	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 169)
<b>Any grade SAE</b>	57 (31.8)	37 (21.9)
<b>Grade 1</b>	0	2 (1.2)
<b>Grade 2</b>	4 (2.2)	2 (1.2)
<b>Grade <math>\geq 3</math></b>	53 (29.6)	33 (19.5)

Source: ELEVATE-TN clinical study report and ELEVATE publication. [8, 10]





	<b>PFS 2-year</b>	93%/87%	79%**	74%	79%**
	<b>PFS-3 years</b>	89.9%/63.9%#	56%**	61%**	
	<b>PFS (median, months)</b>	NR	42,3	43	39,6
<b>AEs</b>	<b>Grade ≥3 AE</b>	70,2%/49,7%	84%	Hem: 62% non-hem: 63%	75%
	<b>Discontinuations</b>	11,2%/8,9%	8,6%	NS	18%

Hem= hematological, NR= not reached, NS= not stated\**read from KM-curve*, \*\**Adopted from Venetoclax + obinutuzumab application to medicinrådet*, #KM estimate of the proportion of subjects who were progression free at the timepoint [8]  
Source: [6, 8, 15, 26-28]

Qualitative description of grade ≥3 AE and SAEs acalabrutinib monotherapy based on ITT data:

- In the ELEVATE-TN study grade ≥3 AE in the acalabrutinib monotherapy arm was **49,7%** while grade ≥3 SAE was 29.6% and of any grade was 31,8%. Neutropenia (9.5%), anemia (6.7%) and thrombocytopenia (2.8%) were the most common grade ≥ 3 AEs. Treatment discontinuation due to AE occurred in 8,9% [6] (table 22).

Qualitative description of SAEs bendamustine + rituximab:

- In the CLL-10 study Grade ≥3 AEs were reported to be **84%** (table 22). Grade ≥ 3 AEs of neutropenia were 55%, thrombocytopenia 14%, anemia 11% and pneumonia 9% [26, 27].
- In the Alliance study Grade ≥3 AEs hematological AEs occurred in 62% in the arm and non-hematological AEs occurred in **63%** (table 19). Grade ≥3 anemia was reported in 10%. Grade ≥3 neutropenia, thrombocytopenia and pneumonia were not reported [15].
- Grade ≥3 AEs in the MABLE study was **75%** (table 19). Grade ≥3 neutropenia 43%, thrombocytopenia 10%, anemia 10% and pneumonia 5% were reported [28].

For Grade ≥3 AE the target is met with acalabrutinib compared to bendamustine + rituximab based on a narrative description. Data are not available across studies for the population without mutations.

### 5.3.5 Quantitative overview AE and SAE

There are no specific data for the population with and without p17/del13 but the AEs and SAEs are not expected to be different in either subgroup vs the ITT population. This quantitative overview will also cover question 6.4.3 in clinical question 6.

The proportions of patients who experienced treatment-emergent adverse events (TEAEs) were comparable between acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab (96.1% vs 95.0% vs 98.8%). Serious adverse events (SAEs) occurred in 38.8%, 31.8% and 21.9% of patients who received acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab, respectively [8].

Note that in the ELEVATE-TN study, TEAEs were defined as any event with an onset date on or after the date of the first dose of study drug, or any ongoing event that worsened in severity after the first dose of study drug, and before 30 days after the date of the last dose of study drug or the date of first starting new anti-cancer therapy. Thus, all AEs and SAEs discussed in this section are TEAEs unless otherwise specified [8]

### 5.3.6 Exposure

The median durations of acalabrutinib treatment were very similar between the acalabrutinib plus obinutuzumab arm (27.7 months; range: 0.7–40.3 months) and the acalabrutinib monotherapy arm (27.7 months; range: 0.3–40.2 months). Because of the fixed number of treatment cycles of chlorambucil and obinutuzumab, the median duration of treatment was much shorter (chlorambucil: 5.5 months [range: 0.5–7.2 months]; obinutuzumab: 5.5–5.6 months) in the acalabrutinib plus obinutuzumab and the chlorambucil plus obinutuzumab arms [8].

Patients who crossed over from chlorambucil plus obinutuzumab to acalabrutinib monotherapy because of IRC-confirmed disease progression had a median duration of exposure to acalabrutinib of 11.0 months (range: 2.0–23.5 months).

### 5.3.7 Adverse events

The most common AEs with acalabrutinib plus obinutuzumab were headache (39.9%), diarrhoea (38.8%) and neutropenia (31.5%), while headache (36.9%), diarrhoea (34.6%) and nausea (22.3%) were the most common AEs with acalabrutinib monotherapy (table 23). Most AEs were grade 1 or 2, with the exception of neutropenia. With chlorambucil plus obinutuzumab, the most common AEs were neutropenia (45.0%), infusion-related reaction (39.6%) and nausea (31.4%) [8].

Grade  $\geq 3$  AEs affecting at least 2% of patients in any arm are shown in Table 25. The most common grade  $\geq 3$  AEs with acalabrutinib plus obinutuzumab were neutropenia (29.8%), thrombocytopenia (8.4%), anaemia (5.6%) and pneumonia (5.6%). Similarly, neutropenia (9.5%), anaemia (6.7%) and thrombocytopenia (2.8%) were the most common grade  $\geq 3$  AEs with acalabrutinib monotherapy. With chlorambucil plus obinutuzumab, neutropenia (41.4%), thrombocytopenia (11.8%) and tumour lysis syndrome (7.7%) were the most common grade  $\geq 3$  AEs [8].

TABLE 23. SUMMARY OF ADVERSE EVENTS ELEVATE (SAFETY POPULATION)

Event	Number (%) of patients		
	Arm B: acalabrutinib + obinutuzumab (n = 178)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 169)
Any grade AE	171 (96.1)	170 (95.0)	167 (98.8)
Grade 1	7 (3.9)	14 (7.8)	4 (2.4)
Grade 2	39 (21.9)	67 (37.4)	45 (26.6)
Grade ≥ 3	125 (70.2)	89 (49.7)	118 (69.8)
<b>Most common AEs (occurred in ≥ 10% of patients)</b>			
Blood and lymphatic system disorders	80 (44.9)	56 (31.3)	92 (54.4)
Neutropenia	56 (31.5)	19 (10.6)	76 (45.0)
Thrombocytopenia	23 (12.9)	13 (7.3)	24 (14.2)
Anaemia	21 (11.8)	25 (14.0)	20 (11.8)
Gastrointestinal disorders	115 (64.6)	118 (65.9)	85 (50.3)
Diarrhoea	69 (38.8)	62 (34.6)	36 (21.3)
Nausea	36 (20.2)	40 (22.3)	53 (31.4)
Constipation	25 (14.0)	20 (11.2)	17 (10.1)
General disorders and administration site conditions	104 (58.4)	84 (46.9)	80 (47.3)
Fatigue	50 (28.1)	33 (18.4)	29 (17.2)
Pyrexia	23 (12.9)	12 (6.7)	35 (20.7)
Oedema peripheral	22 (12.4)	16 (8.9)	12 (7.1)
Chills	20 (11.2)	8 (4.5)	14 (8.3)
Infections and infestations	123 (69.1)	117 (65.4)	74 (43.8)
Upper respiratory tract infection	38 (21.3)	33 (18.4)	14 (8.3)
Urinary tract infection	22 (12.4)	22 (12.3)	8 (4.7)
Nasopharyngitis	20 (11.2)	17 (9.5)	7 (4.1)
Pneumonia	19 (10.7)	13 (7.3)	5 (3.0)

Source: ELEVATE-TN clinical study report. [8]

TABLE 23. SUMMARY OF ADVERSE EVENTS (SAFETY POPULATION) CONTINUED FROM ABOVE

Event	Number (%) of patients		
	Arm B: acalabrutinib + obinutuzumab (n = 178)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 169)
<b>Injury, poisoning and procedural complications</b>	80 (44.9)	52 (29.1)	73 (43.2)
Contusion	42 (23.6)	27 (15.1)	7 (4.1)
Infusion-related reaction	24 (13.5)	0	67 (39.6)
<b>Metabolism and nutrition disorders</b>	59 (33.1)	31 (17.3)	44 (26.0)
Decreased appetite	18 (10.1)	10 (5.6)	13 (7.7)
<b>Musculoskeletal and connective tissue disorders</b>	90 (50.6)	95 (53.1)	39 (23.1)
Arthralgia	39 (21.9)	28 (15.6)	8 (4.7)
Back pain	25 (14.0)	25 (14.0)	14 (8.3)
Pain in extremity	22 (12.4)	11 (6.1)	7 (4.1)
<b>Nervous system disorders</b>	101 (56.7)	96 (53.6)	51 (30.2)
Headache	71 (39.9)	66 (36.9)	20 (11.8)
Dizziness	32 (18.0)	21 (11.7)	10 (5.9)
<b>Respiratory, thoracic and mediastinal disorders</b>	79 (44.4)	76 (42.5)	45 (26.6)
Cough	39 (21.9)	33 (18.4)	15 (8.9)
Dyspnoea	15 (8.4)	12 (6.7)	17 (10.1)
<b>Skin and subcutaneous tissue disorders</b>	89 (50.0)	76 (42.5)	45 (26.6)
Rash	21 (11.8)	25 (14.0)	8 (4.7)

Source: ELEVATE-TN clinical study report.[8]

TABLE 24. GRADE  $\geq 3$  ADVERSE EVENTS REPORTED IN AT LEAST 2% OF PATIENTS IN ANY ARM (SAFETY POPULATION)

	Number (%) of patients		
	Arm B: acalabrutinib + obinutuzumab (n = 178)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 169)
<b>Subjects with <math>\geq 1</math> grade <math>\geq 3</math> AE</b>	125 (70.2)	89 (49.7)	118 (69.8)
<b>Neutropenia</b>	53 (29.8)	17 (9.5)	70 (41.4)
<b>Thrombocytopenia</b>	15 (8.4)	5 (2.8)	20 (11.8)
<b>Anaemia</b>	10 (5.6)	12 (6.7)	12 (7.1)
<b>Febrile neutropenia</b>	3 (1.7)	2 (1.1)	9 (5.3)
<b>Diarrhoea</b>	8 (4.5)	1 (0.6)	3 (1.8)
<b>Upper respiratory tract infection</b>	4 (2.2)	0	1 (0.6)
<b>Pneumonia</b>	10 (5.6)	4 (2.2)	3 (1.8)
<b>Infusion-related reaction</b>	4 (2.2)	0	9 (5.3)
<b>Alanine aminotransferase increased</b>	5 (2.8)	1 (0.6)	3 (1.8)
<b>Neutrophil count decreased</b>	2 (1.1)	0	5 (3.0)
<b>Tumour lysis syndrome</b>	2 (1.1)	0	13 (7.7)
<b>Syncope</b>	4 (2.2)	2 (1.1)	1 (0.6)
<b>Hypertension</b>	5 (2.8)	4 (2.2)	5 (3.0)

Source: ELEVATE-TN clinical study report, [8]

## 5.4 Acalabrutinib vs. C + O and B + R HQoL

### 5.4.1 Relevant studies Acalabrutinib vs C + O and B + R HQoL

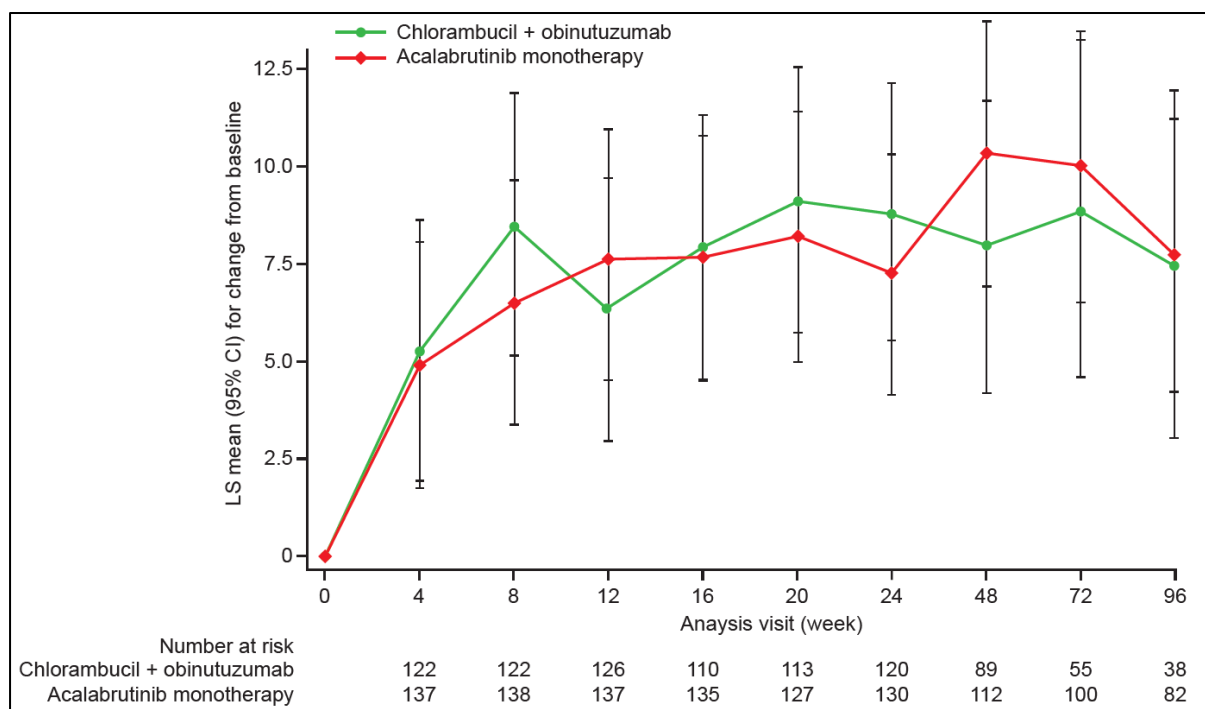
HQoL data are not available for the population without mutations. HQoL data from the ITT population in ELEVATE are used to describe the result for the acalabrutinib mono vs. chlorambucil + obinutuzumab. There are no indirect comparison of HQoL data for acalabrutinib vs bendamustine + rituximab. HQoL is either not included in the studies for the comparator or is not calculated in a way that allows any narrative comparison with bendamustine + rituximab. Data are not available across trials for the specific populations without mutations.

### 5.4.1 Result per study Acalabrutitib vs. C + O and B + R HQoL

#### Acalabrutinib mono vs. chlorambucil + obinutuzumab(ELEVATE)

Change from baseline in EORTC QLQ-C30 for acalabrutinib vs comparison in ELEVATE is shown in figure 10 and table 25.

FIGURE 10. CHANGE FROM BASELINE IN EORTC QLQ-C30 GLOBAL HEALTH STATUS (MMRM), ACALABRUTINIB MONOTHERAPY VS. CHLORAMBUCIL PLUS OBINUTUZUMAB



Source: ELEVATE-TN PRO study report, Figure 30.[8]

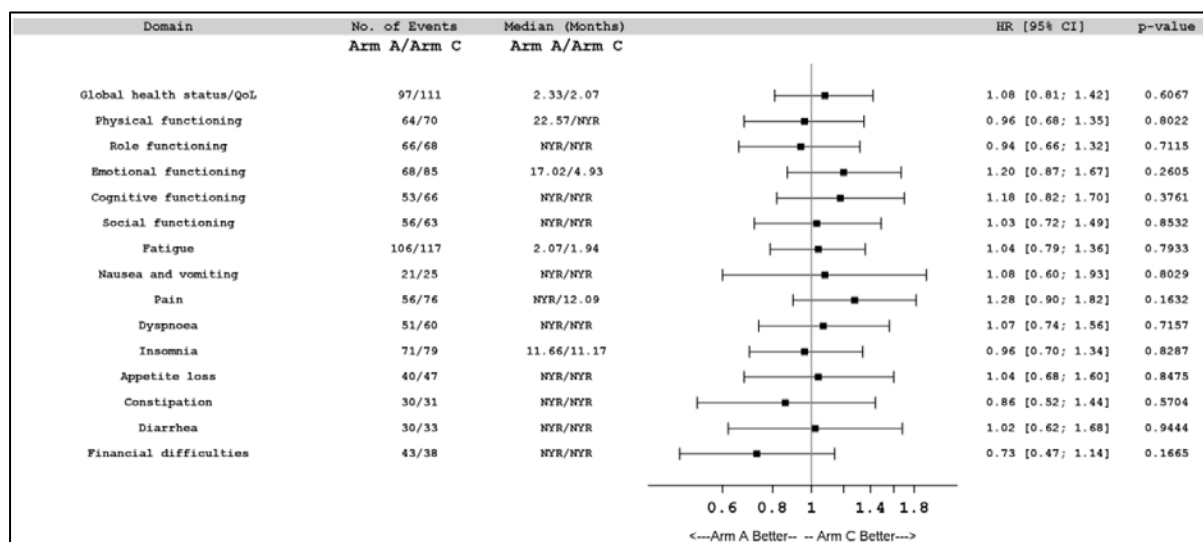
TABLE 25. CHANGE FROM BASELINE IN EORTC QLQ-C30 SCORES ITT POPULATION

Domain	Week	Arm B vs arm A			Arm C vs arm A		
		LS mean change (SE)		Difference (p value)	LS mean change (SE)		Difference (p value)
		Arm B: acalabrutinib + obinutuzumab	Arm A: chlorambucil + obinutuzumab		Arm C: acalabrutinib monotherapy	Arm A: chlorambucil + obinutuzumab	
GHS	24	5.81 (1.50)	7.68 (1.60)	-1.87 (0.2898)	7.23 (1.57)	8.83 (1.67)	-1.60 (0.3859)
	48	5.88 (1.71)	5.38 (2.28)	0.51 (0.8410)	7.72 (1.77)	7.48 (2.25)	0.25 (0.9222)
Fatigue scale	24	-8.16 (1.83)	-12.95 (1.95)	<b>4.80 (0.0244)</b>	-11.01 (1.78)	-14.47 (1.91)	3.46 (0.1014)
	48	-6.33 (2.16)	-11.54 (2.93)	5.21 (0.1113)	-9.06 (2.21)	-12.59 (2.92)	3.54 (0.2901)
Physical functioning	24	1.30 (1.46)	4.41 (1.55)	-3.10 (0.0749)	5.22 (1.43)	6.20 (1.53)	-0.98 (0.5581)
	48	1.39 (1.51)	3.84 (1.97)	-2.46 (0.2541)	2.86 (1.65)	4.84 (2.12)	-1.97 (0.4081)
Role functioning	24	5.50 (1.99)	7.60 (2.11)	-2.10 (0.3812)	3.82 (1.94)	5.41 (2.08)	-1.60 (0.4935)
	48	4.35 (2.09)	11.30 (2.90)	<b>-6.95 (0.0282)</b>	2.29 (2.16)	8.99 (2.84)	<b>-6.70 (0.0358)</b>
Emotional functioning	24	6.82 (1.53)	7.72 (1.63)	-0.89 (0.6183)	8.54 (1.52)	8.31 (1.62)	0.22 (0.9034)
	48	5.58 (1.72)	5.02 (2.36)	0.56 (0.8290)	7.97 (1.79)	5.71 (2.42)	2.26 (0.4079)
Cognitive functioning	24	-0.67 (1.53)	0.77 (1.62)	-1.44 (0.4374)	-0.07 (1.52)	1.76 (1.63)	-1.83 (0.3238)
	48	-2.12 (1.62)	0.28 (2.19)	-2.39 (0.3202)	-1.30 (1.76)	1.66 (2.37)	-2.95 (0.2704)
Social functioning	24	2.91 (1.70)	5.25 (1.81)	-2.34 (0.2350)	4.93 (1.69)	5.56 (1.82)	-0.63 (0.7475)
	48	2.40 (1.90)	7.61 (2.65)	-5.21 (0.0699)	2.12 (2.19)	7.49 (2.85)	-5.37 (0.1009)

Source: ELEVATE-TN PRO study report. [8]

Time to improvement in GHS was shorter with acalabrutinib monotherapy (2.07 vs 2.33 months; HR: 1.08; 95% CI: 0.81–1.42;  $p = 0.6067$ ) compared with chlorambucil plus obinutuzumab, although this difference was not statistically significant. There were no differences in the time to improvement in any of the domains of the EORTC QLQ-C30 with acalabrutinib monotherapy (figure 11) versus chlorambucil plus obinutuzumab.

FIGURE 11. TIME TO FIRST IMPROVEMENT IN EORTC QLQ-C30 SCORES, ACALABRUTINIB VS. CHLORAMBUCIL PLUS OBINUTUZUMAB



Source: ELEVATE-TN PRO study report [8]

## 5.4.2 Comparative analysis 1<sup>st</sup> line without p17/del53 HQoL

### Chlorambucil + Obinutuzimab

Medicinerådet has set a target of 10 % difference. No significant differences was noted and the target cannot be met. Data are not available for the specific populations without mutations but are not expected to be significant different from ITT.

### Bendamustine + rituximab

HQoL is either not included in the studies for the comparator or is not calculated in a way that allows any narrative comparison with bendamustine + rituximab. Data are not available across trials for the specific populations without mutations.

Medicinerådet has set a target of 10 % difference. The target cannot be met due to lack of data.

## 6 Clinical question Acalabrutinib + O vs. O + C and B + R in 1<sup>st</sup> line without p17/del53 .

### 6.1 PFS and PFS rate at 3 years or latest vs. C + O

#### 6.1.1 Relevant studies vs. C + O 1<sup>st</sup> line CLL PFS/PFS rate

As for acalabrutinib the ELEVATE study and the two ITC's NMA and MAIC are the key references used for answering the questions for acalabrutinib + obinutuzumab. See section 5.2 for more details of ELEVATE study.

NMA and MAIC are presented in details in section 5.1.1.

NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus C + O and other comparators another in the network (e.g., odds ratio, relative risk, or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers.

MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison.



## 6.1.2 Results per study Acalabrutinib + O vs. C + O PFS/PFS rate

### NMA

As shown in table 26 through the results of the NMA, acalabrutinib + obinutuzumab, was associated with a lower risk of progression, compared to chlorambucil in combination with obinutuzumab (HR = 0.10 [0.06,0.19]).

Table 26. Results from the PFS NMA in first line for patients without a 17p deletion

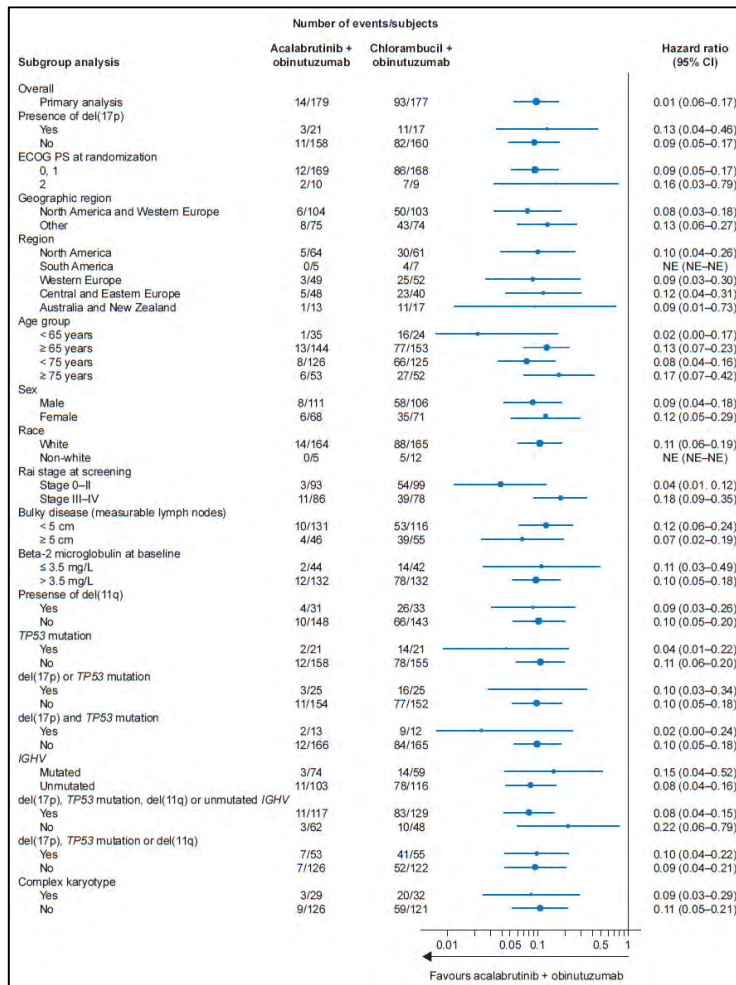
Row vs. Column HR [95%CrI]	Chlor+Obinu	Ibru+Obinu	Acala+Obinu	Acala
<b>Chlor+Obinu</b>	-	4.00 [2.43,6.64]	9.81 [5.35,18.08]	5.03 [3.13,8.06]
<b>Ibru+Obinu</b>	0.25 [0.15,0.41]	-	2.45 [1.11,5.39]	1.26 [0.63,2.49]
<b>Acala+Obinu</b>	<b>0.10</b> <b>[0.06,0.19]</b>	<b>0.41</b> <b>[0.19,0.90]</b>	-	<b>0.51</b> <b>[0.30,0.89]</b>
<b>Acala</b>	0.20 [0.12,0.32]	0.80 [0.40,1.58]	1.95 [1.13,3.37]	-

Source [7, 44]

### ELEVATE-TN

In the subgroup without p17/del53 the results is shown below in figure 12. Comparing acalabrutinib + obinutuzumab with obinutuzumab + chlorambucil resulted in HR=0.10(0.05-0.18)

FIGURE 12. PRIMARY ANALYSIS (ACALABRUTINIB + OBINUTUZUMAB VS CHLORAMBUCIL + OBINUTUZUMAB): PFS SUBGROUP ANALYSIS (IRC ASSESSMENT). ELEVATE-TN



Source: ELEVATE-TN clinical study report [8]

### 6.1.3 Comparative analysis Acalabrutinib + O vs. C + O PFS/PFS rate

#### ELEVATE-TN

PFS rate at 3 years is not available for the subpopulation without p17/del53. As more than 85 % of the study population did not have the mutations the below rate from the overall population should be an indicator for the PFS rate in the group without p17/del53. Treatment with acalabrutinib + obinutuzumab resulted in a 90% reduction in the relative risk of disease progression or death (HR: 0.10; 95% confidence interval [CI]: 0.06–0.17;  $p < 0.0001$ ) versus chlorambucil plus obinutuzumab. Median PFS for acalabrutinib plus obinutuzumab was not reached and the median PFS for chlorambucil plus obinutuzumab was 22.6 months (95% CI: 20.2–27.6) [8].

TABLE 27. PRIMARY AND KEY SECONDARY PFS ANALYSIS (IRC ASSESSMENT)

	Arm B: acalabrutinib + obinutuzumab (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 177)
<b>Death</b>	5 (2.8)	11 (6.2)
<b>Disease progression</b>	9 (5.0)	82 (46.3)
<b>6-month PFS</b>	98.9 (95.5–99.7)	97.0 (92.9–98.7)
<b>12-month PFS</b>	95.9 (91.7–98.0)	84.6 (78.0–89.3)
<b>18-month PFS</b>	94.8 (90.2–97.2)	65.6 (57.7–72.4)
<b>24-month PFS</b>	92.7 (87.4–95.8)	46.7 (38.5–54.6)
<b>30-month PFS</b>	89.6 (82.0–94.1)	34.2 (25.3–43.2)
<b>36-month PFS</b>	89.6 (82.0–94.1)	31.3 (21.8–41.3)

Source: ELEVATE-TN clinical study report [8].

PFS at 3 years in the ITT population showed a difference of 58.3 % which is believed to be valid for the group of patients without mutations(table 27).

Medicinerådet has set a target of 10 % difference at 36 months. We conclude that the target is met vs. the combination of chlorambucil plus obinutuzumab.

As shown in table 26 through the results of the NMA, acalabrutinib + obinutuzumab , was associated with a lower risk of progression, compared to chlorambucil in combination with obinutuzumab (HR = 0.10 [0.06,0.19]).

#### 6.1.4 Comparative analysis Acalabrutinib + O vs. B + R PFS/PFS rate

##### MAIC and NMA

Statistically significant reductions in the risk of disease progression was seen for the acalabrutinib combination therapy compared with bendamustine + rituximab or a risk reductions of 79% (table 28).

TABLE 28. RESULTS FROM THE MAIC FOR ACALABRUTINIB + OBINUTUZUMAB THERAPY COMPARED WITH BENDAMUSTINE+RITUXIMAB

Column vs row Median HR (95% CI)	MAIC	
	Acalabrutinib + obinutuzumab	
	PFS	OS
<b>Bendamustine + rituximab</b>	0.21 (0.10–0.43) <i>p</i> < 0.0001	0.55 (0.20-1.50) <i>p</i> = 0.24

Source [43]

Acalabrutinib + obinutuzumab vs. bendamustine plus rituximab is not evaluated in the population without del(17p)/del53 and also not as PFS rate at 3 years. In the overall population in the NMA the HR = 0.08 (0.04–0.16). In the MAIC the HR in the overall population of acalabrutinib + obinutuzumab vs. bendamustine plus rituximab was 0.21 (0.10-0.43)  $p < 0.001$ . Due to the low number of mutations in the included studies data from the overall population are expected to be representative for the populations without mutations. Data are not available to fully answer the question from Medicinrådet however the PFS results are significantly in favour of acalabrutinib + obinutuzumab based on the indirect comparisons.

AS PFS rates acalabrutinib + obinutuzumab vs. bendamustine + rituximab are not answered by the ITC's we have based on the studies mentioned in table 9 and data shown in table 22 studies also performed a narrative comparison vs. Bendamustine + Rituximab

- In the ELEVATE-TN study, the 2-year PFS rate for acalabrutinib and obinutuzumab was 93% and the estimated 3-year PFS was **89,9%** [8]. The median PFS was not reached [6] (Table 22).
- In the CLL-10 study, The 2 and 3-year estimated PFS rates were 79% and **56%** (read of KM curve) respectively and the median PFS was 42,3 months at a median follow up of 58 months [26, 27] (Table 22).
- In the Alliance study, the percentage of patients with progression-free survival at 2 years was 74% with bendamustine plus rituximab and the estimated 3-year PFS was **61%** (read of KM curve) the median PFS was 43months [15] (Table 22).
- In the MABLE study with a median follow-up of 23,5 months the estimated 2 year PFS (read on KM-curve) was 79% and the median PFS for bendamustin-rituximab was 39,6 months [28] (Table 22).

The 10% target set by Medicinrådet is met based on PFS rate at 2 years against all three bendamustine + rituximab studies. The target is also met with the 3-year PFS for the CLL-10 and Alliance, whilst 3-year PFS estimates is not available for the MABLE study.

## 6.2 Acalabrutinib + O vs. C + O and B + R without del(17p)/del53. OS/OS rate

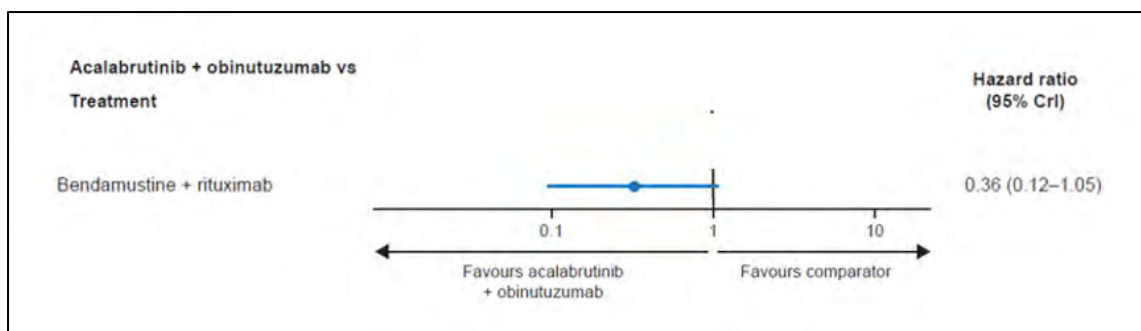
### 6.2.1 Relevant studies 1st line without del(17p)/del53 OS/OS rate

As for acalabrutinib monotherapy the ELEVATE study and the two ITC's NMA and MAIC are the key references used for answering the questions for acalabrutinib + obinutuzumab. See section 5.2 for more details of ELEVATE-TN and studies included in the NMA and MAIC.

## 6.2.2 Result per study Acalabrutinib+O vs C+O/B+R without del(17p)/del53 OS/OS rate

### NMA and MAIC Bendamustine + Rituximab

Figure 13. Forest plot of OS NMA in first line Acalabrutinib + Obinutuzumab vs.B + R(network 1)



Source [7, 44]

### ELEVATE-TN Chlorambucil + obinutuzumab

OS results are not available for the subgroup without P17/del53. The OS data in the overall population are not mature and median OS was not reached in any treatment arm; however, the OS trend favoured acalabrutinib + obinutuzumab vs chlorambucil plus obinutuzumab (HR: 0.47; 95% CI: 0.21–1.06;  $p = 0.0577$ ). Of note, patients who crossed over from chlorambucil plus obinutuzumab to acalabrutinib monotherapy were included in the analysis of OS in the chlorambucil plus obinutuzumab arm; this may have affected the results.

## 6.2.3 Comparative analysis Acalabrutinib + O vs. C + O. OS/OS rate

OS Results are not available for the subgroup without P17/del53. In the ITT population the KM-estimated OS at 12 months was 96.1% (95% CI: 91.9–98.1) for acalabrutinib plus obinutuzumab and 96.5% (95% CI: 92.4–98.4) for chlorambucil plus obinutuzumab. At 36 months, the corresponding OS was 94.9% (95% CI: 90.5–97.3) and 88.1% (95% CI: 80.7–92.8), respectively [8].

A difference of 6.8 % meet the target of 5 % in the ITT population

## 6.2.4 Comparative analysis Acalabrutinib + O vs. B + R. OS/OS rate

OS and OS rate at 3 year results are not available for the subgroup without P17/del53. Due to the low number of mutations in the ITT population should be representative of the without P17/del53 group. As shown in table 28 the MAIC found that the HR was 0.55 (0.20-1.50)  $p = 0.24$  and NMA HR= 0.36 (0.12; 1.05) vs bendamustine + rituximab so the OS trend favoured acalabrutinib +

obinutuzumab. OS data at 3 years is not available for the indirect comparison and the target cannot be met.

AS OS rates vs. bendamustine + rituximab are not answered by the ITC's we have based on studies mentioned in table 8 and results in table 19 also performed a narrative comparison vs. Bendamustine + Rituximab. The comparison is only available for the ITT population.

- In the ELEVATE-TN study, the estimated 3 year OS (read of KM) was **94,9%** [8] and the 2 year overall survival was 95% for acalabrutinib and obinutuzumab [6] (Table 22).
- In the CLL-10 study, the 3-year OS rate for the bendamustin-rituximab arm was **92%** [26] (Table 22)
- In the Alliance study, the estimated 3 year OS (read of KM curve) was **88%** and OS at 2 years was 95% with bendamustine plus rituximab [15] (Table 22).
- The MABLE study with a median follow-up of 23,5months reported an estimated **2 year OS** (read on KM-curve) of **89%** [28] (Table 22).

The 5% target set by Medicinrådet can be met in the ITT population for 3-year OS compared to the Alliance and MABLE studies but cannot be met for CLL-10.

## 6.3 Acalabrutinib + O vs. C + O and B + R. AEs Grade $\geq 3$

### 6.3.1 Relevant studies Acalabrutinib + O vs C + O and B + R AEs Grade $\geq 3$

Data are not available for the specific population without mutations. However, this population represent more than 85% of the ITT group and we regard it as representative to answer this question for without mutations

### 6.3.2 Results per study Acalabrutinib + O vs. C + O and B + R. AEs Grade $\geq 3$

#### Acalabrutinib + obinutuzumab

SAEs, most of which were grade  $\geq 3$ , occurred in 38.8% and 21.9% of patients who received acalabrutinib plus obinutuzumab and chlorambucil plus obinutuzumab, respectively (table 29). Among patients treated with acalabrutinib, the most common SAE was pneumonia, which affected 12 patients (6.7%) receiving acalabrutinib plus obinutuzumab. The most common SAE in patients treated with chlorambucil plus obinutuzumab was tumour lysis syndrome, which occurred in eight patients (4.7%; [8]).

TABLE 29. SUMMARY OF AE GRADE 3 OR MORE AND SAEs (SAFETY POPULATION)

Event	Number (%) of patients	
	Arm B: acalabrutinib + obinutuzumab (n = 178)	Arm A: chlorambucil + obinutuzumab (n = 169)
<b>Any grade AE</b>	171 (96.1)	167 (98.8)
<b>Grade 1</b>	7 (3.9)	4 (2.4)
<b>Grade 2</b>	39 (21.9)	45 (26.6)
<b>Grade ≥ 3</b>	125 (70.2)	118 (69.8)

Event	Number (%) of patients	
	Arm B: acalabrutinib + obinutuzumab (n = 178)	Arm A: chlorambucil + obinutuzumab (n = 169)
<b>Any grade SAE</b>	69 (38.8)	37 (21.9)
<b>Grade 1</b>	1 (0.6)	2 (1.2)
<b>Grade 2</b>	10 (5.6)	2 (1.2)
<b>Grade ≥ 3</b>	58 (32.6)	33 (19.5)

### 6.3.3 Comparative analysis Acalabrutinib + O vs. C + O grade ≥ 3

AE Grade ≥ 3 and discontinuations are not available for the population without P17/del53. Due to the low number of mutations (less than 15%), data from the overall population are used as reference and should be valid for the unmutated population.

AE Grade ≥ 3 was **0.4 %** (-9.6; 10.4) point higher in the acalabrutinib + obinutuzumab group vs. chlorambucil + obinutuzumab RR= 1.01. The target from Medicinrådet/Fagudvalget of 10 % cannot be met.

Groups	AE Grade ≥ 3	no SAE 3 or above	Total patients	Risk Ratio	Relative RR
ACALA + O	125	53	178		0,70225
C + O	118	51	169		0,698224852

DIS	95 % CI	LN(RR)+/-1,96*SQRT(((n1-x1)/x1)/n1 + ((n2-x2)/x2)/n2))	exp of log	95% CI	interpretation	Column1
((n1-x1)/x1)/n1	0,002382022	0,143	1,154301405	0,88; 1,15	excl 1 = Sig. Relativ risiko	
((n2-x2)/x2)/n2	0,002557417	-0,132	0,876	NA	NA	

A difference in SAE grade ≥ 3 in the ITT population was **-13,1 %** (-22.8; -3.4) . RR=1.7

Groups	SAE 3 or above	no SAE 3 or above	Total patients	Risk Ratio	Relative RR
ACALA + O	58	120	178		0,32584
O + Chl	33	136	169		0,195266272

DIS	95 % CI	LN(RR)+/-1,96*SQRT(((n1-x1)/x1)/n1 + ((n2-x2)/x2)/n2))	exp of log	95% CI	interpretation	Column1
((n1-x1)/x1)/n1	0,011623402	0,884	2,420519909	1,15; 2,42	excl 1 = Sig. Relativ risiko	
((n2-x2)/x2)/n2	0,024385871	0,140	1,150	NA	NA	

### 6.3.4 Comparative analysis Acalabrutinib + O vs. B + R grade $\geq 3$

The NMA and MAIC do not include a comparison of safety in 1<sup>st</sup> line CLL of acalabrutinib + obinutuzumab vs. bendamustine plus rituximab. Therefore we did a naïve comparison vs. 3 studies mentioned in table 19. The comparison can only be made based on the ITT population but we estimate it to be representative for the population without p17/del53.

- In the ELEVATE-TN study grade  $\geq 3$  AE in the acalabrutinib plus obinutuzumab arm was reported for the overall population and was **70,2%** while grade  $\geq 3$  SAE was 32,6% and of any grade was 38,8%. The most common grade  $\geq 3$  AEs with acalabrutinib plus obinutuzumab were neutropenia (29.8%), thrombocytopenia (8.4%), anemia (5.6%) and pneumonia (5.6%). Treatment discontinuation due to AE occurred in 11,2% for acalabrutinib combination [6].
- In the CLL-10 study Grade  $\geq 3$  AEs were reported to be **84%** (Table 21). Grade  $\geq 3$  AEs of neutropenia were 55%, thrombocytopenia 14%, anemia 11% and pneumonia 9% [26]
- In the Alliance study Grade  $\geq 3$  AEs hematological AEs occurred in 62% in the arm and non-hematological AEs occurred in **63%** (Table 19). Grade  $\geq 3$  anemia was reported in 10%. Grade  $\geq 3$  neutropenia, thrombocytopenia and pneumonia were not reported [15].
- Grade  $\geq 3$  AEs in the MABLE study was 75% (Table 21). Grade  $\geq 3$  neutropenia 43%, thrombocytopenia 10%, anemia 10% and pneumonia 5% were reported [28].

The target set by Medicinrådet is 10% differences in Grade  $\geq 3$  AEs. For any Grade  $\geq 3$  AE the target in the ITT population is not met with acalabrutinib + obinutuzumab compared to bendamustine + rituximab in Alliance and MABLE but met vs. CLL-10 , based on a narrative description.

### 6.3.5 Quantitative overview AEs and SAEs

See section 5.4.3 to 5.4.6 for collective overview of acalabrutinib mono and acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab

## 6.4 Acalabrutinib + O vs. C + O and B + R. HQoL

### 6.4.1 Relevant studies. Acalabrutinib + O vs. C + O and B + R HQoL

HQoL data are not available for the population without mutations. HQoL data from the ITT population in ELEVATE are used to describe the result for the acalabrutinib + obinutuzumab vs.



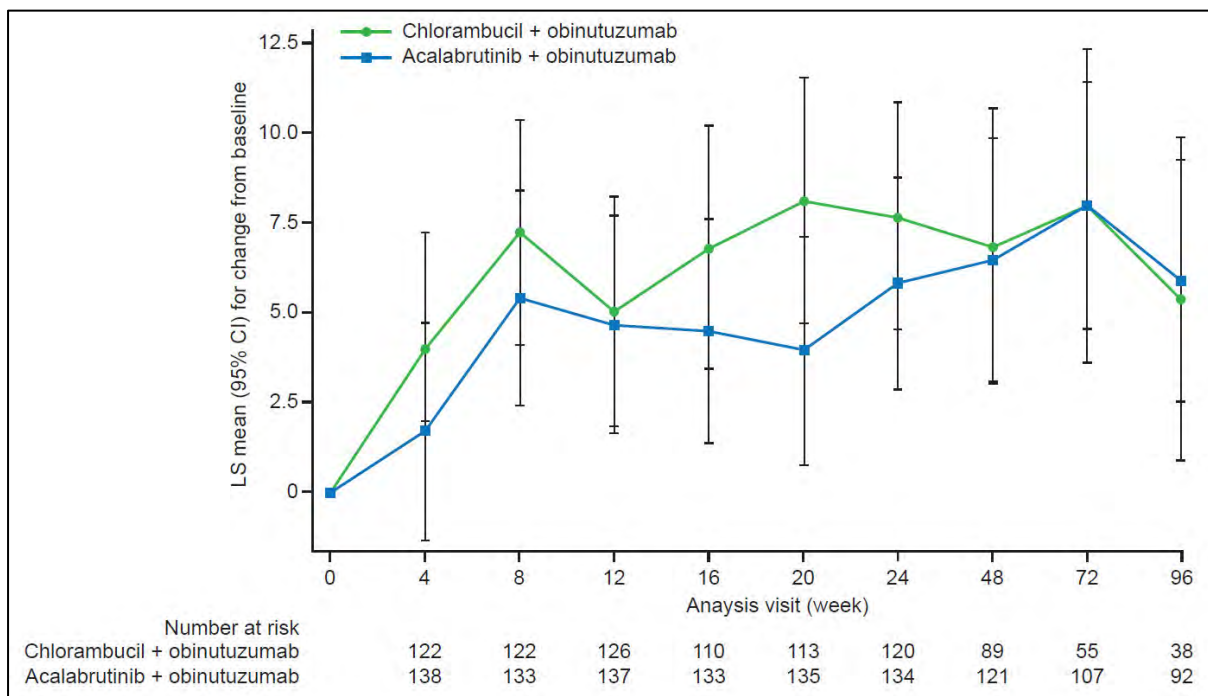
chlorambucil + obinutuzumab. There are no indirect comparison of HQoL data for acalabrutinib + oninutuzumab vs bendamustine + rituximab. HQoL is either not included in the studies for the comparator or is not calculated in a way that allows any narrative comparison with bendamustine + rituximab. Data are not available across trials for the specific populations without mutations.

#### 6.4.2 Result per study Acalabrutitib + O vs. C + O and B + R HQoL

##### EORTC QLQ-C30 scores

Acalabrutinib plus obinutuzumab were associated with improvements in HRQoL from baseline, as assessed using the EORTC QLQ-C30. Most domains of the EORTC QLQ-C30 were improved with acalabrutinib plus obinutuzumab, including the global health status (GHS), fatigue, role functioning, emotional functioning, pain, dyspnoea, insomnia and appetite loss domains. Similar results were seen in the chlorambucil plus obinutuzumab arm (figure 14). These improvements did not wane over time in any treatment arm.

FIGURE 14. CHANGE FROM BASELINE IN EORTC QLQ-C30 GLOBAL HEALTH STATUS (MMRM), ACALABRUTINIB PLUS OBINUTUZUMAB VS CHLORAMBUCIL PLUS OBINUTUZUMAB

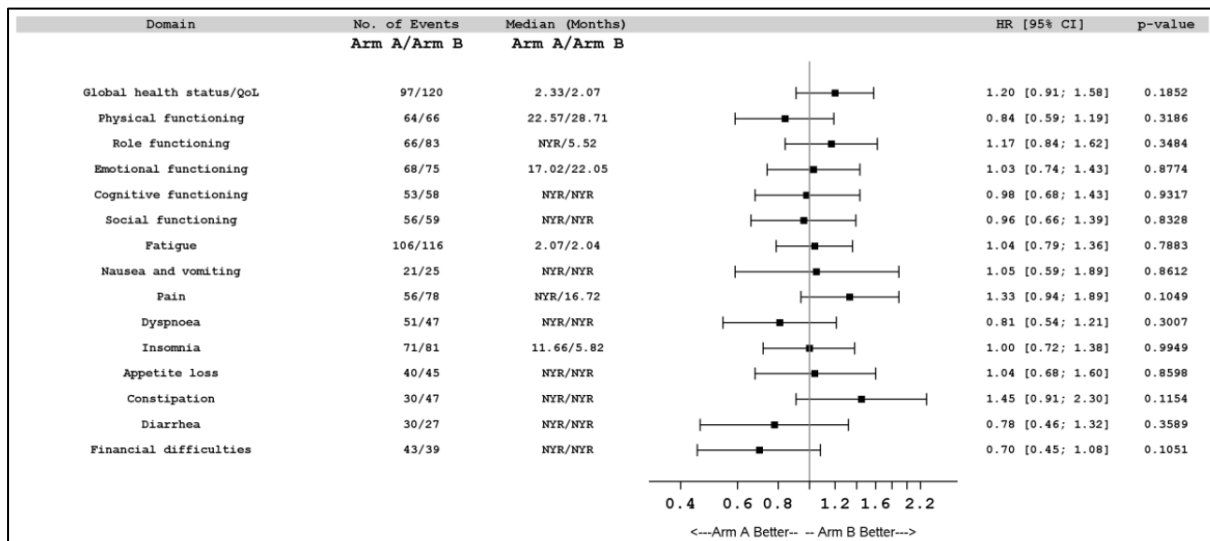


Source: ELEVATE-TN PRO study report, Figure 30 [8]

Comparing changes from baseline to week 24 and week 48, there was no difference in most domains of the EORTC QLQ-C30 between acalabrutinib plus obinutuzumab and chlorambucil plus obinutuzumab. The exceptions were the fatigue scale (week 24 difference: 4.80;  $p = 0.0244$ ), role functioning (week 48 difference:  $-6.95$ ;  $p = 0.0282$ ) and diarrhea (week 24 difference: 5.43;  $p = 0.0027$ ) domains of the EORTC QLQ-C30, where a larger improvement from baseline was seen

with chlorambucil plus obinutuzumab compared with acalabrutinib plus obinutuzumab. Similarly, larger improvements from baseline were seen in the role functioning (week 48 difference: -6.70;  $p = 0.0358$ ) and diarrhea (week 24 difference: 4.53;  $p = 0.0139$ ) domains of the EORTC QLQ-C30 with chlorambucil plus obinutuzumab versus acalabrutinib monotherapy. There were no domains in which the change in score with acalabrutinib plus obinutuzumab was superior to that with chlorambucil plus obinutuzumab. However, the baseline domain scores were generally worse in the chlorambucil plus obinutuzumab arm. Consequently, the change in scores in the chlorambucil plus obinutuzumab arm may be a result of the regression the mean, although more investigation is required [8]. Time to improvement in GHS was shorter with acalabrutinib plus obinutuzumab (2.07 vs 2.33 months; HR: 1.20; 95% CI: 0.91-1.58;  $p = 0.1852$ ) and acalabrutinib monotherapy (2.07 vs 2.33 months; HR: 1.08; 95% CI: 0.81-1.42;  $p = 0.6067$ ) compared with chlorambucil plus obinutuzumab, although this difference was not statistically significant. There were no differences in the time to improvement in any of the domains of the EORTC QLQ-C30 with acalabrutinib plus obinutuzumab (Figure 15) versus chlorambucil plus obinutuzumab.

FIGURE 15. TIME TO FIRST IMPROVEMENT IN EORTC QLQ-C30 SCORES, ACALABRUTINIB PLUS OBINUTUZUMAB VERSUS CHLORAMBUCIL PLUS OBINUTUZUMAB



Source: ELEVATE-TN PRO study report, Figure 43 [8].

### 6.4.3 Comparative analysis Acalabrutinib + O vs. C + O and B + R HQoL

#### Obinutuzumab + chlorambucil

Very small differences in GHS scores were seen at 24 and 48 weeks; -1.87 ( $p=0.2898$ ) and 0.51 ( $p=0.8410$ ).

No significant differences were noted and the target cannot be met. See also section 5.4. Clinical question ACALA monotherapy vs Ibrutinib in 1<sup>st</sup> line CLL with p17/del53.

Data are not available for the specific populations without mutations but are not expected to be significantly different from ITT.

## Bendamustine + rituximab

HQoL is either not included in the studies for the comparator or is not calculated in a way that allows any narrative comparison with bendamustine + rituximab.

Data are not available across trials for the specific populations without mutations.

Medicinrådet has set a target of 10 % difference. The target cannot be met due to lack of data.

## 7 Clinical question acalabrutinib vs ibrutinib in 1st line CLL with p17/del53

### 7.1 Relevant studies Acalabrutinib vs. ibrutinib with p17/del53 PFS/PFS rate

For questions in 1<sup>st</sup> line high-risk patients, Medicinraadet has stated in the protocol that the comparator should be “Danish standard treatment”, in this case either Venetoclax + Obinutuzumab or ibrutinib. As Calquence and Ibrutinib have the same mode of action (ATC L01XE; protein kinase inhibitors), the same approved indications, treatment to progression, and the fact that ibrutinib is the market leader in Denmark, we consider Ibrutinib to be the most relevant comparator to be able to answer the clinical questions in 1<sup>st</sup> line high risk.

No head to head study is available vs. ibrutinib in 1<sup>st</sup> line but a NMA and MAIC was conducted and has addressed the PFS in the ITT and the mutated population. The comparison covers patient with del17.

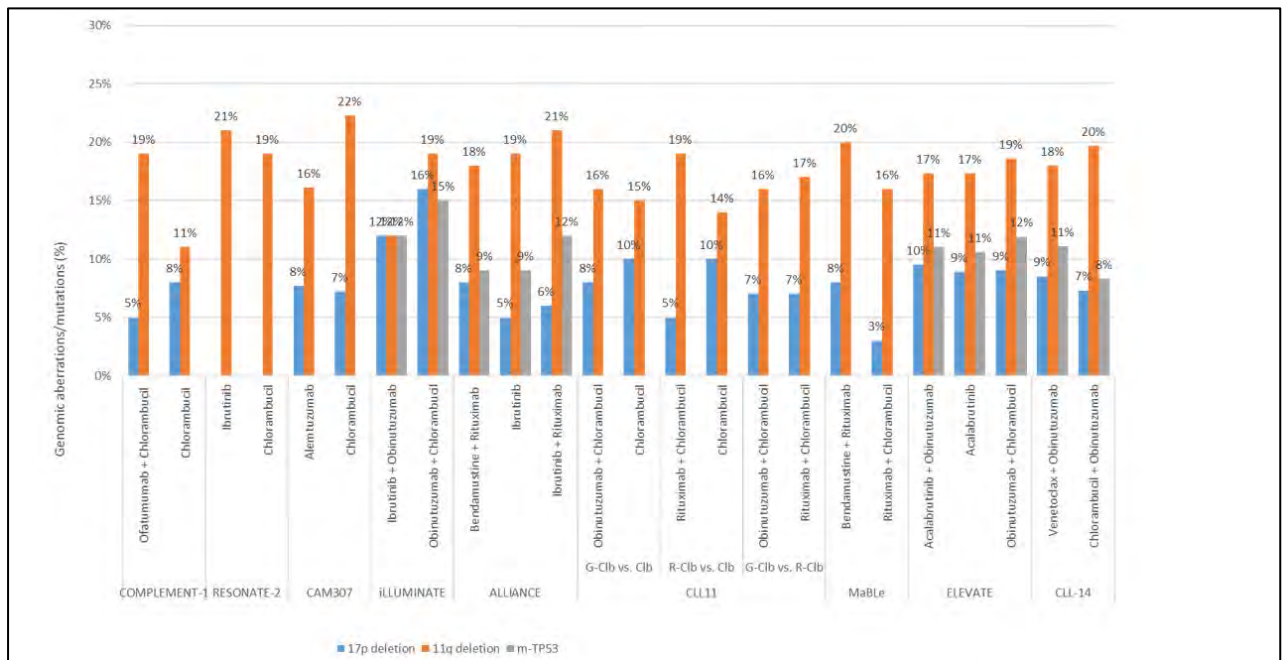
#### NMA and MAIC .

NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator (here acalabrutinib and acalabrutinib + O) versus another (Ibrutinib) in the network (e.g., odds ratio, relative risk, or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers.

MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison.

Overview of proportion of patient with mutations in the different 1<sup>st</sup> line studies are shown in figure 16.

Figure 16. Proportion of patients with 17p deletion, 11q deletion, and m-TP53 at baseline (first line population)



Source NMA [44]

### 7.1.1 Results per study Acalabrutinib vs. ibrutinib with p17/del53 PFS/PFS rate

Results from the MAIC and NMA are shown below in table 30 and 31.

MAIC:

TABLE 30. SUMMARY OF RESULTS FROM THE MAIC FOR ACALABRUTINIB MONO COMPARED WITH IBRUTINIB, UNTREATED CLL

Column vs row Median HR (95% CI)	MAIC	
	Acalabrutinib monotherapy	
	PFS	OS
Ibrutinib	0.92 (0.44–1.95) <i>p</i> = 0.83	0.73 (0.27–2.02) <i>p</i> = 0.55

Source MAIC [43]

## NMA:

TABLE 31. RESULTS OF SUBGROUP ANALYSES FOR NMA OF PFS COMPARING MONOTHERAPY AND COMBINATION VS IBRUTINIB

Column vs row, HR (95% CI)	Overall population		Del(17p)		Without del(17p)		IGHV mutations		Without IGHV mutations	
	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab	Acalabrutinib	Acalabrutinib + obinutuzumab
ibrutinib	0.35 (0.18-0.66)	0.19 (0.09-0.38)	NE	NE	NE	NE	0.47 (0.12-1.82)	0.14 (0.03-0.64)	0.33 (0.12-0.88)	0.24 (0.09-0.69)
ibrutinib + rituximab	0.37 (0.18-0.75)	0.20 (0.09-0.44)	NE	NE	NE	NE	0.56 (0.11-2.97)	0.16 (0.03-0.64)	0.21 (0.07-0.65)	0.15 (0.05-0.51)
ibrutinib + obinutuzumab	0.87 (0.46-1.63)	0.46 (0.23-0.94)	1.43 (0.26-8.01)	0.91 (0.15-5.60)	0.80 (0.40-1.58)	0.41 (0.19-0.90)	2.31 (0.68-7.94)	0.67 (0.16-2.85)	0.77 (0.34-1.75)	0.57 (0.24-1.40)

Source NMA [44]

Results of acalabrutinib vs ibrutinib are only available for the del17p population vs the combination of ibrutinib + obinutuzumab. HR=1.43(0.26; 8.01). [44]. Ibrutinib + obinutuzumab is not a comparator in the protocol.

### 7.1.2 Comparative analysis acalabrutinib vs. ibrutinib with p17/del53 PFS/PFS rate

#### NMA and MAIC

Acalabrutinib monotherapy was associated with significantly better PFS based on the NMA, vs. ibrutinib monotherapy (HR= 0.35(0.18; 0.66) in terms of PFS as reported in table 31. However this is based on overall population.

In the 17p deletion subgroup, the comparison are not credible and characterized by wide intervals likely due to small sample sizes. See below for supporting information based on a narrative comparison.

In the MAIC the HR=0.94 (0.44-1.95) and do not show a significant difference. Based on the PFS outcome from the ITCs in the overall population it is not possible to conclude that acalabrutinib is superior in the patient group with mutations.

AS PFS rates acalabrutinib vs. ibrutinib are not answered by the ITC's we have collected data from 4 studies described below and in table 32,33 and performed a naïve comparison

Table 32 Studies used for narrative comparison.

Study characteristics	ELEVATE-TN [6]	Ahn n=86 [16]	Ahn (TP53) n=51 [16]	RESONATE-2 [14]
Eligibility	<ul style="list-style-type: none"> <li>&gt;65y</li> <li>&lt;65y with CIRS-score &gt; 6</li> <li>del17p/TP53</li> </ul>	<ul style="list-style-type: none"> <li>&gt;65</li> <li>del17p/TP53</li> </ul>	<ul style="list-style-type: none"> <li>&gt;65</li> <li>del17p/TP53</li> </ul>	<ul style="list-style-type: none"> <li>&gt;65</li> <li>No del 17p</li> </ul>
Age (median in years)	A: 70 (65-75) AO:70 (66-75)	66 (33-85)	62 (33-82)	73 (65-89)
ECOG %				
0		NR	NR	44
1	A: 94,4 AO: 92*			48
2	A: 5,6 AO: 7,8			8
CIRS >6 %	A: 16,8 AO: 11,7#	NR	NR	31

<b>Rai stage (%)</b>				
<b>0</b>	A: 1,7 AO: 0			
<b>I</b>	A: 30,2 AO: 26,8	I/II: 32,6	I/II: 37,3	
<b>II</b>	A: 20,1 AO: 24,6			
<b>III</b>	A: 26,8 AO: 27,9	III/IV: 67,4	III/IV: 62,7	III/IV: 44
<b>IV</b>	A: 21,2 AO: 20,7			
<b>IGHV mutated %</b>	A: 42,5 AO: 34,5	33,7	33,3	57
<b>IGHV unmutated %</b>	A: 57,5 AO: 66,5	66,3	66,7	43**
<b>Del17p mutation %</b>	A: 9,5 AO: 8,9	58,1	92,2	0
<b>Tp53 %</b>	A; 11,7 AO: 10,6	4,7	7,8	10

\*ECOG 0-1, \*\* at 5 year follow up unmutated IGHV was reported to be 57%.

### Narrative comparison of PFS acalabrutinib versus ibrutinib with 17pdel/Tp53

Two studies including patients with 17pdel and or Tp53 mutation treated with ibrutinib were chosen for the narrative comparisons.

#### Rationale for study selection for narrative comparisons

The use of ibrutinib in the selected comparator studies is in line with the use of ibrutinib in Danish clinical practice\*. RESONATE-2 and Ahn are also to the best of our knowledge the studies that represent the best fit for a narrative comparison between acalabrutinib and ibrutinib in the patient population that represents clinical questions 3 and 4 in this application. Though, we do acknowledge the highlighted difference demonstrated in the sections below between ELEVATE-TN and the comparator studies (Ahn and RESONATE-2) and also acknowledge the general difficulty in cross trial comparisons, we estimate that a narrative comparison is reasonable based on the similarities highlighted in the sections below between the studies. In addition, some data are not available for the subpopulation in the studies, such as AEs and these are thus demonstrated as stated below for the whole population. We expect that these are representative as to the best of our knowledge TP53 mutation or del 17p are not correlated with the incidence of specific or more frequent AE events.

*\*though as highlighted below RESONATE-2 excluded del 17p patients and this is a deviation from the patient population that in Danish clinical practice would receive ibrutinib, with respect to that 17pdel patients are treated with ibrutinib in Denmark.*

#### ELEVATE-TN

The ELEVATE-TN study [6] is an open label Ph III, multi center randomized study in previously untreated CLL patients that included a) patients > 65 years, b) patients < 65 years with a CIRS-score above 6 and c) patients with del17p (acalabrutinib: 9,5% and acalabrutinib + obinutuzimab: 8.9%) and del17p/mutated TP53 (Acalabrutinib: 11,7% and Acalabrutinib + obinutuzimab: 10,6%) (Table 30). The latter patient population would in Danish clinical practice receive ibrutinib (venetoclax + obinutuzumab was recently also approved for this population) and this is also the relevant patient population in the ELEVATE-TN study for clinical questions 3 and 4. To this end, ibrutinib is chosen as a comparator in clinical questions 3 and 4 that address patients with del17p and/or TP53 mutation.

#### Ahn-Study ibrutinib

The Ahn study [16] is a single-arm, single center, open label, Ph II study that similarly to the ELEVATE-TN study included patients (total number of patients n= 86) above 65 years of age as well as patients with 17pdel/Tp53 mutations (n= 51, treatment naïve(TN) n=34/51). (Table 32). Patients in the Ahn study received ibrutinib treatment which is in accordance with the treatment of

these patients in Danish clinical practice.

In contrast to the ELEVATE-TN study, the Ahn study also included R/R patients which could give a poorer outcome of treatment results compared to patients in first line. With that said the median age in the patients in the Ahn study was 65 years (and a median of 62 years in the TP53 subpopulation) which is younger than the median age of the acalabrutinib treated patients in the ELEVATE-TN study (median of 70 years) which may result in a more favorable response in the Ahn study for ibrutinib and which could balance the response outcome between the two studies. Of note is also that the Ahn study included 51/86 patients with Tp53 mutations, which is a larger part of the patient pool than the corresponding population in the ELEVATE-TN study. However, as stated above the Ahn study is comparable to the ELEVATE-TN study with regards to inclusions criteria (>65 yrs and allowing for TP53/del 17p patients) and also with regards to percentage of IGHV unmutated patients (Table 32).

We, evaluate the studies to be partially comparable and sufficiently suitable for a narrative analysis.

### RESONATE-2 study

The RESONATE-2 study is a Ph III open label, multicenter, randomized study that included patients of a median age of 73 (65 years-89 years) and 10% of the patients in this study were Tp53 mutated [14] (Table 30). However, the study excluded patients with 17p-del which is in contrast to both the ELEVATE-TN study and different from the high-risk patient population in Danish clinical practice treated with ibrutinib. This may also result in a more favorable response outcome in the RESONATE-2 study compared to the same patient population in ELEVATE-TN (and what is seen in clinical practice). On the other hand, the percentage of patients with CIRS >6 is higher in the RESONATE-2 study (31%) as compared to the ELEVATE-TN study (16,8%) (Table 32), thus resulting in an better prognosis in the ELEVATE-TN study. In the acalabrutinib monotherapy arm of the ELEVATE-TN study patients had a median age of 70 years (66 years-75 years) and 8.9% and 10.6% of the patients had 17p deletion and Tp53 mutation respectively. These features with the exception of del 17p population are similar between the two studies. Moreover, the proportion of the included patient populations in each study are similar with regards to ECOG status and Rai III-IV stages (Table 32). We evaluate the patient populations in ELEVATE-TN and RESONATE-2 to be partially comparable to each other and sufficiently suitable for a narrative analysis.

### PFS and PFS rate. Acalabrutinib vs. ibrutinib

Table 33. Narrative vs. ibrutinib with 17pdel/Tp53

Read out		Study				
		ELEVATE-TN Tp53/del17p n=19/16	ELEVATE-RR $\bar{x}$ Tp53 n =121 del17p n=100	Ahn et al (Tp53) n=51 (TN n= 34/51)	RESONATE-2 (Tp53) n=12	RESONATE-2 n=136
Follow-up (Median, months)		28,3	41	58	60	60
Survival	OS 2-year	95%		84%		98%
	OS 5 years	-		85.3% (n=51)	-	83%
	PFS 2 years	71%*/74%*		82% (n=51) and 85%** (n = 34)	-	-
	PFS 5 years	-		74.4% (n=34)	56%	70%
Adverse Events	Grade $\geq 3$ AE	49,7% #	A: 68.8 % (n=266) I: 74.9% (n= 263)	54% (24m Follow-up) / 29% # (5 years Follow-up)	-	83%

\*read from KM-curve, \*\*Adopted from Venetoclax + obinutuzumab application to Medicinrådet, # overall population  $\bar{x}$  Only safety is assessed for this study in this section

- In the ELEVATE-TN study, the 2-year PFS rates for acalabrutinib monotherapy in the Tp53 and del17p subpopulations were **71%** and **74%** respectively (read off the KM curves) [6] (Table 33).
- In the Ahn study the 2-year PFS rate was **82%** in the whole Tp53 population and **85%** (read of KM\_curve) for the TN TP53 mutated population. The 5-year PFS rate was 74,4% [16, 17] (Table 33).
- In the RESONATE-2 study the 5 year PFS rate was 56% in the Tp53 population [14] (Table 33).

Based on a narrative comparison in mutated patients, it is not possible to confirm an advantage for PFS rate at 3 years due to the studies report at different points in time. The conclusion from the naïve comparison is mixed and cannot confirm a 10 % PFS benefit for acalabrutinib vs. ibrutinib in high risk patients.

## 7.2 Acalabrutinib vs. Ibrutinib 1st line with p17/del53 OS/OS rate

### 7.2.1 Relevant studies Acalabrutinib vs. Ibrutinib with p17/ del53 OS/OS rate

No head to head study is available vs. ibrutinib in overall 1<sup>st</sup> line CLL and neither in the mutated population but the NMA and MAIC has addressed the OS in the overall population . The comparison covers patient with del17. See section 5.2 for more details of ELEVATE and studies included in the NMA and MAIC. A naïve comparison between ELEVATE and Ahn study is also included.

### 7.2.2 Result per study and studies Acalabrutinib vs. Ibrutinib OS/OS rate

No head to head study is available vs. ibrutinib to describe OS in the high risk group but a NMA and MAIC was conducted and has addressed the OS but only in the ITT populations.

#### MAIC

Data is only available for overall populations. This variation could be explained by immature OS data and in some trials, the ability of progressed patients in the comparator arm to cross over to the treatment arm [43]. OS was also assessed in the NMA. However unlike PFS, only the ITT population was included for OS, as subgroup data were not available for OS to perform the NMAs.



### 7.2.3 Comparative analysis Acalabrutinib vs. Ibrutinib with p17/ del53 OS/OS rate

#### NMA and MAIC

Results for acalabrutinib vs. ibrutinib in OS were variable, with greater risk reductions being seen with acalabrutinib monotherapy than ibrutinib HR= 0.73(0.27; 2.02).

NMA Acalabrutinib vs ibrutinib resulted in a HR=0.44 (0.16; 1.27) in the overall population [44].

In the comparative studies OS for the ITT population demonstrated greater risk reductions with acalabrutinib monotherapy than ibrutinib. However, variation were observed in the comparative studies that could be explained by immature OS data and in some trials, the ability of progressed patients in the comparator arm to cross over to the treatment arm. For the mutated population data are not available and valid due very small size of the group and immature OS data.

As ELEVATE do not report OS data in the high risk group we have not found it applicable to do a naïve comparison.

The specific question concerns OS rate at 3 years. The acalabrutinib + obinutuzumab combination cannot meet the target from Medicinrådet based on the available OS data as these are not reported in ELEVATE-TN for the mutated population.

## 7.3 Acalabrutinib vs. Ibrutinib 1<sup>st</sup> line with p17/ del53 AE Grade ≥3

### 7.3.1 Relevant studies Acalabrutinib vs. Ibrutinib AE Grade ≥3 with p17/ del53

No head to head study is available vs. ibrutinib in overall 1<sup>st</sup> line CLL and neither in the mutated population but the NMA and MAIC has addressed Grade ≥3 in the overall population . Medicinrådet find it relevant to extrapolate the adverse event profiles seen in the direct comparative study between acalabrutinib and ibrutinib( ELEVATE RR, 2<sup>nd</sup> line) [5] to the naïve comparisons in 1<sup>st</sup> line so the study is also included in this section. This assumption also include the population with p17/del53.

Note that in the ELEVATE RR study, TEAEs were defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event that worsened in severity after the first dose of study drug, and before 30 days after the date of the last dose of study drug or the date of first starting new anti-cancer therapy. Thus, all AEs and SAEs discussed in this section are TEAEs unless otherwise specified.

The comparison covers patient with del17. See section 5.2 for more details of ELEVATE and studies included in the NMA and MAIC. A naïve comparison between ELEVATE, Ahn and RESONATE2 study is also included.

### 7.3.2 Results per study Acalabrutinib vs. Ibrutinib AE Grade ≥3 with p17/del53

#### MAIC

The MAIC also compared the incidence of specific AEs and SAEs for the selected regimens. After matching, lower incidences and some significant, of several AEs were observed for acalabrutinib monotherapy compared with ibrutinib (table 34) . [43].

TABLE 34. SAFETY OUTCOMES AFTER MATCHING FOR ACALABRUTINIB MONOTHERAPY VERSUS IBRUTINIB

	Acalabrutinib monotherapy	Ibrutinib	RD (%)		Odds ratio	
	ESS = 79 [A]	N = 136 [B]	Mean (95% CI) [A - B]	P-value	OR (95% CI)	P-value
<b>Any grade AE</b>						
Diarrhoea	45.4	45.0	0.4 (-12.3, 13.1)	0.95	1.0 (0.7, 1.5)	0.93
Vomiting	10.0	17.0	-7.0 (-15.2, 1.0)	0.10	0.5 (0.3, 1.0)	0.07
Nausea	20.0	23.0	-3.0 (-13.7, 7.0)	0.58	0.8 (0.5, 1.4)	0.50
Pyrexia	6.2	20.0	-13.8 (-21.6, -6.0)	<0.001	0.3 (0.1, 0.6)	< 0.001 <sup>a</sup>
Hypertension	6.4	18.0	-11.6 (-19.9, -3.0)	<0.01	0.3 (0.1, 0.8)	< 0.05 <sup>a</sup>
Neutropenia	13.0	17.0	-4.0 (-12.9, 5.0)	0.38	0.7 (0.4, 1.4)	0.32
Arthralgia	15.9	20.0	-4.1 (-14.1, 5.0)	0.42	0.8 (0.4, 1.4)	0.35
AF	6.4	10.0	-3.6 (-11.1, 3.0)	0.34	0.6 (0.2, 1.7)	0.34
Major haemorrhage	1.8	7.0	-5.2 (-10.2, 0.0)	< 0.05 <sup>a</sup>	0.2 (0.1, 1.2)	0.08
Fatigue	21.6	33.0	-11.4 (-23.1, 0.0)	0.07	0.6 (0.4, 0.9)	< 0.05 <sup>a</sup>
Cough	23.5	28.0	-4.5 (-16.0, 7.0)	0.18	0.8 (0.5, 1.3)	0.34
Anaemia	18.8	23.0	-4.2 (-15.3, 6.0)	0.53	0.8 (0.4, 1.4)	0.38
PE	7.5	21.0	-13.5 (-21.7, -5.0)	< 0.001 <sup>a</sup>	0.3 (0.2, 0.6)	< 0.001 <sup>a</sup>
<b>Grade 3-4 AEs</b>						
Arthralgia	0.0	2.0	-2.0 (-4.4, 0.0)	0.1	0 (0, 0)	-
PE	0.0	1.0	-1.0 (-2.7, 0.0)	0.24	0 (0, 0)	-
Nausea	0.0	1.0	-1.0 (-2.7, 0.0)	0.24	0 (0, 0)	-
Cough	1.5	0.0	1.5 (-1.2, 4.0)	0.31	0 (0, 0)	-
Fatigue	0.1	1.0	-0.9 (-2.6, 0.0)	0.26	0.1 (0.0, 1.9)	0.14
Pyrexia	0.0	0.0	0 (0.0, 0.0)	-	0 (0, 0)	-
Vomiting	0.5	0.0	0.5 (-0.5, 1.0)	0.32	0 (0, 0)	-
AF	0.0	4.0	-4.0 (-7.3, 0.0)	< 0.05	0 (0, 0)	-
Anaemia	6.9	7.0	-0.1 (-6.8, 6.0)	0.98	1.0 (0.4, 2.6)	0.98
Neutropenia	12.8	12.0	0.8 (-7.5, 9.0)	0.85	1.1 (0.5, 2.1)	0.83
Diarrhoea	2.0	4.0	-2 (-6.8, 2.0)	0.41	0.5 (0.1, 3.3)	0.46
Hypertension	3.1	5.0	-1.9 (-7.3, 3.0)	0.5	0.6 (0.1, 2.7)	0.52
Major haemorrhage	1.8	6.0	-4.2 (-9.0, 0.0)	0.08	0.3 (0.1, 1.4)	0.12
Infections	12.4	24.0	-11.6 (-21.9, -1.0)	< 0.05 <sup>a</sup>	0.5 (0.2, 0.9)	< 0.05 <sup>a</sup>

<sup>a</sup>p < 0.05. MAIC study report [43]

## Qualitative comparison of Grade ≥3 AEs of clinical interest . Narrative acalabrutinib vs ibrutinib and data from ELEVATE-RR

In order to highlight some of the differences of the two BTK inhibitors with regards to safety profiles, grade ≥3 AE of clinical interest reported in ELEVATE-TN are described below in table 35 for all four studies:

In ELEVATE-TN [6], AE of clinical interest grade ≥3 included hypertension (2%) bleeding (1.7%) and infections (14%). No grade ≥3 atrial fibrillation was observed. (Table 35).

In ELEVATE-RR[5] grade ≥3 AE of clinical interest included hypertension ( A: 4.1% I: 9.1%), bleeding (A: 3.8% I: 4.6%), atrial fibrillation (A: 4.9% I: 3.8%) and infection (A:30.8% I: 30%). (Table 35).

Grade 3 or 4 AEs in the **Ahn** et al.[16] study were reported infection (9.3%), atrial fibrillation (6%) whilst data on hypertension was not reported and no bleeding of grade 3 or above occurred on study.(Table 35).

**RESONATE-2** [14]; Grade ≥3 hypertension was 9% and atrial fibrillation was 5%, grade ≥3 infections were reported in the extended follow-up (3-years) to be 23% (with 2 fatal outcomes)(Table 35).

Table 35. Grade ≥3 AEs of clinical interest

Study		ELEVATE-TN	ELEVATE-RR	Ahn	RESONATE-2
AE of clinical interest grade ≥3 (%)	Hypertension	2,2%	A: 4.1% I: 9.1%	NR	9%
	Bleeding	1,7%	A: 3.8% I: 4.6%	NO	NR
	Infection	14%	A: 30.8% I: 30%	9,3%	23%
	Atrial fibrillation	NO	A: 4.9% I: 3.8%	6%	5%

NO= not observed, NR= not reported

Collectively, these data demonstrate a lower incidence of Grade ≥3 atrial fibrillation and hypertension in the ELEVATE-TN study compared to the Ahn and RESONATE-2 studies, while grade ≥3 infections and discontinuation due to AEs are highest in the RESONATE-2 study and lowest in the Ahn study. With regards to ELEVATE-RR, Grade ≥3 hypertension is lower in the acalabrutinib arm of the study compared to the Ibrutinib arm of the study as well as compared to Ibrutinib arm in the RESONATE-2 study. Bleeding is also lower in the acalabrutinib vs Ibrutinib arm in the Elevate-RR study. Infections are generally higher in the ELEVATE-RR study than in ELEVATE-TN, Ahn and RESONATE-2 studies, but comparable between the Acabrutinib and Ibrutinib arms of the ELEVATE-RR study. One of the secondary endpoints in ELEVATE RR showed that patients treated with acalabrutinib had statistically significantly lower incidence of atrial fibrillation compared to patients treated with ibrutinib (9.4% vs. 16.0%, respectively, p = 0.0228). With regards to Grade ≥3 Atrial fibrillation it was slightly lower for Ibrutinib arm compared to the acalabrutinib arm in the ELEVATE-RR study but lower compared to Ahn and RESONATE-2 studies.

### 7.3.3 Comparative analysis Acalabrutinib vs. Ibrutinib with p17/ del53 Grade $\geq 3$ AEs

Based on the MAIC in the ITT populations the relative benefit is in favor of acalabrutinib for most individual listed AE and grade 3-4 events (table 34), with some of the difference being significant. As Medicinrådet is asking for grade 3-4 totals we cannot conclude, based on the individual event listed in table 32, that acalabrutinib can meet the target set by Medicinrådet. Data are not comparable and there is lack of data in the mutated population.

Due to the individual based reporting in the MAIC we also assessed the question through a naïve comparison:

- In the ELEVATE-TN study AEs are not reported for the subpopulation. At a median follow up of 28.1 months grade  $\geq 3$  AE in the acalabrutinib monotherapy arm for the whole population was **49,7%** (Table 33) while grade  $\geq 3$  serious AE was 29.6% and of any grade was 31,8%. [6].
- In the 24 month follow up, the Ahn study, reported grade 3 or 4 AE events for the Tp53 population in 28/51 patients (54%) and in the 5-year follow-up grade 3 or 4 AEs for the whole population was reported to be (25/86 patients) **29%** (Table 33). [16, 17]
- In the RESONATE-2 study, grade  $\geq 3$  AE for the whole population was reported to be **83%** (Table 33) and serious AEs occurring in more than 2 ibrutinib treated patients was reported in the extended follow up (3 years) to be 30,8%.
- In ELEVATE-RR, grade  $\geq 3$  AE for the whole study population was reported to be **68.8%** for acalabrutinib and **74.9%** for Ibrutinib. In addition, serious AEs of grade  $\geq 3$  were **47.4%** for acalabrutinib and **52.5%** for ibrutinib [5].

As requested by the Medicine council, a narrative description of the safety data in ELEVATE-RR will follow below. This is based on the an expectation of no differences in safety between 1L and R/R treatment and also no differences in safety profile in populations with or without 17p del/Tp53 mutation is expected.

ELEVATE-RR was designed with three safety outcomes as secondary endpoints: the incidence of atrial fibrillation, the incidence of grade  $\geq 3$  infections, and the incidence of Richter's transformation. The trial met a key secondary endpoint for safety, showing patients treated with acalabrutinib had statistically significantly lower incidence of atrial fibrillation (any grade) compared to patients treated with ibrutinib (9.4% vs. 16.0%, respectively,  $p = 0.0228$ ). The incidence of atrial fibrillation/flutter in patients without previous history of atrial fibrillation/flutter was 6.2% for the acalabrutinib arm and 14.9% for the ibrutinib arm. Moreover, the onset of atrial fibrillation occurred at a median of 28.8 (0.4–52.0) months in the acalabrutinib arm and at a median of 16.0 (0.5–48.3) months with Ibrutinib [5].

The incidence of grade  $\geq 3$  infections and Richter's transformation were comparable between the treatments. Compared with ibrutinib, acalabrutinib was associated with a lower incidence of grade  $\geq 3$  AEs, as well as a lower incidence of serious adverse events (SAEs) and AEs that led to treatment discontinuation (see table 36 for details) [5].

Most common adverse events had a similar or lower incidence in patients treated with acalabrutinib compared to ibrutinib, with the exception of headache, dyspnoea, and cough (see table 37). Grade  $\geq 3$  most common AE were statistically higher for ibrutinib with regards to diarrhea (Acalabrutinib 1.1% vs Ibrutinib 4.9%) and hypertension (Acalabrutinib 4.1% vs Ibrutinib 8.7%) whereas headache (Acalabrutinib 1.5% vs Ibrutinib 0%) and fatigue (Acalabrutinib 3.4% vs Ibrutinib 0%), see table 37 [5].

TABLE 36. OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS IN ELEVATE-RR

Safety Population	Acalabrutinib (n = 266)	Ibrutinib (n = 263)
Treatment-Emergent Adverse Events	260 (97.7%)	256 (97.3%)
▪ Grade $\geq 3$	183 (68.8%)	197 (74.9%)
▪ Grade 5	20 (7.5%)	28 (10.6%)
Serious TEAE	143 (53.8%)	154 (58.6%)
▪ Grade $\geq 3$	126 (47.4%)	138 (52.5%)
▪ Grade 5	20 (7.5%)	28 (10.6%)
Treatment-Related TEAE	203 (76.3%)	223 (84.8%)
TEAE Leading to Treatment Discontinuation	39 (14.7%)	56 (21.3%)
TEAE Leading to Dose Reduction	17 (6.4%)	15 (5.7%)
TEAE Leading to Drug Interruption	141 (53.0%)	147 (55.9%)

With respect to events of clinical interest, the incidence of cardiac events, hypertension, and haemorrhage were lower in patients treated with acalabrutinib, though the rates of major haemorrhage were comparable.

TABLE 37. TREATMENT-EMERGENT AEs REPORTED IN  $\geq 20\%$  OF SUBJECTS TREATED IN ANY ARM IN ELEVATE-RR[5]

Events, n (%)	Grade $\geq 3$	
	Acalabrutinib (n=266)	Ibrutinib (n=263)
Diarrhea <sup>a,b</sup>	3 (1.1)	<b>13 (4.9)</b>
Headache <sup>a,b</sup>	<b>4 (1.5)</b>	0
Cough <sup>a</sup>	2 (0.8)	1 (0.4)
URTI	5 (1.9)	1 (0.4)
Neutropenia	52 (19.5)	60 (22.8)
Pyrexia	8 (3.0)	2 (0.8)
Arthralgia <sup>a</sup>	0	2 (0.8)
Hypertension <sup>a,b</sup>	11 (4.1)	<b>23 (8.7)</b>
Anemia	31 (11.7)	34 (12.9)
Fatigue <sup>b</sup>	<b>9 (3.4)</b>	0
Nausea	0	1 (0.4)
Contusion <sup>a</sup>	0	1 (0.4)
Pneumonia	28 (10.5)	23 (8.7)
Atrial fibrillation <sup>a</sup>	12 (4.5)	9 (3.4)
Thrombocytopenia	26 (9.8)	18 (6.8)

Higher incidence in **bold red** for terms with statistical differences.

Among most common AEs above, grade 5 were reported in 5 (1.9%) acalabrutinib patients (pyrexia, n=1; pneumonia, n=4) and 4 (1.5%) ibrutinib patients (URTI, n=1; pneumonia, n=3).

<sup>a</sup>Based on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for any grade events.

<sup>b</sup>Based on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for grade  $\geq 3$  events.

Includes AEs reported at  $\geq 15\%$  incidence (any grade) in either arm.

AE, adverse event; URTI, upper respiratory tract infection.

### Grade 3 or more AE relative risk(ELEVATE RR)

Groups	AE Grade ≥ 3	No Grade	Total patients	Risk Ratio	Relative RR
Acalabrutinib	183	83	266		0,68797
Ibrutinib	197	66	263		0,74904943

DIS	95% CI	LN(RR)+/-1,96*SQRT(((n1-x1)/x1)/n1) + ((n2-x2)/x2)/n2)	exp of log	95% CI	interpretation	Column1
((n1-x1)/x1)/n1	0,001705082		0,022	1,022158278	0.83; 1.02	excl 1 = Sig. Relativ risiko
((n2-x2)/x2)/n2	0,001273861		-0,192	0,825	NA	NA

### Grade 3 or more SAE relative risk(ELEVATE RR)

Groups	TEAE Grade ≥ 3	No TEAE	Total patients	Risk Ratio	Relative RR
Acalabrutinib	126	140	266		0,47368
Ibrutinib	138	125	263		0,524714829

DIS	95% CI	LN(RR)+/-1,96*SQRT(((n1-x1)/x1)/n1) + ((n2-x2)/x2)/n2)	exp of log	95% CI	interpretation	Column1
((n1-x1)/x1)/n1	0,004177109		0,069	1,071214434	0.76; 1.07	excl 1 = Sig. Relativ risiko
((n2-x2)/x2)/n2	0,003444095		-0,273	0,761	NA	NA

The 10% target set by Medicinraadet for grade ≥3 AE can be met against the RESONATE-2 study with both the ELEVATE-TN and ELEVATE-RR studies but not the Ahn study. As this is based on mixed ITT and mutated data we cannot conclude that the target can be met. In the head-to-head study ELEVATE RR, the absolute difference was 5.9% (and RR=0.92) but the 10% target cannot be met.

## 7.4 Acalabrutinib vs. Ibrutinib 1<sup>st</sup> line with p17/ del53 HQoL

### 7.4.1 Relevant studies Acalabrutinib vs. Ibrutinib with p17/ del53 HQoL

HQoL is not available from the NMA or MAIC. HQoL is either not included in the studies for comparator or is not calculated in a way that allows any narrative comparison with comparator.

### 7.4.2 Results per study Acalabrutinib vs. Ibrutinib with p17/ del53 HQoL

HQoL is either not included in the studies for comparator or is not calculated in a way that allows any narrative comparison with comparator

### 7.4.3 Comparative analysis Acalabrutinib vs. Ibrutinib with p17/ del53 HQoL

HQoL is either not included in the studies for comparator or is not calculated in a way that allows any narrative comparison with comparator

## 8 Clinical question Acalabrutinib + O vs. Ibrutinib in 1<sup>st</sup> line with p17/del53

### 8.1 Acalabrutinib + O vs. Ibrutinib PFS/PFS rate

#### 8.1.1 Relevant studies Acalabrutinib + O vs. ibrutinib 1<sup>st</sup> line with p17/del53 PFS/PFS rate

Ibrutinib was chosen as comparator due to availability of data from the indirect comparisons and also because it is market leader in Denmark, a BTK drug and has treatment to progression as with acalabrutinib.

No head to head study is available for acalabrutinib + O vs. ibrutinib both a NMA and MAIC has addressed the PFS and OS in the overall population.

#### NMA and MAIC .

NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus Ibrutinib another in the network (e.g., odds ratio, relative risk, or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers.

MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison.

Please see section 7.1 and table 32 and 38 for further details of studies relevant for narrative comparison.

#### 8.1.1 Result per study Acalabrutinib + O vs. ibrutinib PFS/PFS rate

Below in table 38, we have listed the overview of data to be used in the narrative comparison.

Table 38. narrative acalabrutinib + obinutuzumab vs. Ibrutinib

Read out		Study				
		ELEVATE-TN Tp53/del17p n=19/16	ELEVATE-RR $\alpha$ Tp53 n =121 del17p n=100	Ahn et al (Tp53) n=51 (TN n= 34/51)	RESONATE-2 (Tp53) n=12	RESONATE-2 n=136
Follow-up (Median, months)		28,3	41	58	60	60
Survival	OS 2-year	95%		84%		98%
	OS 5-year	-		85.3% (n=51)	-	83%
	PFS 2 years	95%/88%		82% (n=51) and 85%** (n = 34)	-	-
	PFS 5 years	-		74.4% (n=34)	56%	70%
Adverse Events	Grade $\geq 3$ AE	70,2% #	A: 68.8 % (n=266) I: 74.9% (n= 263)	54% (24m Follow-up) / 29% # (5 years follow-up)	-	83%

\*read from KM-curve, \*\*Adopted from Venetoclax + obinutuzumab application to Medicinrådet, #HR= high risk (patients with del17, del 11q, TP53 mutations or unmutated IGHV).  $\alpha$  Only safety is assessed for this study in this section

## MAIC

Table 39. Summary of results from the MAIC for acalabrutinib compared with other regimens in untreated CLL [43]

Column vs row Median HR (95% CI)	MAIC	
	Acalabrutinib + obinutuzumab	
	PFS	PFS
ibrutinib	0.61 (0.24–1.55) $p = 0.30$	0.61 (0.24–1.55) $p = 0.30$

Source MAIC [43]

## NMA:

Results(table 31) of acalabrutinib + obinutuzumab vs ibrutinib are only available (del17p population) vs the combination of ibrutinib + obinutuzumab. HR=0.91(0.15; 5.60) [44]. Ibrutinib + obinutuzumab is not a comparator in the protocol from Medicinrådet. The data for the ITT population will be referred to in the comparative analysis.

### 8.1.2 Comparative analysis Acalabrutinib + O vs. ibrutinib with p17/del53 PFS/PFS rate

Acalabrutinib + obinutuzumab was associated with significantly better efficacy based on the NMA, vs. ibrutinib monotherapy HR= 0.19(0.09; 0.38) in terms of PFS as reported in table 31. However this is based on overall population.

The MAIC, in the overall population show HR values in favour of the acalabrutinib combination vs ibrutinib but with wide CI intervals.



Based on the indirect comparison the PFS target from Medicinraadet cannot be met due to lack of comparative data in the mutated population. As the ITC's do not look at the mutated population and do not cover PFS rates a naïve assessment was performed:

- As demonstrated in Table 38, the 2-year PFS rates for acalabrutinib + obinutuzumab in the Tp53 and del17p subpopulation in the ELEVATE-TN study were **95%** and **88%** respectively [6] (Table 38).
- In the Ahn study the 2-year PFS rate was **82%** in the whole Tp53 population and **85%** (read of KM\_curve) for the TN TP53 mutated population. The 5-year PFS rate was 74,4% [16, 17] (Table 38).
- In the RESONATE-2 study the 5-year PFS rate was **56%** in the Tp53 population [14] (Table 38).

Based on a narrative comparison in mutated patients, the 10% target set by Medicinraadet can be met in the 2-year PFS rate of the TN Tp53-mutated populations comparing ELEVATE-TN and Ahn. Target cannot be met with RESONATE-2 (Table 38). It is however not possible to confirm an advantage for PFS rate at 3 years due to the studies report at different points in time. The conclusion from the naïve comparison is mixed and cannot confirm in general a 10 % PFS benefit for acalabrutinib + obinutuzumab vs. ibrutinib in high risk patients.

## 8.2 Acalabrutinib + O vs. ibrutinib 1<sup>st</sup> line CLL with p17/del53 OS/OS rate

### 8.2.1 Relevant studies Acalabrutinib + O vs. Ibrutinib with p17/del53 OS/OS rate

No head to head study is available for acalabrutinib + O vs. ibrutinib in 1<sup>st</sup> line CLL both overall and in the mutated population but the NMA and MAIC has addressed the OS in the ITT population. See section 5.2 and table A4 for more details of ELEVATE and ibrutinib studies (RESONATE-2, ILLUMINATE and Tedeschi 2019) included in the NMA and MAIC. A naïve comparison between ELEVATE and Ahn study is also included.

### 8.2.2 Result per study Acalabrutinib + O vs. Ibrutinib with p17/del53 OS/OS rate

#### MAIC

Data is only available for overall populations so not specific data for the mutations. Results for OS were variable, with greater risk reductions being seen with acalabrutinib + obinutuzumab than ibrutinib HR= 0.88 (0.31; 2.52) and HR=0.53(0.21; 0.47) vs. ibrutinib + obinutuzumab. This variation could be explained by immature OS data and in some trials, the ability of progressed patients in the comparator arm to cross over to the treatment arm (table 40) [43].

TABLE 40. RESULTS FROM THE MAIC FOR ACALABRUTINIB + O THERAPY COMPARED WITH IBRUTINIB FOR PATIENTS WITH UNTREATED CLL

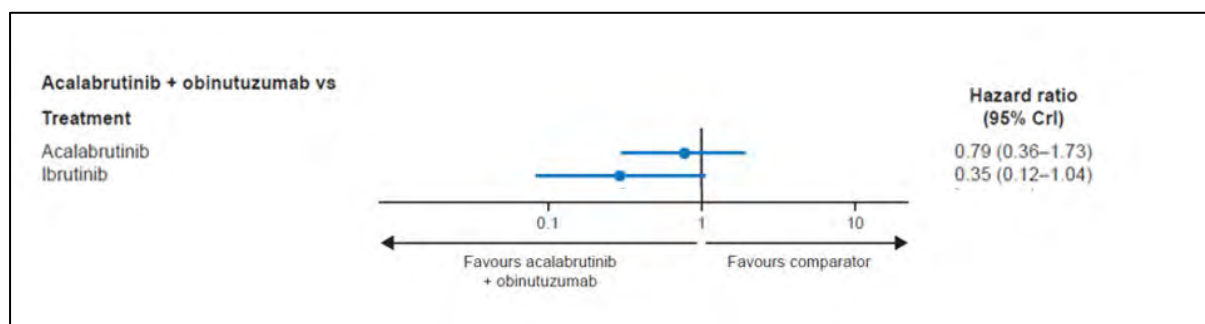
Column vs row Median HR (95% CI)	Acalabrutinib + obinutuzumab	
	PFS	OS
Ibrutinib	0.61 (0.24–1.55) <i>p</i> = 0.30	0.88 (0.31–2.52) <i>p</i> = 0.81

Source: 1L CLL MAIC report.[43]

### NMA

OS vs ibrutinib was also assessed in the NMA. Unlike PFS, only the ITT population was on interest for OS, as subgroup data were not available for OS to perform the NMAs. Acalabrutinib + obinutuzumab vs ibrutinib resulted(network 1) in HR=0.35(0.12-1.04) [44].

FIGURE 17. FOREST PLOT OF OS FROM NETWORK 1 FOR ACALABRUTINIB PLUS OBINUTUZUMAB, VERSUS COMPARATORS



NMA study report [44]

### 8.2.3 Comparative analysis acalabrutinib + O vs. Ibrutinib with p17/del53. OS/OS rate

In the comparative studies OS for the ITT population demonstrated greater risk reductions(not significant) with acalabrutinib + obinutuzumab than ibrutinib .

Results from the NMA showed that Acalabrutinib + obinutuzumab vs ibrutinib resulted in a HR=0.35(0.12-1.04) [44]. Results from the MAIC showed a greater risk reductions being seen with acalabrutinib + obinutuzumab than ibrutinib HR= 0.88 (0.31; 2.52).

However, variation were observed in the comparative studies that could be explained by immature OS data and in some trials, the ability of progressed patients in the comparator arm to cross over to the treatment arm. For the mutated population data are not available and valid due very small size of the group and immature OS data.

The specific question concerns OS rate at 3 years. The acalabrutinib + obinutuzumab combination cannot meet the target from Medicinrådet based on the available OS data as these are not reported for the mutated population.

As ELEVATE do not report OS data in the high risk group we have not found it applicable to do a naïve comparison.

### 8.3 Acalabrutinib + O vs. ibrutinib in patient with p17/del53 AE Grade $\geq 3$

#### 8.3.1 Relevant studies Acalabrutinib + O vs. ibrutinib p17/del53 AE Grade $\geq 3$

No head to head study is available vs. ibrutinib in overall 1<sup>st</sup> line CLL and neither in the mutated population but the NMA and MAIC has addressed Grade  $\geq 3$  in the ITT population . See section 5.2 for more details of ELEVATE and studies (RESONATE-2, ILLUMINATE and Tedeschi 2019) included in the NMA and MAIC. A naïve comparison between ELEVATE, Ahn and RESONATE2 study is also included below. Medicinrådet find it relevant to extrapolate the adverse event profiles seen in the direct comparative study between acalabrutinib and ibrutinib( ELEVATE RR, 2<sup>nd</sup> line) [5] to the naïve comparisons in 1<sup>st</sup> line so the study is also included in this section. This assumption also include the population with p17/del53.

Note that in the ELEVATE RR study, TEAEs were defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event that worsened in severity after the first dose of study drug, and before 30 days after the date of the last dose of study drug or the date of first starting new anti-cancer therapy. Thus, all AEs and SAEs discussed in this section are TEAEs unless otherwise specified. To evaluate/compare the level of Grade  $\geq 3$  of acalabrutinib + obinutuzumab vs ibrutinib with acabrutinib monotherapy as common comparator we have also provided a further indirect analysis based on ELEVATE-RR and ELEVATE-TN.

#### 8.3.2 Result per study Acalabrutinib + O vs. Ibrutinib with del17/p53 AE Grade $\geq 3$

##### MAIC

After matching, the incidences of various AEs were significantly lower for acalabrutinib plus obinutuzumab compared with Ibrutinib, while the incidences of grade 3/4 neutropenia were significantly higher.

Table 41. Safety outcomes before and after matching acalabrutinib + O vs. ibrutinib monotherapy

	ACA + OB		Before matching				ACA + OB		After matching					
	N=126 <sup>a</sup> [A]	N=136 [B]	Mean RD (%)	95% CI [A - B]	p-value	OR (95% CI)	p-value	ESS N=58 [A]	N=136 [B]	Mean RD (%)	95% CI [A - B]	p-value	OR (95% CI)	p-value
Any diarrhoea	36.5	45.0	-5.5	(-20.4, 3.4)	0.16	0.7 (0.5, 1)	0.05	38.3	45.0	-6.7	(-20.2, 6.8)	0.33	0.8 0.51,1.14	0.18
Any vomiting	15.1	17.0	-1.9	(-10.5, 7.0)	0.67	0.9 (0.5, 1.5)	0.62	12.1	17.0	-4.9	(-13.6, 3.8)	0.27	0.7 0.36,1.26	0.21
Any nausea	19.0	23.0	-4	(-13.8, 5.9)	0.43	0.8 (0.5, 1.3)	0.34	20.2	23.0	-2.8	(-14.1, 8.5)	0.63	0.8 0.49,1.47	0.56
Any pyrexia	14.3	20.0	-5.7	(-14.8, 3.4)	0.22	0.7 (0.4, 1.2)	0.15	15.4	20.0	-4.6	(-14.3, 5.1)	0.35	0.7 0.41,1.29	0.28
Any hypertension	9.5	18.0	-8.5	(-16.7, 0.2)	< 0.05 <sup>a</sup>	0.5 (0.2, 0.9)	< 0.05 <sup>a</sup>	9.5	18.0	-8.5	(-18.0, 1.0)	0.08	0.5 0.219,1.10	0.08
Any neutropenia	36.9	17.0	21.9	(11.3, 3.25)	< 0.001 <sup>a</sup>	3.1 (2, 4.9)	<	36.4	17.0	19.4	(9.3, 29.6)	< 0.001	2.8 1.78,4.41	< 0.001
Any atrragia	23.0	20.0	3	(-7.0, 13.0)	0.55	1.2 (0.7, 1.9)	0.47	22.3	20.0	2.3	(-8.8, 13.5)	0.68	1.2 0.67,1.97	0.61
Any AF	3.2	10.0	-6.8	(-12.7, 0.9)	< 0.05 <sup>a</sup>	0.3 (0.1, 0.9)	< 0.05 <sup>a</sup>	3.9	10.0	-6.1	(-12.3, 0.1)	0.06	0.37 0.13,1.07	0.07
Any major haemorrhage	2.4	7.0	-4.6	(-9.7, 0.4)	0.07	0.3 (0.1, 1.1)	0.08	6.7	7.0	-0.3	(-6.1, 7.4)	0.94	1.0 (0.3, 3.0)	0.93
Any fatigue	27.8	33.0	-5.2	(-16.4, 5.9)	0.36	0.8 (0.5, 1.2)	0.23	23.5	33.0	-9.5	(-21.5, 2.6)	0.12	0.6 0.38,1.01	0.06
Any cough	24.6	28.0	-3.4	(-14.1, 7.3)	0.53	0.8 (0.5, 1.3)	0.43	18.6	28.0	-9.4	(-19.6, 0.8)	0.07	0.6 0.37,0.95	< 0.05
Any anaemia	15.9	23.0	-7.1	(-16.7, 0.2)	0.14	0.6 (0.4, 1.1)	0.08	20.3	23.0	-2.7	(-15.2, 9.8)	0.67	0.9 0.46,1.58	0.61
Any PE	12.7	21.0	-8.3	(-17.3, 0.7)	0.07	0.5 (0.3, 1)	< 0.05 <sup>a</sup>	14.5	21.0	-6.5	(-16.2, 3.2)	0.19	0.6 0.36,1.15	0.14
Grade 3-4 arthralgia	1.6	2.0	-0.4	(-3.6, 2.8)	0.8	0.8 (0.1, 4.8)	0.8	1.4	2.0	-0.6	(-3.6, 2.5)	0.72	0.7 0.12,4.31	0.71
Grade 3-4 PE	0.0	1.0	-1	(-2.7, 0.7)	0.24	0	-	0	1.0	-1	(-2.7, 0.7)	0.24	0	-
Grade 3-4 nausea	0.0	1.0	-1	(-2.7, 0.7)	0.24	0	-	0	1.0	-1	(-2.7, 0.7)	0.24	0	-
Grade 3-4 cough	0.0	0.0	0	(0.0, 0.0)	-	0	-	0	0.0	0	(0.0, 0.0)	0.00	0	-
Grade 3-4 fatigue	0.0	1.0	-1	(-2.7, 0.7)	0.24	0	-	0	1.0	-1	(-2.7, 0.7)	0.24	0	-
Grade 3-4 pyrexia	0.0	0.0	0	(0.0, 0.0)	-	0	-	0	0.0	0	(0.0, 0.0)	-	0	-
Grade 3-4 vomiting	0.8	0.0	0.8	(-0.8, 2.3)	0.32	0	-	1.2	0.0	1.2	(-1.0, 3.4)	0.3	0	-
Grade 3-4 AF	0.8	4.0	-3.2	(-6.8, 0.4)	0.08	0.2 (0.0, 1.6)	0.13	0.9	4.0	-3.1	(-6.8, 0.6)	0.1	0.2 (0.0, 1.7)	0.15
Grade 3-4 anaemia	8.7	7.0	1.7	(-4.8, 8.3)	0.6	1.3 (0.6, 2.9)	0.57	11.7	7.0	4.7	(-4.0, 13.3)	0.29	1.8 (0.7,4.3)	0.22
Grade 3-4 neutropenia	35.7	12.0	23.7	(13.7, 33.7)	< 0.001 <sup>a</sup>	4.1 (2.4, 6.9)	<	32.7	12.0	20.7	(10.7, 30.7)	< 0.001	3.6 (2.1, 6.1)	< 0.001
Grade 3-4 diarrhoea	4.8	4.0	0.8	(-2.2, 3.7)	0.76	1.2 (0.4, 3.7)	0.75	4.3	4.0	0.3	(-4.6, 5.2)	0.9	1.1 (0.34, 3.5)	0.89
Grade 3-4 hypertension	4.0	5.0	-1	(-6.0, 4.0)	0.69	0.8 (0.3, 2.4)	0.68	2	5.0	-3	(-7.1, 1.1)	0.15	0.4 (0.1, 1.3)	0.12
Grade 3-4 haemorrhage	1.6	6.0	-4.4	(-9.0, 0.1)	0.06	0.3 (0.0, 1.2)	0.08	2.4	6.0	-3.6	(-8.6, 1.4)	0.16	1.0 (0.1, 1.6)	0.20
Grade 3-4 infections	19.6	24.0	-4.2	(-14.2, 5.9)	0.42	0.8 (0.5, 1.3)	0.32	20.6	24.0	-3.4	(-15.3, 8.5)	0.57	0.8 (0.5, 1.4)	0.5

<sup>a</sup>p < 0.05. MAIC study report [43]

### AEs of clinical interest

Grade ≥3 AE of clinical interest in acalabrutinib plus obinutuzumab arm of the ELEVATE-TN study included atrial fibrillation (0,6%), hypertension (2,8%) bleeding (1,7%) and infections (20,8%) [6]. Data from the ELEVATE-TN, ELEVATE-RR, RESONATE-2 study and the Ahn study are detailed in section 7.2.2, Table 35 and below in table

Collectively, these data comparing acalabrutinib + obinutuzumab with ibrutinib in the Ahn and RESONATE-2 study demonstrate (similarly to the comparisons with acalabrutinib monotherapy) a lower incidence of grade ≥3 atrial fibrillation and grade ≥3 hypertension in the ELEVATE-TN study compared to the Ahn and RESONATE-2 studies, while grade ≥3 infections and discontinuation due to AEs are highest in the RESONATE-2 study and lowest in the Ahn study.

### 8.3.3 Comparative analysis Acalabrutinib + O vs. Ibrutinib with p17/ del53 Grade $\geq 3$ AE

Based on the MAIC (ITT populations) the relative effect is in favor of acalabrutinib + O for various individual listed AE and grade 3-4 events, with some of the differences being significant. However the incidences of grade 3/4 neutropenia were significantly higher for Acalabrutinib + O. As Medicinrådet is asking for grade 3-4 totals we cannot conclude, based on the individual events listed in table 41, that acalabrutinib + obinutuzumab can meet the target set by Medicinrådet. Data are not comparable and there is lack of data in the mutated population.

Due to the individual based reporting in the MAIC we also assessed the question through a naïve comparison:

- In the ELEVATE-TN study, AEs were not reported for the subpopulation. Grade  $\geq 3$  AE in the acalabrutinib plus obinutuzumab arm was reported for the overall population was **70,2%** (Table 38), while grade  $\geq 3$  serious AE was 32,6% and of any grade was 38,8%. [6].
- In the 24month follow up, the Ahn study, reported grade 3 or 4 AE events for the Tp53 population in 28/51 patients (54%) and in the 5-year follow-up grade 3 or 4 AEs for the whole population was reported to be (25/86 patients) **29%** (Table 38). 5 [16, 17]
- In the RESONATE-2 study, grade  $\geq 3$  AE for the whole population was reported to be **83%** (Table 38) and serious AEs occurring in more than 2 ibrutinib treated patients was reported in the extended follow up (3 years) to be 30,8%. [14].
- In ELEVATE-RR, grade  $\geq 3$  AE for the whole study population was reported to be **74.9%** for ibrutinib. In addition, serious AEs of grade  $\geq 3$  were 52.5% for ibrutinib (Table 38). [5]

#### Indirect comparison ELEVATE-TN and ELEVATE-RR

##### Feasibility Assessment

To first determine if a comparison between acalabrutinib + obinutuzumab in ELEVATE-TN and ibrutinib monotherapy in ELEVATE-RR could be made, a feasibility assessment was conducted. The feasibility assessment considered:

- Factors which may potentially be prognostic of adverse events or modify the relationship between treatment and the incidence of adverse events and how these differ between studies
- Trial follow-up and duration of treatment exposure which could influence the time in which events could occur
- Homogeneity of the safety profile of acalabrutinib monotherapy between the trials as the connecting treatment to see if any unmeasured factors may be influencing safety outcomes

##### Identification of Prognostic Factors & Treatment-Effect Modifiers

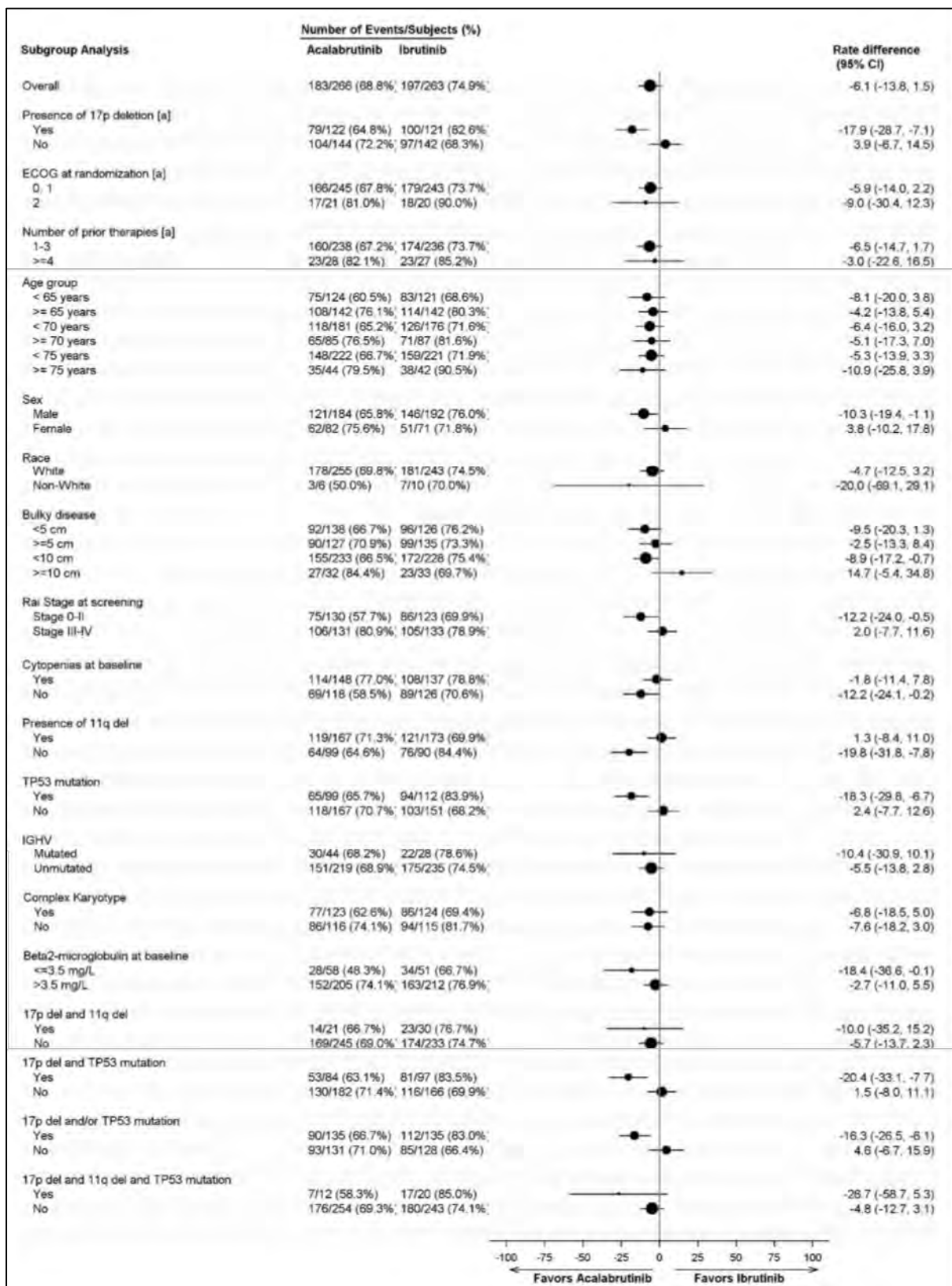
Whilst it may be possible to consider that the safety profile would be comparable between previously untreated and relapsed/refractory patients, it is not possible to exclude that patient or disease characteristics may increase the propensity for adverse events (e.g., older or more frail patients may be at increased risk). As shown in the previously submitted matching-adjusted indirect comparison (MAIC), adjusting for baseline characteristics to match the RESONATE-2 trial [15] of ibrutinib resulted in an estimated increase in the proportion of patients experiencing specific adverse events such as diarrhoea, neutropenia, and anaemia. Key characteristics that differed between the trials were age,  $\beta$ 2-microglobulin, creatinine clearance, and the proportion with unmutated IGHV.

Within ELEVATE-RR, several factors were associated with an increased risk of grade  $\geq 3$  treatment-emergent adverse events (TEAE) in patients treated with acalabrutinib, including ECOG performance status, number of prior therapies, age, Rai stage, cytopenias at baseline, and  $\beta$ 2-microglobulin (Figure ). In terms of treatment-effect modifiers, logistic regression subgroup analysis of the ELEVATE-RR trial shows that the difference in the rate of grade  $\geq 3$  treatment-emergent adverse events between acalabrutinib and ibrutinib was significantly modified by 17p deletion ( $p < 0.001$ ), 11q deletion ( $p < 0.001$ ), TP53 mutation ( $p < 0.001$ ), and bulky disease  $\geq 10$ cm ( $p < 0.01$ ) (Figure ).

Therefore, the main factor to consider to establish a comparison between trial populations in terms of heterogeneity and transferability of the results between the contexts were cytogenetic abnormalities, as these were the key treatment-effect modifier that would not be transferable across non-randomised studies. Other factors of interest which may be prognostic and worth consideration for a heterogeneity assessment are age, Rai stage, performance status, baseline cytopenias, and  $\beta$ 2-microglobulin. Whilst number of prior treatments may be a consideration, this is clearly violated when comparing results across treatment lines and so is not considered further.

Considering the baseline characteristics of the trials presented in table 42, patients in ELEVATE-TN were slightly older than those in ELEVATE-RR but had a lower prevalence of other risk factors such as del(17p), del(11q), TP53 mutations, and bulky disease. The trials were similar in terms of performance status, disease stage, and levels of  $\beta$ 2-microglobulin.

FIGURE 18. FOREST PLOT OF SUBGROUP ANALYSIS FOR GRADE ≥3 TREATMENT-EMERGENT ADVERSE EVENTS FROM ELEVATE-RR



**TABLE 42. COMPARISON OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS BETWEEN ELEVATE-TN AND ELEVATE-RR**

Characteristic	ELEVATE-TN		ELEVATE-RR	
	Acalabrutinib + O (n = 179)	Acalabrutinib Monotherapy (n = 179)	Acalabrutinib Monotherapy (n = 268)	Ibrutinib Monotherapy (n = 265)
Age, median (range), years	70 (41-88)	70 (44-87)	66 (41-89)	65 (22-88)
≥75 years, n (%)	53 (29.6)	50 (27.9)	44 (16.4)	43 (16.2)
Male sex, n (%)	111 (62.0)	111 (62.0)	185 (69.0)	194 (73.2)
ECOG PS score, n (%)				
0 – 1	169 (94.4)	165 (92.2)	247 (92.2)	243 (91.7)
2	10 (5.6)	14 (7.8)	20 (7.5)	22 (8.3)
Bulky disease ≥5 cm, n (%)	46 (25.7)	68 (38.0)	128 (47.8)	136 (51.3)
β2-microglobulin >3.5mg/L, n (%)	132 (73.7)	140 (78.2)	207 (77.2)	214 (80.8)
Rai stage 3 or 4, n (%)	86 (48.0)	87 (48.6)	131 (48.9)	134 (50.6)
Cytopenias at baseline, n (%)	93 (52.0)	85 (47.5)	148 (55.2)	137 (51.7)
Cytogenetic abnormalities, n (%)				
del(17p)	17 (9.5)	16 (8.9)	121 (45.1)	120 (45.3)
del(11q)	31 (17.3)	31 (17.3)	167 (62.3)	175 (66.0)
Complex karyotype	29 (16.2)	31 (17.3)	124 (46.3)	125 (47.2)
TP53 mutated	21 (11.7)	19 (10.6)	100 (37.3)	112 (42.3)
IGHV unmutated	103 (57.5)	119 (66.5)	220 (82.1)	237 (89.4)

#### Treatment Exposure & Homogeneity of Safety Profile

The median follow-up of ELEVATE-RR as presented at ASCO in 2021 was 41 months. The primary analysis on ELEVATE-TN was conducted after 28 months, however a longer follow-up of 47 months was also presented at ASCO. Whilst the rate of adverse events has decreased with time, one cannot eliminate the possibility of bias in comparing a median duration of exposure to acalabrutinib monotherapy of 38.3 months in ELEVATE-RR compared to 27.7 or 45.7 months in ELEVATE-TN, depending on the data cut-off.

To compare trial results based on exposure to acalabrutinib, summary safety statistics from the two datacuts of ELEVATE-TN are presented alongside those for ELEVATE-RR in table 43. Given the poorer prognosis of patients in ELEVATE-RR, more patients discontinue treatment in a shorter time period (56% in 41 months vs. 31% in 47 months).

Despite this shorter exposure to treatment, the overall incidence of adverse events was higher in ELEVATE-RR, with more grade ≥3 TEAEs, more serious TEAEs, and more treatment-related TEAEs, though the proportion of patients experiencing any TEAE was similar between trials. The incidence of specified events of clinical interest were somewhat similar between the studies, except for grade ≥3 infections and secondary primary malignancies, which were more prevalent in ELEVATE-RR. With regards to common adverse events, the incidence of these were somewhat similar between trials, though grade ≥3 cytopenias were more common in ELEVATE-RR but this may be associated with the slightly higher prevalence of cytopenias at baseline in ELEVATE-RR.



TABLE 43 COMPARISON OF SAFETY OUTCOMES FOR PATIENTS TREATED WITH ACALABRUTINIB MONOTHERAPY IN ELEVATE-TN AND ELEVATE-RR

Outcome	ELEVATE-TN (n = 179)				ELEVATE-RR (n = 266)	
	28 month FU		47 month FU		41 month FU	
<b>Disposition</b>						
Duration of exposure (months), median	27.7		45.7		38.3	
Discontinued study treatment	36 (20.1)		55 (30.7)		141 (55.5)	
Discontinued due to adverse events	16 (8.9)		22 (12.3)		40 (14.9)	
<b>Summary of TEAEs</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>
TEAE	170 (95.0)	89 (49.7)	173 (96.6)	93 (51.9)	260 (97.7)	183 (68.8)
Serious TEAE	57 (31.8)	53 (29.6)	70 (39.1)	NR	143 (53.8)	126 (47.4)
Treatment-related TEAE	118 (65.9)	40 (22.3)	NR	NR	203 (76.3)	109 (41.0)
<b>Events of clinical interest</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>
Cardiac events <sup>a</sup>	25 (14.0)	9 (5.0)	34 (19.0)	15 (8.4)	64 (24.1)	23 (8.6)
Atrial fibrillation	7 (3.9)	0	11 (6.1)	2 (1.1)	25 (9.4)	13 (4.9)
Bleeding	70 (39.1)	3 (1.7)	75 (41.9)	5 (2.8)	101 (38.0)	10 (3.8)
Major bleeding <sup>b</sup>	3 (1.7)	3 (1.7)	7 (3.9)	5 (2.8)	12 (4.5)	10 (3.8)
Hypertension	8 (4.5)	4 (2.2)	13 (7.3)	5 (2.8)	25 (9.4)	11 (4.1)
Infections	117 (65.4)	25 (14.0)	132 (73.7)	29 (16.2)	208 (78.2)	82 (30.8)
Secondary primary malignancies Excluding non-melanoma skin cancer	15 (8.4) 5 (2.8)	2 (1.1) 2 (1.1)	24 (13.4) 11 (6.1)	5 (2.8) 4 (2.2)	50 (18.8) 24 (9.0)	23 (8.6) 16 (6.0)
<b>Most common AEs (≥25% in any study)</b>						
Diarrhoea	62 (34.6)		72 (40.2)		92 (34.6)	
Headache	66 (36.9)		68 (38.0)		92 (34.6)	
Cough	33 (18.4)		40 (22.3)		77 (28.9)	
Upper respiratory tract infection	33 (18.4)		46 (25.7)		71 (26.7)	
<b>Most common grade ≥3 AEs (≥5% in any study)</b>						
Neutropenia	17 (9.5)		20 (11.2)		52 (19.5)	
Anaemia	12 (6.7)		NR		31 (11.7)	
Pneumonia	4 (2.2)		NR		28 (10.5)	
Thrombocytopenia	5 (2.8)		NR		26 (9.8)	

Data are n (%) unless otherwise specified. TEAE, treatment-emergent adverse events. NR, not reported.

<sup>a</sup>Cardiac events could include atrial fibrillation, angina pectoris, palpitations, atrioventricular block complete, myocardial ischemia, tachycardia, bradycardia, cardiac failure, left ventricular failure, myocardial infarction, pericardial effusion, acute myocardial infarction, and supraventricular tachycardia.

<sup>b</sup>Defined as any serious or grade  $\geq 3$  hemorrhagic event, or any grade hemorrhagic event in the central nervous system.

## Conclusions of Feasibility Assessment

There appears to be some heterogeneity in the safety profile of ELEVATE-TN and ELEVATE-RR, which may be attributable to a different risk of experiencing adverse events between the trials associated with baseline characteristics. Patients with cytogenetic abnormalities typically have a poorer prognosis in CLL, and therefore more stringent monitoring of patients may lead to greater recording of treatment-emergent adverse events, or there may indeed be a biologic mechanism for this.

The difference in age between the two trials may be a prognostic factor in terms of the absolute incidence of adverse events, and the different proportion of patients with high risk features such as del(17p), del(11q) or TP53mut may modify the relative incidence of adverse events. Consequently, an analysis which matches samples based on baseline characteristics would be preferred in order to quantify differences in the adverse event profile when comparing acalabrutinib + obinutuzumab to ibrutinib monotherapy. However, as this comparison is only relevant for previously untreated CLL patients with del(17p)/TP53mut, this is a small subgroup of ELEVATE-TN and any matching algorithm would reduce the effective sample size even further to the extent that a reliable comparison could not be conducted. It is therefore AstraZeneca's recommendation that a formal quantitative comparison of safety between acalabrutinib + obinutuzumab and ibrutinib cannot be conducted in this population.

## Relative Safety Assessment

Results from the ITT population of ELEVATE-TN show that patients treatment with acalabrutinib + obinutuzumab had a slightly higher rate of experience an adverse event than patients treated with acalabrutinib monotherapy, though a greater proportion of these were grade  $\geq 3$  and these were also more likely to be related to treatment (table 43 and 44). The probability of experiencing a serious TEAE was also marginally higher with acalabrutinib + obinutuzumab.

Results from the head-to-head ELEVATE-RR show that acalabrutinib monotherapy is associated with a slightly more favourable safety profile compared to ibrutinib monotherapy. The incidence of grade  $\geq 3$  and serious adverse events was lower with acalabrutinib monotherapy compared with ibrutinib, as well as having fewer treatment related adverse events.

It can therefore be inferred that both acalabrutinib + obinutuzumab and ibrutinib monotherapy have a slightly inferior safety profile to acalabrutinib monotherapy. To what extent this slight inferiority is similar between the treatments and whether the safety profile is comparable between these treatments is unknown. Previous research has also shown that adding an anti-CD20 antibody to ibrutinib is associated were a greater frequency of adverse events [1]. Whether the risk of adding an anti-CD20 antibody to acalabrutinib outweighs the safety benefits observed with acalabrutinib over ibrutinib cannot be quantified from this assessment.

Looking at the specific differences between treatments in both of the trials, it can be seen that adding obinutuzumab to acalabrutinib increases the risk of specific adverse events such as neutropenia (31.5% vs. 10.6%), fatigue (28.1% vs. 18.4%), pyrexia (12.9% vs. 6.7%), infusion-related reactions (13.5% vs. 0%), arthralgia (21.9% vs. 15.6%), and dizziness (18.0% vs. 11.7%). In terms of severe (grade  $\geq 3$ ) adverse events, adding obinutuzumab to acalabrutinib increases the risk of neutropenia (29.8% vs. 9.5%) and thrombocytopenia (8.4% vs. 2.8%).

When comparing acalabrutinib monotherapy to ibrutinib, ibrutinib use is associated with an increased risk of diarrhoea (46.0% vs. 34.6%), arthralgia (22.8% vs. 15.8%), contusion (18.3% vs. 11.7%), atrial fibrillation (15.6% vs. 9.0%), hypertension (22.8% vs. 8.6%), urinary tract infections (13.7% vs. 8.3%), muscle spasms (13.3% vs. 6.0%) and dyspepsia (12.2% vs. 3.8%). Ibrutinib is also associated with an increased risk of adverse events of clinical interest for patients treated with BTKis, such as atrial fibrillation (16.0% vs. 9.4%), bleeding (51.3% vs. 38.0%), and hypertension (23.2% vs. 9.4%).

TABLE 44. SUMMARY OF SAFETY OUTCOMES FOR PATIENTS TREATED WITH ACALABRUTINIB + OBINUTUZUMAB IN ELEVATE-TN AND IBRUTINIB MONOTHERAPY ELEVATE-RR

Outcome	Acalabrutinib + Obinutuzumab (n = 178)				Ibrutinib (n = 266)	
	28 month FU		47 month FU		41 month FU	
<b>Disposition</b>						
Duration of exposure (months), median	27.7		46.6		35.5	
Discontinued study treatment	33 (18.4)		45 (25.1)		155 (58.5)	
Discontinued due to adverse events	18 (10.1)		23 (12.8)		59 (22.3)	
<b>Summary of TEAEs</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>
TEAE	171 (96.1)	125 (70.2)	176 (98.8)	132 (74.2)	256 (97.3)	197 (74.9)
Serious TEAE	69 (38.8)	58 (32.6)	85 (47.8)	NR	154 (58.6)	138 (52.5)
Treatment-related TEAE	144 (80.9)	86 (48.3)	NR	NR	223 (84.8)	121 (46.0)
<b>Events of clinical interest</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>	<b>All Grades</b>	<b>Grade ≥3</b>
Cardiac events <sup>a</sup>	25 (14.0)	8 (4.5)	37 (20.8)	14 (7.9)	79 (30.0)	25 (9.5)
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	1 (0.6)	42 (16.0)	10 (3.8)
Bleeding	76 (42.7)	3 (1.7)	84 (47.2)	5 (2.8)	135 (51.3)	12 (4.6)
Major bleeding <sup>b</sup>	5 (2.8)	3 (1.7)	7 (3.9)	5 (2.8)	14 (5.3)	12 (4.6)
Hypertension	13 (7.3)	5 (2.8)	14 (7.9)	6 (3.4)	61 (23.2)	24 (9.1)
Infections	123 (69.1)	37 (20.8)	134 (75.3)	42 (23.6)	214 (81.4)	79 (30.0)
Secondary primary malignancies Excluding non-melanoma skin cancer	19 (10.7) 10 (5.6)	7 (3.9) 6 (3.4)	28 (15.7) 15 (8.4)	13 (7.3) 10 (5.6)	36 (13.7) 20 (7.6)	15 (5.7) 14 (5.3)
<b>Most common AEs (≥25% in any study)</b>						
Neutropenia	56 (31.5)		60 (33.7)		65 (24.7)	
Diarrhoea	69 (38.8)		73 (41.0)		121 (46.0)	
Fatigue	50 (28.1)		50 (28.1)		44 (16.7)	
Headache	71 (39.9)		71 (39.9)		53 (20.2)	

Arthralgia	39 (21.9)	47 (26.4)	60 (22.8)
Cough	39 (21.9)	46 (25.8)	56 (21.3)
Most common grade ≥3 AEs (≥5% in any study)			
Neutropenia	53 (29.8)	55 (30.9)	60 (22.8)
Thrombocytopenia	15 (8.4)	NR	18 (6.4)
Anaemia	10 (5.6)	NR	34 (12.9)
Pneumonia	10 (5.6)	NR	23 (8.7)
Diarrhoea	8 (4.5)	9 (5.1)	13 (4.9)
Hypertension	5 (2.8)	NR	23 (8.7)

#### Conclusion indirect comparison ELEVATE-TN and ELEVATE-RR

The overall number of adverse events experienced with either acalabrutinib + obinutuzumab or ibrutinib may be comparable, with similar levels of severity in grading, but the specific adverse events underlying that number differ between treatments with different implications for an individual patient's safety. Therefore, one must consider a qualitative assessment of the relative safety and the implications of this on a per patient basis. Acalabrutinib monotherapy appears to be the preferential strategy in terms of safety over both alternatives, however the additional safety and tolerability burden of adding obinutuzumab to acalabrutinib must be weighed against the potential efficacy benefits it offers.

#### Overall conclusion

The 10% target set by Medicinraadet for Grade ≥3 AE cannot be met for the combination in either the ITT and high risk population.

## 8.4 Acalabrutinib + O vs. Ibrutinib 1<sup>st</sup> line with p17/ del53 HQoL

### 8.4.1 Relevant studies Acalabrutinib + O vs. Ibrutinib with p17/ del53 HQoL

HQoL is not available from the NMA or MAIC. HQoL is either not included in the studies for the comparator or is not calculated in a way that allows any narrative comparison with comparator

### 8.4.2 Results per study Acalabrutinib + O vs. Ibrutinib with p17/del53 HQoL

HQoL is either not included in the studies for comparator or is not calculated in a way that allows any narrative comparison with comparator.

### 8.4.3 Comparative analysis Acalabrutinib + O vs. Ibrutinib with p17/del53 HQoL

HQoL is either not included in the studies for comparator or is not calculated in a way that allows any narrative comparison with comparator.

## 9 Clinical question Acalabrutinib vs Ibrutinib R/R CLL.

### 9.1.1 Presentation of relevant studies. Acalabrutinib vs Ibrutinib R/R CLL PFS/PFS rate

For questions in R/R, Medicinraadet has stated in the protocol that comparator should be “Danish standard treatment”. As Calquence and Ibrutinib have the same mode of action, the same approved indications, treatment to progression and the fact that ibrutinib is market leader in R/R in Denmark, we consider Ibrutinib to be the most relevant comparator for this clinical question. This is also supported by the fact that a head-to-head study (ELEVATE RR) in high risk patients was published in July 2021.

So for this clinical question both direct and indirect treatment comparisons of acalabrutinib vs. ibrutinib in R/R CLL are available.

#### ELEVATE R/R (ACE-CL-006)

ELEVATE R/R (ACE-CL-006) is a Phase III, open-label study, evaluating the efficacy and safety of acalabrutinib vs. ibrutinib as monotherapy in 533 patients with high-risk relapsed/refractory chronic lymphocytic leukemia (R/R CLL) [5]. The trial is the first Phase III trial to evaluate two BTKis in patients with CLL. Primary endpoint included PFS. Secondary endpoints included incidence of atrial fibrillation, treatment-emergent grade  $\geq 3$  infections, Richter’s transformation (RT), and OS [5].

The trial is designed to address patients with high risk cytogenetics and health conditions. Key inclusions criteria included presence of  $\geq 1$  of either 17p del and/or 11q del [5].

After a median follow-up of 41 months, acalabrutinib was demonstrated to be non-inferior to ibrutinib in high-risk patients with previously treated CLL, with a median PFS as assessed by the independent review committee (IRC) of 38.4 months in both arms (HR 1.00; 95% CI 0.79 to 1.27; figure 18). Results were generally comparable across all evaluated subgroups, including age, race, sex, ECOG status, geographic region, presence of chromosomal abnormalities (17p deletion), number of prior therapies, tumor load and disease stage (Rai), as well as on investigator-assessed PFS (HR 0.90; 95% CI 0.69 to 1.16). Full results of subgroup analyses can be found in figure 19[5]

Figure 18. Kaplan-Meier plot of IRC-assessed progression-free survival in ELEVATE-RR

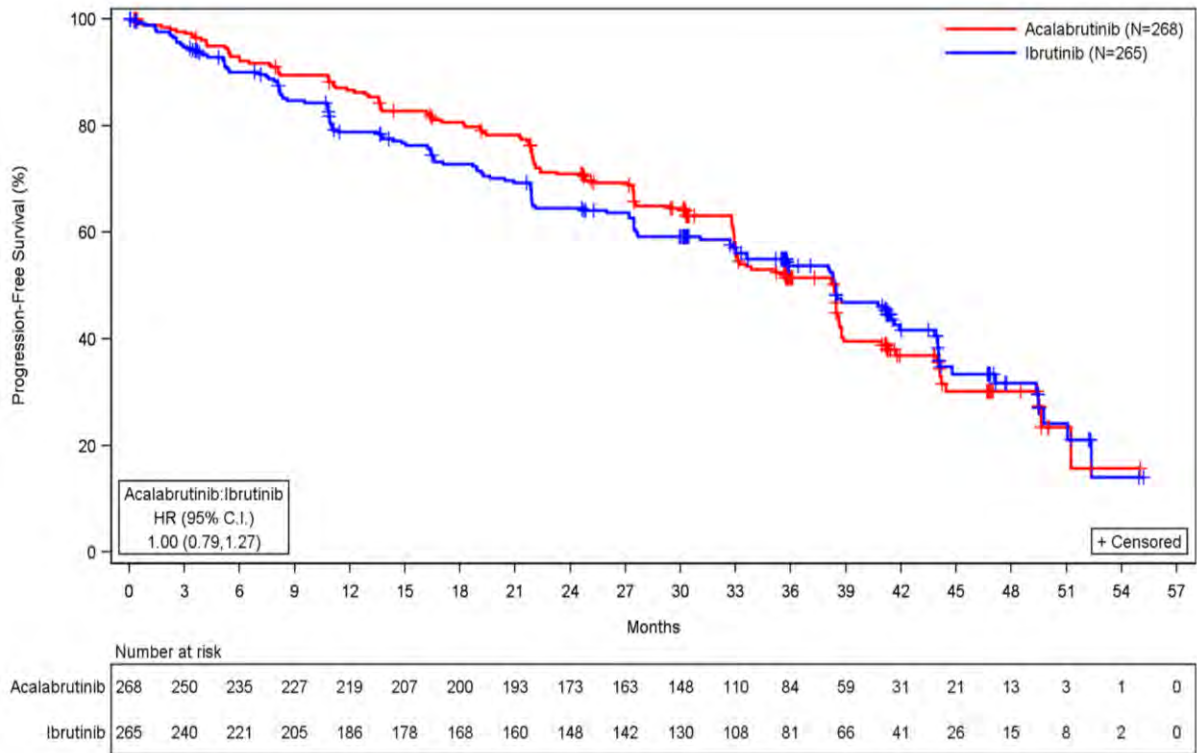
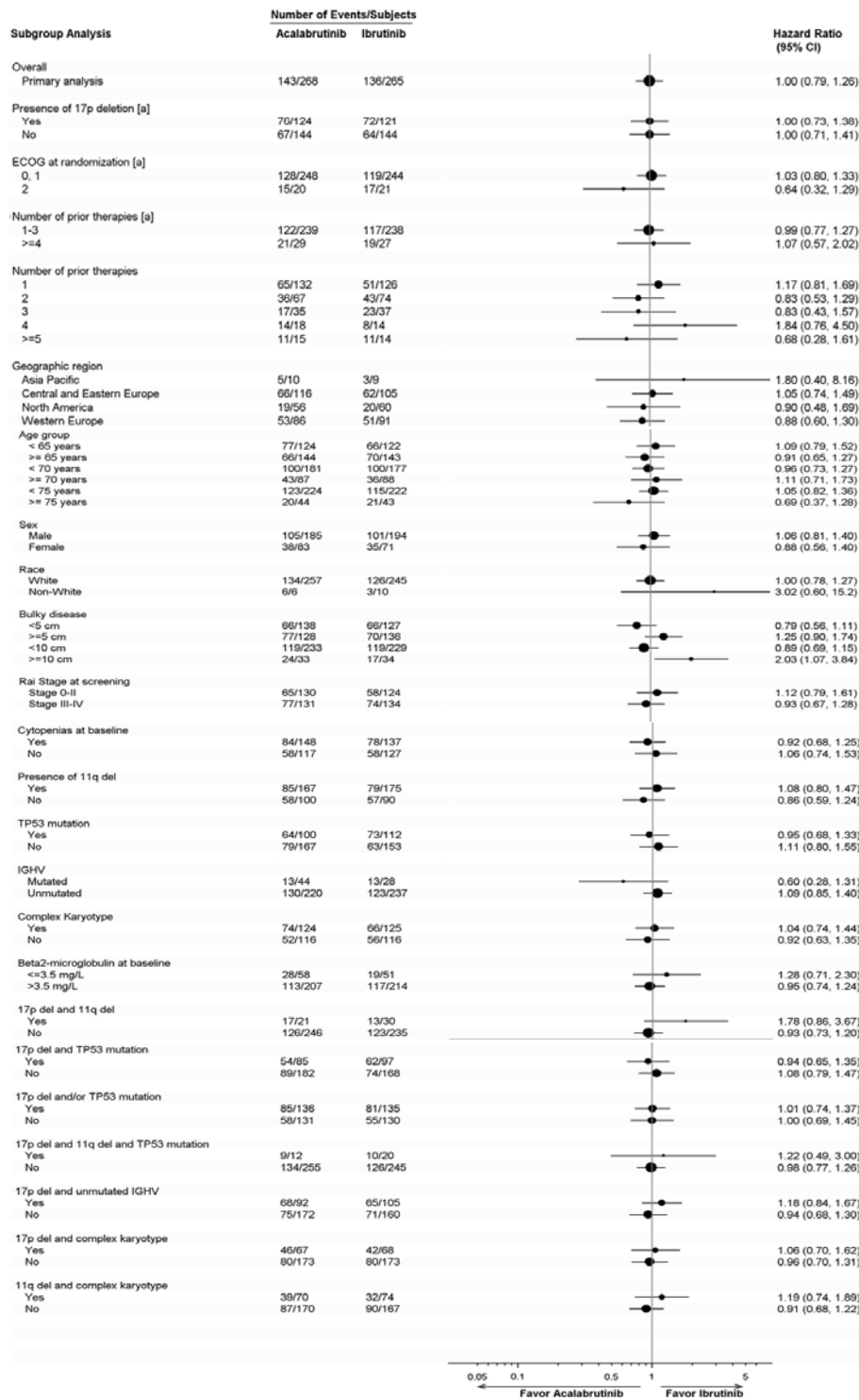


FIGURE 19. IRC-ASSESSED PROGRESSION-FREE SURVIVAL IN PRE-SPECIFIED SUBGROUPS IN ELEVATE-RR



## NMA and MAIC

There are several methods for Indirect treatment comparisons (ITCs), and for robustness AstraZeneca has conducted both NMAs and MAICs for comparing the efficacy versus ibrutinib. To support the ITCs a narrative comparison between ASCEND and RESONATE is also included.

NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator (acalabrutinib) versus another (ibrutinib) in the network (e.g., odds ratio, relative risk, or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers.

MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison.

## NMA

A systematic literature review (SLR) was conducted to identify randomized controlled trials previously conducted in R/R CLL up to 19<sup>th</sup> August, 2019. Following completion of the SLR, 56 studies for the R/R population and 19 with mixed line populations were identified. A network meta-analysis (NMA) was then conducted in R/R CLL patients. The scopes of the NMAs are reported in table 45.

Table 45. NMA R/R CLL [44]

Eligibility criteria	R/R population
Population	Relapsed/refractory adult patients
Intervention	■ Acalabrutinib monotherapy
Comparators	■ Ibrutinib ■ Venetoclax + rituximab ■ Idelalisib + rituximab ■ Idelalisib + ofatumumab ■ Bendamustine + rituximab ■ Idelalisib + bendamustine + rituximab ■ Ibrutinib + bendamustine + rituximab

Outcomes were PFS and OS and only RCT were included. Among the trials identified through the SLR, eight were finally considered as relevant for the NMAs in R/R patients. Table 46 provides an overview of these studies.



TABLE 46. TRIALS INCLUDED IN THE NMA COMPARING ACALABRUTINIB WITH SELECTED COMPARATORS IN PATIENTS WITH R/R CLL

Author, year	Population	Trial name	Sample size	Phase	Intervention	Comparator	Median follow-up
<b>Furman 2014</b>	R/R CLL	NR	220	3	IR	Rituximab + placebo	NR
<b>Jones 2017</b>	R/R CLL	NR	261	3	Idelalisib + ofatumumab	Ofatumumab	16.1 months
<b>Brown 2018</b>	R/R CLL	RESONATE	391	3	Ibrutinib	Ofatumumab	19 months
<b>Ghia 2020</b>	R/R CLL	ASCEND	310	3	Acalabrutinib	IR/BR <sup>a</sup>	~ 16 months
<b>Chanan-Khan 2016</b>	R/R CLL	HELIOS	578	3	Ibrutinib + BR	Placebo + BR	17 months
<b>Huang 2018</b>	R/R CLL	NR	160	3	Ibrutinib	Rituximab	NR
<b>Zelenetz 2017</b>	R/R CLL	NR	416	3	Idelalisib + BR	BR + placebo	14 months
<b>Seymour 2018</b> <b>Kater 2019</b>	R/R CLL	MURANO	389	3	Venetoclax + rituximab	BR	23.8 months (NMA) 36 months (MAIC)

[9, 19, 30, 32-37] Source: NMA report.[44]

Details of the individual study is highlighted in table 4 and section 4.2. Following the selection of the relevant trials to be included in the networks of interest, a feasibility assessment was conducted in each population comparing the baseline characteristics and study designs of the trials. The identification of potential prognostic factors and treatment effect modifiers was done through a review of the literature and survival analyses using directly the IPD from the ASCEND and ELEVATE trials. Bayesian NMAs were then conducted for both PFS and OS for the two populations in line with NICE guidelines [46] using the log hazard ratio (HR) for each trial as inputs. Both FE and RE models were conducted through WinBUGs and the preferred model was selected based on the Deviance Information Criterion (DIC) values.

In both population, trials were considered similar enough to be compared in the same network. However, some discrepancies were found and some assumptions had to be made in order to conduct the analyses.

In the R/R population, potential heterogeneity was identified regarding the distribution of Rai or Binet stages, the ECOG score (0-2 in ASCEND while 0-1 in all other trials), ethnicity (Huang 2018[36] included only Asian patients) and the 17p deletion status (patients excluded in HELIOS). In the two populations, some trials allowed patients to crossover to the alternative treatment arm after disease

progression. The methods to adjust for crossovers in the analyses were not consistent, leading to discrepancies in terms of the adjusted results reported.

As a result of the feasibility assessment, only patients with an ECOG score of 0 or 1 were kept in the ASCEND trial to maintain comparability with the inclusion criteria of comparator trials. In addition, some assumptions were necessary to make for the R/R population in order to obtain connected networks, while maintaining randomization. Firstly, an assumption was made that idelalisib+rituximab and bendamustine+rituximab were equivalent so that the pooled comparator arm from the ASCEND trial was used in the NMA. Secondly, it was assumed that idelalisib+ofatumumab and idelalisib+rituximab were equivalent for the base case. Sensitivity analyses were made using alternative assumptions to assess the impact. The ITT results were used in all trials and therefore analyses were not adjusted for crossover to maintain consistency.

## MAIC

Three of the studies identified in the SLR conducted for the NMA were also included in the MAIC: RESONATE, ASCEND and MURANO [11, 19, 33]. The MAIC approach used individual patient-level trial data from the acalabrutinib trial ASCEND, and adjusted the trial population to match average baseline characteristics reported for the comparator trials: RESONATE (ibrutinib) and MURANO (venetoclax + rituximab) [44]. Individual patients in the acalabrutinib arm of the ASCEND trial were assigned weights, such that weighted mean baseline characteristics in the ASCEND trial exactly matched those reported for patients in the comparator trials. Weights were obtained from a logistic regression model (estimated odds [relative propensity] of being in the comparator trials relative to ASCEND). These weights were used to calculate the ESS, and then to recalculate clinical outcomes from ASCEND. The choice of matching parameters was made in consultation with clinical opinion and the NICE guidance on MAIC, and was subject to external validation [45]. Table 47 shows the baseline characteristics used for matching.

TABLE 47. BASELINE CHARACTERISTICS MATCHED IN THE MAICs

Baseline characteristic	ASCEND vs RESONATE	ASCEND vs MURANO
Age	✓	✓
Sex	✓	✓
Presence of bulky disease ≥ 5 cm	✓	–
Presence of del(17p)	✓	✓
Presence of del(11q)	✓	–
TP53 status	–	✓
ECOG PS 0	✓	✓
ECOG PS 1	✓	✓
ECOG PS 2	–	✓
Beta-2 microglobulin > 3.5 mg/L	✓	–
Rai stage at screening (1 or 2, or 0–2)	✓	✓
Rai stage 3 or 4 at screening	✓	✓
One previous line of therapy	✓	✓
Two previous lines of therapy	✓	✓
≥ 3 previous lines of therapy	✓	✓
Complex karyotype	✓	–
IGHV mutation status	✓	✓
CrCl < 60 mL/min	✓	–

Source: R/R CLL MAIC report.[47]

### 9.1.2 Results per study Acalabrutinib vs. Ibrutinib R/R. PFS/PFS rate

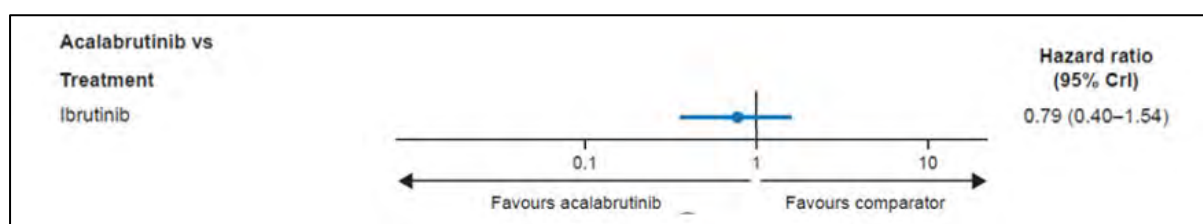
#### ELEVATE RR [5]

PFS as assessed by the independent review committee (IRC) was 38.4 months in both arms (HR 1.00; 95% CI 0.79 to 1.27). The conclusion from ELEVATE RR is that in the high risk CLL population [cytopenia at baseline, del(11q), TP53 mutation, unmutated IGHV, complex Karyotype, Beta2-microglobuline], the PFS hazard ratios of acalabrutinib versus ibrutinib were comparable. The same were observed when high risk factors were combined[5]. The conclusion is supported by the NMA and MAIC below:

#### NMA

Results from the NMA in the overall population suggest that acalabrutinib is at least as effective as ibrutinib in patients with R/R CLL, as summarized in figure 20 [44].

FIGURE 20. FOREST PLOT OF THE BASE-CASE NMA IN R/R CLL PFS



Source: NMA report [44]

Compared with ibrutinib monotherapy, the results of the NMA suggest that acalabrutinib monotherapy reduces the risk of disease progression or death by approximately 20%, but increases the risk of death (according to OS), although neither result was statistically significant [44].

The pooled investigator's choice arm in the NMA analysis corresponds to IR and BR, which were assumed to have equivalent efficacy. Thus, the pooled investigator's choice comparison provides data for the relative efficacy of acalabrutinib versus IR. Results for the NMA are in good agreement with those from the ASCEND trial (PFS – trial: HR: 0.31; 95% CI: 0.20–0.49; NMA: HR: 0.32; 95% CI: 0.20–0.51. OS – trial: HR: 0.84; 95% CI: 0.42–1.66; NMA: HR: 0.79; 95% CI: 0.39–1.65). Together, these suggest that acalabrutinib reduces the risk of disease progression or death by approximately 70% compared with IR, and may reduce the risk of death by approximately 20% [44].

## MAIC

Data is only available for the overall population. The results of the MAIC are consistent with those of the NMA and suggest that acalabrutinib monotherapy reduces the risk of disease progression or death by approximately 30% compared with ibrutinib monotherapy, although the difference was not statistically significant (table 48). Results for OS suggest a similar risk reduction for acalabrutinib versus ibrutinib. Both regimens were associated with a high ORR before and after matching (after matching – acalabrutinib: 92%; ibrutinib: 90%) [43].

We are not yet aware of if the MAIC in RR CLL will be published. We have marked results from the MAIC as confidential but will update Medicinrådet on the availability of the data

TABLE 48. SUMMARY OF RESULTS FROM THE MAIC FOR ACALABRUTINIB THERAPY COMPARED WITH OTHER RECOMMENDED REGIMENS FOR PATIENTS WITH R/R CLL

Column vs row Median HR (95% CI)	
Ibrutinib	

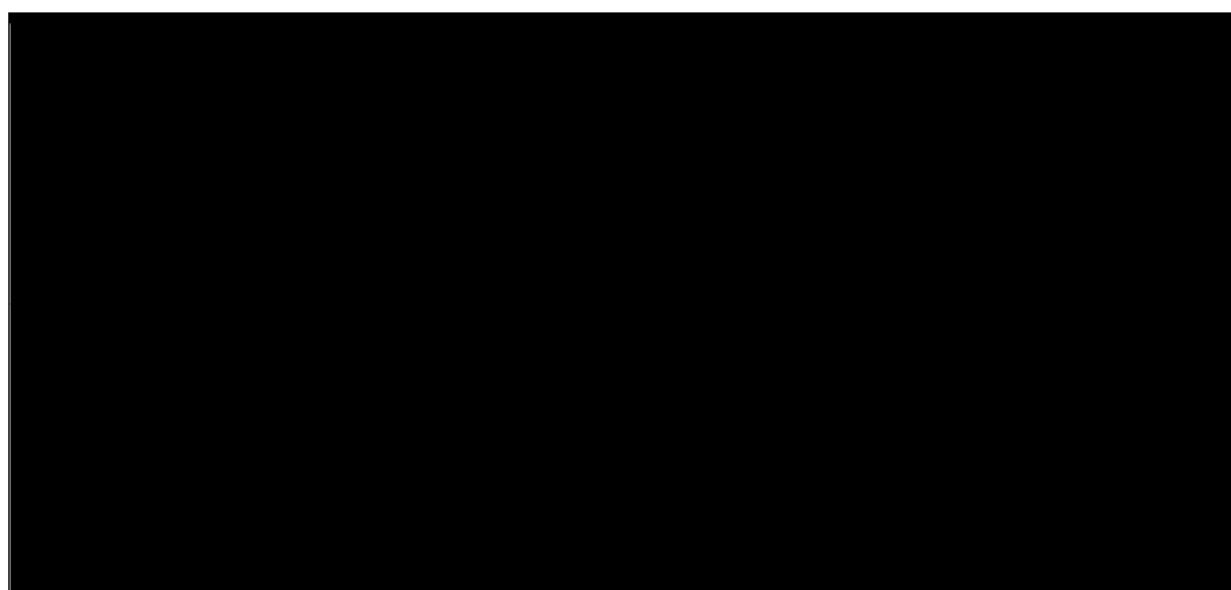
Source: R/R CLL MAIC report [43].

Both the NMA and the MAIC showed that acalabrutinib is associated with similar efficacy to ibrutinib, for PFS (see Table 49). The PFS curve from the MAIC analysis are shown in figure 21, respectively.

Table 49 . Efficacy PFS of acalabrutinib vs. Ibrutinib, HR and 95% CI

	NMA	MAIC (after matching)
PFS	0.79 (0.40; 1.54)	

Figure 21 . PFS before and after matching in MAIC of acalabrutinib vs. Ibrutinib



### 9.1.3 Comparative analysis. Acalabrutinib vs. ibrutinib R/R PFS/PFS rate

#### ELEVATE RR[5]

HR was = 1.00 (0.79 to 1.27) in the ELEVATE RR study and acalabrutinib cannot meet the target set by Medicinrådet for PFS and PFS rate.

#### NMA and MAIC

Both the NMA, MAIC and the narrative comparison showed that acalabrutinib is associated with similar level of efficacy to ibrutinib, for PFS. HRs are in favour of acalabrutinib but with wide intervals.

In the NMA a subgroup analysis for the population with a 17p deletion revealed that the HR for PFS for acalabrutinib versus ibrutinib was 0.24 (0.05, 1.25).

As the ITC's do not include PFS rate this was assessed in a naïve comparison

The RESONATE [14, 21] study was chosen as a comparator in the narrative analysis since patients included in this study are in agreement with the patient population that would receive ibrutinib according to Danish clinical practice (R/R). The study is also comparable to the ASCEND [9] study in terms of including R/R CLL patients, the median age in the studies are similar (67 versus 68 years in RESONATE vs ASCEND respectively), type of prior therapies are similar though median number of therapies are higher in the RESONATE (median of 3) compared to ASCEND (median of 1). Percentage of IGHV-mutated patients are similar between the studies, but 17p del patients are more frequent in the RESONATE study (18% versus 32%). Overall, we evaluate that the studies are comparable and also in line with the population that would receive Ibrutinib (R/R) according to Danish clinical practice though the patient population in the RESONATE study may represent a population with poorer prognosis than in the ELEVATE study due to higher number of del 17p patients (for details please see table A2 for each individual study).

- In the ASCEND trial (median follow up of 16,1 months) PFS was 83% and the estimated 12-month PFS was **88%** (95% CI, 81% to 92%) for acalabrutinib [9]. In the final analysis, at a median follow-up of 22.0 months, the 18-m PFS rate was 82% [10]. Acalabrutinib treatment also resulted in improved median PFS in all prespecified subgroup analyses, including patients with high-risk genomic features, such as del(17p) plus TP53 mutation.
- In the RESONATE study, the 12-month PFS was **90%** [18] and the extended follow-up reported a 3-year PFS rate of 74% [20]. In the final analysis from RESONATE [21] with median follow-up of 65.3 months (range, 0.3-71.6) in the ibrutinib arm the median PFS was 44.1 months and the 60 month landmark PFS rate was 40% (the 3-year PFS rate at a 44 months follow-up was 59%)[13]. The PFS benefit with ibrutinib was preserved in the genomic high-risk population with del(17p), TP53 mutation, del(11q), and/or unmutated IGHV status (median PFS 44.1 months).

Due to different follow up and maturity we cannot conclude based on the ITC's that PFS rate target set by Medicinrådet can be met.

## 9.2 Acalabrutinib vs. Ibrutinib R/R. OS/OS rate

### 9.2.1 Relevant studies. Acalabrutinib vs Ibrutinib R/R OS/OS rate

For this question results for OS/OS rate are available from the head-to-head trials ELEVATE-RR comparing acalabrutinib vs ibrutinib. Also as above we will also use OS indirect treatment comparisons of acalabrutinib vs. ibrutinib in R/R CLL.

Also a narrative comparison between ASCEND and RESONATE is included. See section 9.1.1 for further details about included studies.

### 9.2.2 Result per study Acalabrutinib vs Ibrutinib R/R OS/OS rate

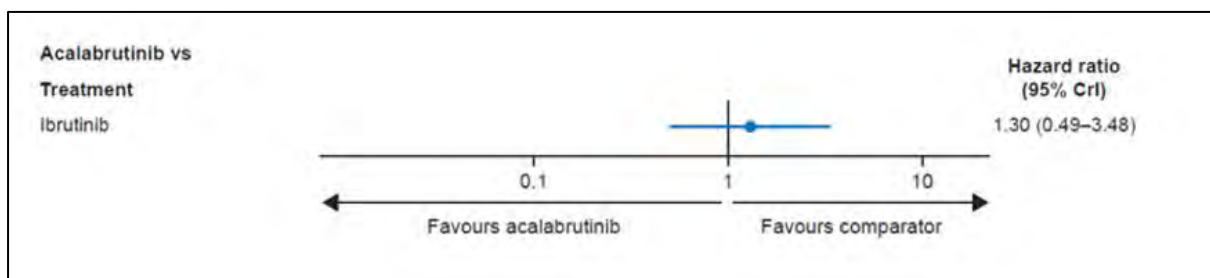
#### ELEVATE RR

Median OS was not reached in either arm with 36-month survival at 80.7% in the acalabrutinib arm and 75.8% in the ibrutinib arm (HR 0.82; 95% CI 0.59 to 1.15) [5].

#### NMA

The result from the NMA are shown below in figure 22.

FIGURE 22. FOREST PLOT OF THE BASE-CASE NMA IN R/R CLL VS IBRUTINIB PFS [44]



### 9.2.3 Comparative analysis Acalabrutinib vs. Ibrutinib R/R OS/OS rate

#### MAIC

The MAIC in the overall population showed [REDACTED] and the NMA HR= 1.30(0.49-3.48). OS data in the ASCEND trial are immature and we cannot draw conclusion from the ITCs.

The naïve comparison confirm that it is not possible to draw a conclusion due to lack of mature data in ASCEND.

- In the ELEVATE-RR study, at a median follow up of 41 months, median OS was not reached in either arm. 63 patients (23.5%) were dead in the acalabrutinib arm versus 73 patients (27.5%) in the ibrutinib arm with a HR of 0.82, 95% CI (0.59, 1.15) in favor of acalabrutinib, with a p value of 0.2517 [5].
- In the ASCEND trial OS at 12 months was 94% (95% CI, 89% to 97%) in the acalabrutinib-monotherapy arm. In the final analysis, at a median follow-up of 22.0 months, the 18-m OS rate was 88% [9]
- In the final analysis from RESONATE with up to 6 years of post-randomization follow-up, median OS was 67.7 months (95% CI: 61.0-NR) in the ibrutinib arm [21].

The target of 5 % difference from Medicinrådet cannot be met in the ELEVATE-RR and this is supported by the naïve and indirect comparison [43, 44].

## 9.3 Acalabrutinib vs. Ibrutinib R/R. AE grade $\geq 3$

### 9.3.1 Relevant studies Acalabrutinib vs. Ibrutinib R/R AE grade $\geq 3$

As comparator we have included ibrutinib. Both direct and indirect treatment comparisons of acalabrutinib vs. ibrutinib in R/R CLL are available.

Also a narrative comparison between ASCEND and RESONATE is included. See section 9.1.1 for further details about included studies.

In the ASCEND and ELEVATE-RR study, TEAEs were defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event that worsened in severity after the first dose of study drug, and before 30 days after the date of the last dose of study drug or the

date of first starting new anti-cancer therapy. Thus, all AEs and SAEs discussed in this section are TEAEs unless otherwise specified.

An SAE was defined as an AE that resulted in death, was life threatening, required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, resulted in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product, or was considered a significant medical event by the investigator based on their medical judgement.

### 9.3.2 Results per study Acalabrutinib vs. Ibrutinib R/R AE grade $\geq 3$

#### ELEVATE RR [5]

The safety and tolerability of acalabrutinib were consistent with the profile seen in the broader acalabrutinib clinical development program. Compared with ibrutinib, acalabrutinib was associated with a lower incidence of grade  $\geq 3$  AEs, as well as a lower incidence of serious adverse events (SAEs) (see table 36 for details). The follow up for acalabrutinib treatment was 38.3 months, compared with 35.5 months for ibrutinib.

The most commonly observed specific AEs in patients treated with acalabrutinib were diarrhoea, headache, cytopenias, and respiratory symptoms, similar to those observed in ASCEND. With respect to events of clinical interest, the incidence of cardiac events, hypertension, and haemorrhage were lower in patients treated with acalabrutinib, though the rates of major haemorrhage were comparable (table 50).

Table 50

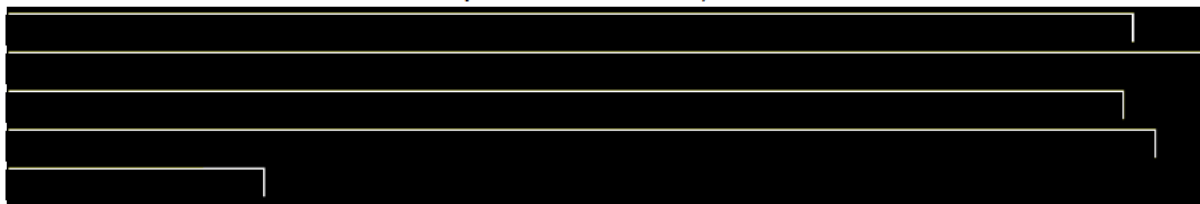
Event of Clinical Interest	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
		Grade $\geq 3$		Grade $\geq 3$
Cardiac Events		23 (8.6%)		25 (9.5%)
▪ Atrial Fibrillation / Flutter		13 (4.9%)		10 (3.8%)
▪ Ventricular Tachyarrhythmias		0		1 (0.4%)
Anaemia		31 (11.7%)		34 (12.9%)
Leukopenia		59 (22.2%)		63 (24.0%)
▪ Neutropenia		58 (21.8%)		63 (24.0%)
▪ Other Leukopenia		3 (1.1%)		1 (0.4%)
Thrombocytopenia		27 (10.2%)		18 (6.8%)
Haemorrhage		10 (3.8%)		12 (4.6%)
▪ Major Haemorrhage		10 (3.8%)		12 (4.6%)
Hepatotoxicity		5 (1.9%)		4 (1.5%)
Hypertension		11 (4.1%)		24 (9.1%)
Infections		82 (30.8%)		79 (30.0%)
Interstitial Lung Diseases / Pneumonitis		1 (0.4%)		2 (0.8%)
Second Primary Malignancies		23 (8.6%)		15 (5.7%)
▪ Excluding Non-Melanoma Skin Cancer		16 (6.0%)		14 (5.3%)
Tumour Lysis Syndrome		1 (0.4%)		1 (0.4%)



In addition, acalabrutinib was associated with a statistically significant reduction in the secondary endpoint of the incidence of atrial fibrillation, as well as a favourable adverse event profile in general. Therefore, acalabrutinib is likely to have comparable efficacy to ibrutinib in clinical practice, but has the potential to offer patient benefits in terms of safety. These safety findings were consistent with those observed in ASCEND (overall incidence of grade  $\geq 3$  AEs in patients treated with acalabrutinib were 69% and 75% for ASCEND and ELEVATE-RR, respectively).

#### MAIC

The MAIC also compared the incidences of AEs for acalabrutinib versus ibrutinib. Results for the comparison suggested that the incidence of AEs (any grade and grade 3/4 AEs) was lower with acalabrutinib than with ibrutinib. Compared with ibrutinib, acalabrutinib was associated with



#### Narrative comparison

- In ASCEND, Grade 3/4 AEs occurred in 45% of the patients receiving acalabrutinib monotherapy and serious adverse events occurred in 29% of patients treated with acalabrutinib monotherapy. AEs of clinical interest were atrial fibrillation (1%), hypertension (2%), major bleeding (2%), infections (15%) and second primary malignancies excluding non-melanoma skin cancer (3%). The most common grade 3/4 AEs in patients receiving acalabrutinib monotherapy were neutropenia (16%), anemia (12%), and pneumonia (5%) [9] [10].
- The prevalence of grade  $\geq 3$  AEs with ibrutinib in the RESONATE study decreased after the first year and remained stable thereafter, with rates of 62%, 48%, 46%, 46%, 48%, and 32% during years zero to one, one to two, two to three, three to four, four to five, and five to six, respectively [21]. Commonly reported grade  $\geq 3$  hematologic AEs included neutropenia (25%), thrombocytopenia (10%), and anemia (9%). Commonly reported grade  $\geq 3$  nonhematologic AEs included pneumonia (21%), hypertension (9%), urinary tract infection (7%), diarrhea (7%), and atrial fibrillation (6%). Grade  $\geq 3$  infection occurred in 45% and 10% experienced major hemorrhages. [21].

To further support the narrative comparisons in a qualitative manner, data from four studies listed below are also presented.

- A Danish multicenter retrospective study including 205 patients diagnosed with CLL or SLL and treated with Ibrutinib outside of clinical trials, were included [49].
- A systemic review and network meta-analysis including 3207 patients analyzing ibrutinib, ibrutinib plus anti-CD20 antibody, and acalabrutinib, with regards to safety [50]

- A retrospective single-center cohort study of 290 adult patients treated with acalabrutinib for a hematologic malignancy where major adverse cardiac events (MACE) was investigated, (4.) a pooled analysis of cardiovascular events from clinical trials evaluating acalabrutinib monotherapy in patients with CLL [51].

A pooled analysis of cardiovascular events from clinical trials evaluating acalabrutinib monotherapy in patients with CLL [52].

#### Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib

In a recently published Danish multicenter retrospective study including 205 patients diagnosed with CLL or SLL and treated with Ibrutinib outside of clinical trials prior to 2019, the median age was 73 years and 54.4% had mutated Tp53 or del 17p (19% treatment-naïve). The estimated overall survival at 12 months was 88.8% (95%CI: 84.3-93.3) and the estimated progression-free survival at 12 months was 86.3% (95% CI: 81.3-91.2%). No significant differences in OS or PFS was observed between treatment naive and R/R patients and no significant difference in OS or PFS was observed in patients with TP53 /del17p mutations and patients without.

With a median follow up of 21.4 months (IQR, 11.9-32.8), 48.8% patients had at least one grade  $\geq 3$  AE and 42.0% discontinued ibrutinib, hereof 54.7% due to AEs, a number that is higher in real world settings than seen in clinical trials. The three most common AEs leading to discontinuation in the study were atrial fibrillation, infections (39% of the patients were hospitalized with grade  $\geq 3$  infections.) and gastro intestinal AEs. Interestingly, no grade  $\geq 3$  atrial fibrillation was observed in the study [49]. Though similar data for acalabrutinib outside of clinical trials in Denmark does not exist at this point in time, the study does highlight a potential unmet need with regards to AEs of ibrutinib, the potential role of acalabrutinib in this regard is discussed in section 10.3.

#### Adverse Events in Clinical Trials of Ibrutinib and Acalabrutinib for B-Cell Lymphoproliferative Disorders: A Systematic Review and Network Meta-Analysis

In a recent systemic review and network meta-analysis including 27 prospective clinical trials, 12 multicenter single-arm, 9 multicenter randomized, 5 single center single-arm, and 1 single center randomized, data from 29 study arms including 3207 patients analyzing 3 groups - ibrutinib, ibrutinib plus anti-CD20 antibody, and acalabrutinib, the authors demonstrated there was a significant difference favoring acalabrutinib for grade 3 hypertension (OR 0.15, 95% 0.08-0.27)  $p < 0.0001$ , grade 3 atrial fibrillation (OR 0.04, 95% 0.01-0.25)  $p = 0.0009$ , and grade 3 infections (OR 0.62, 95% 0.46-0.85),  $p = 0.003$  [50].

#### Evaluation of the Incidence and Risk Factors Associated with Major Cardiovascular Events in Patients Receiving Acalabrutinib Therapy

In addition a recent retrospective single-center cohort study of 290 adult patients treated with acalabrutinib for a hematologic malignancy major adverse cardiac events (MACE) was investigated. MACE was defined as cardiac arrhythmias (including atrial and ventricular arrhythmias), myocardial infarction, stroke, heart failure, and CV death. The majority had CLL (89% with a median age of 64 years). 27% were previously treated with ibrutinib. 67% had a prior cardiac history, including 49% with baseline hypertension. MACE occurred in 6%, atrial fibrillation in 4% and newly diagnosed heart failure in 1.4% patients. Moreover, the authors report that the same incidences for ibrutinib have previously been reported to be 16%, 13% and 3.7% respectively. Of the patients who developed

MACE during acalabrutinib treatment, 7 (39%) died. Causes of death were related to infection, respiratory failure, or progression to hospice care. For survival outcomes, 79% of patients were expected to be alive at 3 years post acalabrutinib therapy, and 75% at 5 years. Among patients who experienced a MACE event, survival outcomes were worse ( $P = 0.046$ ), with 71% of patients expected to be alive at 3 years compared to 50% at 5 years. The authors concluded acalabrutinib was associated with a lower, but significant risk of MACE compared to ibrutinib and that the occurrence of these cardiac events appears to associate with worse survival outcomes [51].

#### Pooled Analysis of Cardiovascular Events from Clinical Trials Evaluating Acalabrutinib Monotherapy in Patients with Chronic Lymphocytic Leukemia (CLL).

Finally, in a pooled analysis of cardiovascular events from clinical trials evaluating acalabrutinib monotherapy in patients with CLL (ACE-CL-001 [NCT02029443]; ACE-CL-007 [ELEVATE-TN, NCT02475681]; ACE-CL-309 [ASCEND, NCT02970318]; 15-H-0016 [NCT02337829]), Brown et al [52] reported that 762 pts were included (treatment-naïve:  $n=352$  [46%]; relapsed/refractory:  $n=410$  [54%]; median age: 67 years [range: 32-89]). At a median exposure of 24.9 months, 4% had grade  $\geq 3$  cardiac AEs, 0.9% discontinued treatment due to cardiac AEs and among grade  $\geq 3$  cardiac AEs, 25% were reported during the first 6 months on treatment. Most patients with cardiac AEs had pre-existing risk factors that may have contributed to their development. The incidence of atrial fibrillation with acalabrutinib (4%) was comparable to that of the general CLL population (6.1%; Shanafelt TD, et al [53]).

#### 9.3.3 Comparative analysis Acalabrutinib vs. Ibrutinib R/R Grade $\geq 3$ AE and SAE

[REDACTED] and do not meet the target set by Medicinraadet. We conclude overall, also based on the individual AE differences, that acalabrutinib has a more acceptable safety profile than ibrutinib in R/R CLL. To support this we also did a naïve comparison.

In the section above we have mentioned other studies incl. the Danish RWE that have looked at the AE, SAEs and discontinuations of ibrutinib, but below focused on the ASCEND vs RESONATE study.

- In ASCEND, Grade 3/4 AEs occurred in 45% of the patients receiving acalabrutinib monotherapy and serious adverse events occurred in 29% of patients treated with acalabrutinib monotherapy. AEs of clinical interest were atrial fibrillation (1%), hypertension (2%) major bleeding (2%), infections (15%) and second primary malignancies excluding non-melanoma skin cancer (3%). The most common grade 3/4 AEs in patients receiving acalabrutinib monotherapy were neutropenia (16%), anemia (12%), and pneumonia (5%) [9] [10].
- The prevalence of grade  $\geq 3$  AEs with ibrutinib in the RESONATE study decreased after the first year and remained stable thereafter, with rates of 62%, 48%, 46%, 46%, 48%, and 32% during years zero to one, one to two, two to three, three to four, four to five, and five to six, respectively [21]. Overall, 57% of the patients in the ibrutinib group and 47% of the patients in the ofatumumab group had at least one adverse event of grade 3 or higher. Adverse events of

grade 3 or higher that occurred more frequently in the ibrutinib group than in the ofatumumab group included diarrhea (4% vs. 2%) and atrial fibrillation (3% vs. 0%) Commonly reported grade  $\geq 3$  hematologic AEs included neutropenia (25%), thrombocytopenia (10%), and anemia (9%). Commonly reported grade  $\geq 3$  nonhematologic AEs included pneumonia (21%), hypertension (9%), urinary tract infection (7%), diarrhea (7%), and atrial fibrillation (6%). Grade  $\geq 3$  infection occurred in 45% and 10% experienced major hemorrhages. [21].

In the ELEVATE-RR, head to head study, acalabrutinib, in addition to demonstrating a favourable adverse event profile in general, was associated with a statistically significant reduction in the secondary endpoint of the incidence of atrial fibrillation as well as grade  $\geq 3$  diarrhea and hypertension. Whereas grade  $\geq 3$  headache and fatigue occurred less frequently with ibrutinib[5]. Therefore, acalabrutinib is likely to have comparable efficacy to ibrutinib in clinical practice, but has the potential to offer patient benefits in terms of safety. These safety findings were consistent with those observed in ASCEND (overall incidence of grade  $\geq 3$  AEs in patients treated with acalabrutinib were 69% and 75% for ASCEND and ELEVATE-RR, respectively). The qualitative comparison in section 9.3.1 and the narrative comparisons further support a more favorable safety and cardiac adverse event profile with acalabrutinib.

## 9.4 Acalabrutinib vs Ibrutinib R/R. HQoL

### 9.4.1 Presentation of relevant studies Acalabrutinib vs. Ibrutinib R/R HQoL

The MAIC and NMA do not compare HQoL and we have not been able to do a narrative comparison vs ibrutinib studies. The result from the ASCEND study is listed below.

### 9.4.2 Result per study Acalabrutinib vs Ibrutinib R/R HQoL

#### ELEVATE-RR

The first publication did not report HQoL data.

#### ASCEND

Acalabrutinib demonstrated a numerical improvement in global health status (GHS)/health-related quality of life (HRQoL) of the EORTC QLQ-C30 scale in patients at weeks 24 and 48, compared with scores recorded at screening; these improvements were numerically slightly greater than with IR/BR. At baseline, mean (standard deviation [SD]) EORTC QLQ-C30 GHS scores were 59.3 (19.5) and 58.7 (19.3) in the acalabrutinib and IR/BR arms, respectively. Mean GHS scores increased in both study arms, with slightly larger improvements among patients treated with acalabrutinib compared with those receiving IR/BR (mean [SD]: week 24, +7.4 [1.8] vs +6.7 [1.8],  $p = 0.73$ ; week 48, +7.2 [1.9] vs +3.7 [2.1],  $p = 0.15$

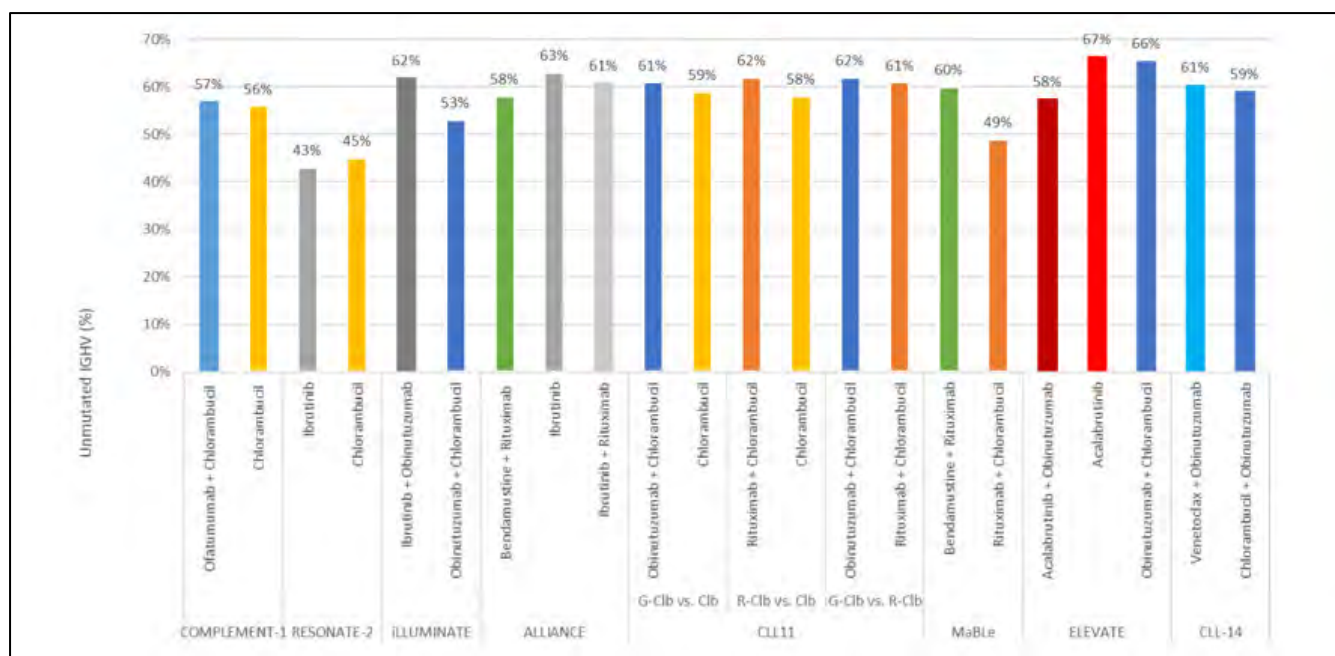
### 9.4.3 Comparative analysis Acalabrutinib vs. Ibrutinib R/R HQoL

The ASCEND study did not show significant improvement vs. IR/BR. The MAIC and NMA do not compare HQoL and we have not been able to do a narrative comparison vs ibrutinib studies and therefore acalabrutinib cannot meet the target set by Medicinrådet.

## 10 Other considerations

### 10.1 IGHV status

Figure 23. Proportion of patients with unmutated IgHV (first line population)



Source NMA report [44]

#### 1. line CLL

The data inputs used for the NMA and corresponding to the six studies included in the network are reported in table 51. In this subgroup, the sample sizes ranged from 82 patients in RESONATE-2 to 259 in CLL11 [44].

Table 51. PFS inputs for the first line population with IGHV mutation [6, 13, 15, 24, 29, 31]

Study name	Sample size	Comparisons	HR [CI]
ALLIANCE	142	Ibrutinib vs. BendamustineR	0.65 [0.26,1.66]
		IbrutinibR vs. BendamustineR	0.55 [0.21,1.46]
RESONATE-2	82	Ibrutinib vs. Chlorambucil	0.17 [0.07,0.41]
CLL11	259	ChlorambucilR vs. Chlorambucil	0.25 [0.15,0.41]
		Chlorambucil+Obinu vs. Chlorambucil	0.11 [0.06,0.22]
ILLUMINATE	91	Ibrutinib+Obinu vs. Chlorambucil+Obinu	0.30 [0.12,0.75]
ELEVATE	191	Acalabrutinib+Obinu vs. Chlorambucil+Obinu	0.20 [0.07,0.61]
		Acalabrutinib vs. Chlorambucil+Obinu	0.69 [0.31,1.56]
CLL14	159	Venetoclax+Obinu vs. Chlorambucil+Obinu	0.64 [0.28,1.46]

The results from the PFS NMA for the subgroup of patients with an IgHV mutation are reported in table 52. Both acalabrutinib mono and combination therapy were associated with lower risks of progression vs. chemo/chemoimmunotherapy.

Table 52. Results for the PFS network for the first line population with IGHV mutation.

Row vs. Column HR [CrI]	Benda+R	Ibr	Ibr+R	Chlor+R	Chlor	Chlor+Obinu	Ibr+Obinu	Acala+Obinu	Acala	Ven+Obinu
Benda+R	-	1.52 [0.60,3.89]	1.83 [0.69,4.85]	0.99 [0.26,4.01]	0.25 [0.07,0.92]	2.25 [0.55,9.67]	7.47 [1.40,41.68]	11.12 [1.87,69.97]	3.23 [0.64,17.18]	3.50 [0.69,18.67]
Ibr	0.66 [0.26,1.67]	-	1.20 [0.46,3.20]	0.66 [0.24,1.82]	0.16 [0.07,0.40]	1.48 [0.50,4.45]	4.93 [1.20,20.64]	7.37 [1.55,35.06]	2.14 [0.55,8.32]	2.32 [0.59,9.11]
Ibr+R	0.55 [0.21,1.45]	0.83 [0.31,2.19]	-	0.54 [0.14,2.21]	0.14 [0.04,0.51]	1.24 [0.29,5.35]	4.12 [0.75,23.29]	6.13 [0.98,38.54]	1.78 [0.34,9.34]	1.92 [0.36,10.35]
Chlor+R	1.01 [0.25,3.87]	1.53 [0.55,4.21]	1.84 [0.45,7.39]	-	0.25 [0.15,0.41]	2.27 [1.35,3.81]	7.55 [2.66,21.71]	11.23 [3.31,38.47]	3.26 [1.25,8.61]	3.53 [1.34,9.36]
Chlor	4.02 [1.08,14.13]	6.08 [2.52,14.81]	7.34 [1.97,27.19]	3.99 [2.42,6.59]	-	9.04 [4.73,17.24]	30.17 [9.87,92.82]	44.84 [12.50,164.68]	12.96 [4.67,36.96]	14.13 [4.96,40.17]
Chlor+Obinu	0.45 [0.10,1.82]	0.67 [0.22,2.01]	0.81 [0.19,3.45]	0.44 [0.26,0.74]	0.11 [0.06,0.21]	-	3.33 [1.34,8.36]	4.96 [1.63,15.03]	1.44 [0.64,3.25]	1.56 [0.68,3.57]
Ibr+Obinu	0.13 [0.02,0.72]	0.20 [0.05,0.83]	0.24 [0.04,1.34]	0.13 [0.05,0.38]	0.03 [0.01,0.10]	0.30 [0.12,0.75]	-	1.49 [0.35,6.30]	0.43 [0.13,1.46]	0.47 [0.14,1.60]
Acala+Obinu	0.09 [0.01,0.54]	0.14 [0.03,0.64]	0.16 [0.03,1.02]	0.09 [0.03,0.30]	0.02 [0.01,0.08]	0.20 [0.07,0.62]	0.67 [0.16,2.85]	-	0.29 [0.11,0.75]	0.31 [0.08,1.25]
Acala	0.31 [0.06,1.57]	0.47 [0.12,1.82]	0.56 [0.11,2.97]	0.31 [0.12,0.80]	0.08 [0.03,0.21]	0.69 [0.31,1.56]	2.31 [0.68,7.94]	3.43 [1.33,8.90]	-	1.08 [0.34,3.46]
Ven+Obinu	0.29 [0.05,1.45]	0.43 [0.11,1.70]	0.52 [0.10,2.74]	0.28 [0.11,0.75]	0.07 [0.02,0.20]	0.64 [0.28,1.46]	2.14 [0.63,7.33]	3.18 [0.80,12.68]	0.92 [0.29,2.97]	-

### Subgroup without an IgHV mutation

The last subgroup analysis conducted for PFS in first line was for patients without an IgHV mutation. The network for this subgroup is the same as for patients with the mutation. The corresponding data inputs are reported in table 53.

In terms of sample sizes, the trials ranged from 118 patients in RESONATE-2 to 450 patients in CLL11.

Table 53. PFS network for the first line population for patients without an IGHV mutation [6, 13, 15, 24, 29, 31, 44]

Study name	Sample size	Comparisons	HR [CI]
ALLIANCE	218	Ibrutinib vs. BendamustineR	0.31 [0.17,0.56]
		IbrutinibR vs. BendamustineR	0.49 [0.28,0.85]
RESONATE-2	118	Ibrutinib vs. Chlorambucil	0.08 [0.04,0.17]
CLL11	450	ChlorambucilR vs. Chlorambucil	0.54 [0.38,0.76]
		Chlorambucil+Obinu vs. Chlorambucil	0.23 [0.16,0.34]
ILLUMINATE	123	Ibrutinib+Obinu vs. Chlorambucil+Obinu	0.15 [0.08,0.27]
ELEVATE	338	Acalabrutinib+Obinu vs. Chlorambucil+Obinu	0.09 [0.05,0.16]
		Acalabrutinib vs. Chlorambucil+Obinu	0.12 [0.07,0.20]
CLL14	244	Venetoclax+Obinu vs. Chlorambucil+Obinu	0.22 [0.12,0.38]

The results from the PFS NMA in first line for patients with an unmutated IgHV are presented in table 54. Similar results to the base case and the subgroups related to the 17p deletion status were obtained. Acalabrutinib monotherapy and in combination were found to reduce the risk of progression vs. all comparators in this subgroup [44].

Table 54. PFS results for the first line population without IgHV mutation [44]

Row vs. Column HR [CrI]	Benda+R	Ibr	Ibr+R	Chlor+R	Chlor	Chlor+Obinu	Ibru+Obinu	Acala+Obinu	Acala	Ven+Obinu
Benda+R	-	3.24 [1.78,5.92]	2.04 [1.17,3.55]	0.48 [0.18,1.34]	0.26 [0.10,0.69]	1.14 [0.42,3.19]	7.57 [2.35,25.00]	13.18 [4.01,44.48]	9.87 [3.14,31.66]	5.16 [1.62,16.84]
Ibr	0.31 [0.17,0.56]	-	0.63 [0.36,1.12]	0.15 [0.07,0.34]	0.08 [0.04,0.17]	0.35 [0.15,0.81]	2.34 [0.84,6.53]	4.08 [1.44,11.61]	3.05 [1.13,8.19]	1.60 [0.58,4.37]
Ibr+R	0.49 [0.28,0.85]	1.59 [0.89,2.80]	-	0.24 [0.09,0.64]	0.13 [0.05,0.33]	0.56 [0.21,1.53]	3.71 [1.16,12.07]	6.48 [1.98,21.39]	4.85 [1.55,15.07]	2.53 [0.81,8.06]
Chlor+R	2.06 [0.74,5.57]	6.67 [2.95,15.04]	4.21 [1.56,11.26]	-	0.54 [0.38,0.76]	2.34 [1.71,3.22]	15.63 [7.92,31.20]	27.19 [13.42,55.74]	20.34 [10.85,38.36]	10.63 [5.52,20.56]
Chlor	3.82 [1.45,9.73]	12.34 [5.88,25.92]	7.80 [3.05,19.75]	1.85 [1.31,2.61]	-	4.34 [2.97,6.30]	28.93 [14.21,59.20]	50.30 [24.00,106.91]	37.56 [19.57,73.12]	19.70 [9.91,39.17]
Chlor+Obinu	0.88 [0.31,2.41]	2.84 [1.24,6.53]	1.80 [0.66,4.85]	0.43 [0.31,0.59]	0.23 [0.16,0.34]	-	6.67 [3.64,12.27]	11.61 [6.11,21.98]	8.69 [5.04,14.97]	4.53 [2.56,8.09]
Ibru+Obinu	0.13 [0.04,0.43]	0.43 [0.15,1.19]	0.27 [0.08,0.86]	0.06 [0.03,0.13]	0.03 [0.02,0.07]	0.15 [0.08,0.28]	-	1.74 [0.72,4.22]	1.30 [0.57,2.94]	0.68 [0.29,1.57]
Acala+Obinu	0.08 [0.02,0.25]	0.24 [0.09,0.69]	0.15 [0.05,0.51]	0.04 [0.02,0.07]	0.02 [0.01,0.04]	0.09 [0.05,0.16]	0.57 [0.24,1.40]	-	0.75 [0.41,1.37]	0.39 [0.17,0.93]
Acala	0.10 [0.03,0.32]	0.33 [0.12,0.88]	0.21 [0.07,0.65]	0.05 [0.03,0.09]	0.03 [0.01,0.05]	0.12 [0.07,0.20]	0.77 [0.34,1.75]	1.33 [0.73,2.45]	-	0.52 [0.23,1.16]
Ven+Obinu	0.19 [0.06,0.62]	0.63 [0.23,1.72]	0.40 [0.12,1.24]	0.09 [0.05,0.18]	0.05 [0.03,0.10]	0.22 [0.12,0.39]	1.47 [0.64,3.39]	2.56 [1.08,6.06]	1.91 [0.87,4.26]	-

**R/R**

Patients having an IgHV mutation R/R population were also investigated. The data inputs of this subgroup NMA are reported in the table 55 below. Sample sizes ranged in this subpopulation from 52 in ASCEND to 104 patients in Seymour 2017 [44].

Table 55. PFS data inputs for the subgroup NMA on patients with an IgHV mutation in the R/R population

Study name	Sample size	Treatments	HR [CI]
ASCEND [9]	52	Acalabrutinib vs. IC arm pooled	0.38 [0.13 ; 1.15]
Jones 2017 [35]	56	IdelaO vs. Ofatumumab	0.31 [0.13 ; 0.70]
RESONATE [18]	85	Ibrutinib vs. Ofatumumab	0.15 [0.07 ; 0.32]
Seymour 2018 [32]	104	VenetoclaxR vs. BendamustineR	0.11 [0.04 ; 0.31]
Zelenetz 2017 [37]	70	IdelaBR vs. BendamustineR	0.30 [0.13 ; 0.69]

Source: NMA report [44]

The data inputs reported above were used to obtain the results given in table 56 for this patient subgroup.

Table 56. PFS results for the subgroup NMA on patients with an IgHV mutation in the R/R population

Row vs. Column HR [95%CrI]	Acalabrutinib	Pool IC arm*	Ofatumumab	Ibrutinib	VenetoclaxR	Idelalisib + BR
Acalabrutinib	-	0.38 [0.13,1.11]	0.12 [0.03,0.46]	0.81 [0.17,3.83]	3.47 [0.79,15.39]	1.26 [0.33,4.99]
Pool IC arm*	2.65 [0.90,7.74]	-	0.31 [0.13,0.72]	2.14 [0.69,6.69]	9.13 [3.28,25.5]	3.33 [1.46,7.66]
Ofatumumab	8.50 [2.19,32.75]	3.23 [1.39,7.47]	-	6.90 [3.19,14.93]	29.44 [7.82,111.16]	10.80 [3.27,35.10]
Ibrutinib	1.23 [0.26,5.84]	0.47 [0.15,1.45]	0.14 [0.07,0.31]	-	4.27 [0.92,19.53]	1.56 [0.38,6.34]



VenetoclaxR	0.29 [0.06,1.27]	0.11 [0.04,0.31]	0.03 [0.01,0.13]	0.23 [0.05,1.09]	-	0.37 [0.10,1.39]
Idelalisib + BR	0.79 [0.20,3.05]	0.30 [0.13,0.68]	0.09 [0.03,0.31]	0.64 [0.16,2.64]	2.74 [0.72,10.14]	-

Source: NMA report.[44]

In comparison with the base case analysis in the ITT R/R population, similar conclusions could be drawn for the relative treatment effect of acalabrutinib versus comparators on PFS outcomes in the R/R patients with an IgHV mutation. However, there was a higher level of uncertainty associated with the results, as shown by the larger credibility intervals. Briefly, in the ITT R/R patients treated with acalabrutinib were more likely to have a PFS event compared to those receiving venetoclax in combination with rituximab (not significant), however acalabrutinib monotherapy was less likely to have a PFS event compared to those all other comparators (not significant).

#### Patients without an IgHV mutation

The last subgroup of interest was the group of patients without an IgHV mutation. The network used was the same as that in the base case analysis. The corresponding data inputs are reported in table 57. The subpopulation of patients without an IgHV mutation ranged from 181 patients in RESONATE to 346 patients in Zelenetz 2017 [37].

Table 57. PFS data inputs for the subgroup NMA on patients without an IgHV mutation in the R/R population

Study name	Sample size	Treatments	HR [CI]
ASCEND	213	Acalabrutinib vs. IC arm pooled	0.31 [0.19 ; 0.52]
Jones 2017	205	IdelaO vs. Ofatumumab	0.24 [0.16 ; 0.37]
RESONATE	181	Ibrutinib vs. Ofatumumab	0.08 [0.04 ; 0.13]
Seymour 2017	246	VenetoclaxR vs. BendamustineR	0.16 [0.10 ; 0.26]
Zelenetz 2017	346	IdelaBR vs. BendamustineR	0.36 [0.27 ; 0.48]

Source: NMA report [44].

The results presented in table 58 were obtained using these data inputs in the subpopulation of patients without an IgHV mutation and are detailed below.

Table 58. PFS results for the subgroup NMA on patients without an IgHV mutation in the R/R population

Row vs. Column HR [95%CrI]	Acalabrutinib	Pool IC arm*	Ofatumumab	Ibrutinib	VenetoclaxR	Idelalisib + BR
Acalabrutinib	-	0.31 [0.19,0.51]	0.07 [0.04,0.14]	0.99 [0.43,2.29]	1.94 [0.98,3.87]	0.86 [0.49,1.54]
Pool IC arm*	3.23 [1.96,5.30]	-	0.24 [0.16,0.37]	3.20 [1.62,6.33]	6.26 [3.88,10.11]	2.78 [2.09,3.70]
Ofatumumab	13.45 [7.04,25.71]	4.17 [2.74,6.33]	-	13.34 [7.78,22.90]	26.10 [13.82,49.25]	11.59 [6.96,19.26]
Ibrutinib	1.01 [0.44,2.35]	0.31 [0.16,0.62]	0.07 [0.04,0.13]	-	1.95 [0.85,4.48]	0.87 [0.41,1.81]
VenetoclaxR	0.52 [0.26,1.02]	0.16 [0.10,0.26]	0.04 [0.02,0.07]	0.51 [0.22,1.18]	-	0.44 [0.26,0.78]
Idelalisib + BR	1.16 [0.65,2.05]	0.36 [0.27,0.48]	0.09 [0.05,0.14]	1.15 [0.55,2.41]	2.25 [1.28,3.92]	-

Source: NMA report [44].

As above, there were no significant differences in the PFS efficacy of acalabrutinib versus ibrutinib or any of the combination therapies based on creditable intervals. This was also confirmed in the ELEVATE-RR study comparing acalabrutinib with ibrutinib where HR= 0.60 (0.28; 1.31) in the IGHV mutated population (small population) and HR=1.09 (0.85; 1.40) in the unmutated group.

IGHV Mutated	13/44	13/28		0.60 (0.28 to 1.31)
Unmutated	130/220	123/237		1.09 (0.85 to 1.40)

## Conclusion

In conclusion, acalabrutinib mono therapy and in combination with obinutuzimab demonstrates lower risk of progression compared to chemo/chemoimmunotherapy in both IgHV mutated and unmutated patients in first line. The same reduction in risk of progression was seen for acalabrutinib mono and combination therapy compared to venetoclax+obinutuzumab and ibrutinib mono or ibrutinib+obinutuzumab combination therapies in IGHV unmutated patients.

No significant differences in the risk of progression were observed for acalabrutinib monotherapy compared to venetoclax+obinutuzumab and ibrutinib mono or ibrutinib+obinutuzumab combination therapies in IGHV mutated and unmutated R/R patients.

## 10.2 Combination of Acalabrutinib with obinutuzimab vs acalabrutinib

When comparing acalabrutinib monotherapy and acalabrutinib plus obinutuzumab in a post hoc analysis, the HR was found to be 0.49 (95% CI: 0.26–0.95). In the NMA the HR was [95%CrI] = 0.53 [0.32,0.87]

Median OS was not reached in any treatment arm; however, the OS trend favours acalabrutinib plus obinutuzumab (HR: 0.47;  $p = 0.0577$ ) and acalabrutinib monotherapy (HR: 0.60;  $p = 0.1556$ ), compared with chlorambucil plus obinutuzumab

The proportion of patients with grade  $\geq 3$  TEAEs was lower with acalabrutinib monotherapy (49.7%) compared with acalabrutinib plus obinutuzumab (70.2%). SAEs, most of which were grade  $\geq 3$ , occurred in 38.8% and 31.8% patients who received acalabrutinib plus Obinutuzumab and acalabrutinib monotherapy respectively. See also indirect treatment of ELEVATE-TN and ELEVATE-RR in question 8.

## 10.3 Sequential treatment acalabrutinib and ibrutinib

### Acalabrutinib and C481-mutation

Acquired resistance to ibrutinib is mediated most commonly by C481S mutations in *BTK*, which decreases binding affinity and changes binding from irreversible to reversible. In a Ph 1/2 study at Ohio state University by Woyach et al, the authors investigated the mechanism of resistance to Acalabrutinib. Twelve months after the initiation of Acalabrutinib, patients were investigated every 3-6 cycles for *BTK* C481S or for

any *BTK* or *PLCG2* mutations. 105 patients were included in this analysis and 38 (36%) were treatment-naïve (TN), 50 (48%) were relapsed/refractory (RR), and 17 (16%) were previously intolerant of Ibrutinib. The median age was 62 (range 33-84) and median number of prior therapies was 1 (range 0-11). The patients were generally high-risk, with 66% having unmutated IGHV, 24% with del(11)(q22.3), 15% with del(17)(p13.1), and 28% with complex karyotype ( $\geq 3$  abnormalities). With a median follow-up of 47.5 months (range 37.7-58.5) 30% of pts (n=31) had discontinued therapy, 17 for progression of disease (CLL in 16 pts, Richter's transformation in 1), and 14 for other reasons. *BTK* C481 mutations were found in 11/16 patients investigated (69%; C481S in 10, C481R and C481Y in 1). The results demonstrated that CLL relapse on Acalabrutinib is mediated predominantly by mutations in *BTK* similar to Ibrutinib [54].

*BTK* mutation has also been detected in another phase II study in 6 out of 9 patients relapsing on Acalabrutinib [55]. Like ibrutinib, acalabrutinib binds covalently to *BTK* and is, therefore, not suitable for the treatment of patients with resistance-associated *BTK* hotspot mutation C481 [56].

#### Ibrutinib intolerant patients.

In CLL pts treated with the Bruton tyrosine kinase (*BTK*) inhibitor Ibrutinib, the most common reason for discontinuation was adverse events (AEs; 50%-63%) [57]. Similarly, in a Danish multicenter retrospective study including 205 patients diagnosed with CLL or SLL and treated with Ibrutinib outside of clinical trials, [49] (section 9.3.2 in this application), 48.8% patients had at least one grade  $\geq 3$  AE and 42.0% discontinued ibrutinib, hereof 54.7% due to AEs. In a Phase 2, multicenter, international, open-label study (ACE-CL-208; NCT02717611) patients with R/R CLL ( $\geq 1$  prior therapy) who discontinued ibrutinib due to Gr 3/4 AEs or persistent/recurrent Gr 2 AEs and had progressive disease (PD) after ibrutinib discontinuation were included. 60 patients were treated and 52/55 (95%) patients with available baseline samples were wild type for *BTK* and *PLCG2*, i.e intolerant to ibrutinib but not resistant. Median number of prior therapies was 2 (range 1-10). Median duration of prior ibrutinib therapy was 6 months (range <1-55); common AEs that led to ibrutinib discontinuation were atrial fibrillation/flutter (25%), diarrhea (12%), arthralgia (10%) and rash (12%). At a median follow-up of 19 months (range 1-31), 67% of pts remained on acalabrutinib; discontinuations were mostly due to PD (13%) and AEs (10%; pneumonia [n=2], diarrhea, headache, ascites, arthralgia, subdural hematoma [all n=1]). Orr was 77% and median PFS was not reached [58]. At an updated follow-up of a median of 23 months, 62% remained on Acalabrutinib, Serious AEs of any grade occurred in 21 patients (35%) and 12% discontinued due to AEs. Most AEs were Grade 1 and 2 and ORR was 72% [59]

Moreover, in a multicenter phase 1/2 study (ACE-CL-001) the efficacy and safety of acalabrutinib was evaluated in a cohort of patients with CLL or SLL who were intolerant to ibrutinib. The primary objective was to determine the safety of Acalabrutinib in patients intolerant to ibrutinib, as assessed by frequency, severity, and attribution of AEs. Among 33 treated patients (61% men; median age, 64 years; range, 50-82 years), median duration of prior ibrutinib treatment was 11.6 months (range, 1-62 months); median time from ibrutinib discontinuation to acalabrutinib start was 47 days (range, 3-331 days). 91% had ibrutinib as their most recent prior treatment. After a median of 19.0 months (range, 0.2-30.6 months), 23 patients remained on acalabrutinib; 10 had discontinued (progressive disease, n= 4; AEs, n =3). Of 61 ibrutinib-related AEs associated with intolerance, 72% did not recur

and 13% recurred at a lower grade with Acalabrutinib. Overall response rate was 76%. Among 25 responders, median duration of response was not reached. Median progression-free survival (PFS) was not reached and 1-year PFS was 83.4% (95% confidence interval, 64.5%-92.7%) [55, 60].

In these studies, Acalabrutinib was well tolerated with a high response rate in patients who were previously intolerant to ibrutinib.

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## 12 Appendices

### 12.1 Literature search

See separate document for details about included and excluded references.

### 12.2 Main characteristics of included studies

Table A2 Main study characteristics ELEVATE-TN

Table A2 Main study characteristics ELEVATE-TN	
<b>Trial name</b>	ELEVATE-TN
<b>NCT number</b>	NCT02475681.
<b>Objective</b>	The aim of the study was to compare the efficacy and safety of acalabrutinib-obinutuzumab or acalabrutinib monotherapy with obinutuzumab-chlorambucil to ascertain if acalabrutinib with or without obinutuzumab had a therapeutic advantage over chemoimmunotherapy in patients with untreated chronic lymphocytic leukaemia.
<b>Publications – title, author, journal, year</b>	Sharman JP, Egyed M, Jurczak W et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet 2020;395:1278-1291. [6]

**Table A2 Main study characteristics ELEVATE-TN**

<b>Study type and design</b>	<p>ELEVATE-TN is a phase 3, randomised, multicentre, open-label study. Eligible patients had untreated chronic lymphocytic leukaemia and were aged 65 years or older, or older than 18 years with co-morbidities (creatinine clearance of 30–69 mL/min or CIRS &gt;6).</p> <p>Patients were randomly assigned (1:1:1) to receive acalabrutinib and obinutuzumab (arm B), acalabrutinib monotherapy (arm C), or obinutuzumab and chlorambucil (arm A). Patients were stratified based on the presence or absence of del 17p/TP53, ECOG PS score (0–1 vs 2), and geographic region. Patients and investigators were not masked to treatment. A masked independent review committee (IRC) assessed progression and response data. Treatments were administered in 28-day cycles.</p>
<b>Follow-up time</b>	<p>One interim analysis was planned when approximately 111 IRC-assessed progression-free survival events had occurred (ie, 67% of the planned events for the final analysis) or when 24 months had elapsed since the last patient was randomly assigned (timed analysis). Data-cutoff for the interim analysis was on Feb 8, 2019 based on timed analysis after 24 months and the primary endpoint was met. Median follow-up was of 28.3 months.</p>

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p><b><u>Inclusion Criteria:</u></b></p> <ul style="list-style-type: none"> <li>• Men and women: <math>\geq 65</math> years of age OR <math>&gt; 18</math> and <math>&lt; 65</math> years of age, provided that they meet at least one of the following criteria:             <ol style="list-style-type: none"> <li>1. Creatinine clearance 30 to 69 mL/min.</li> <li>2. A score higher than 6 on the Cumulative Illness Rating Scale-Geriatric.</li> </ol> </li> <li>• ECOG performance status of 0, 1, or 2.</li> <li>• Diagnosis of CD20+ CLL.</li> <li>• Active disease meeting <math>\geq 1</math> of the following IWCLL 2008 criteria for requiring treatment.</li> <li>• Meet the following laboratory parameters:             <ul style="list-style-type: none"> <li>✓ ANC <math>\geq 750</math> cells/<math>\mu</math>L, or <math>\geq 500</math> cells/<math>\mu</math>L in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.</li> <li>✓ Platelet count <math>\geq 50,000</math> cells/<math>\mu</math>L, or <math>\geq 30,000</math> cells/<math>\mu</math>L in subjects with documented bone marrow involvement, and without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded.</li> <li>✓ Serum AST and ALT/SGPT <math>\leq 3.0</math> x ULN.</li> <li>✓ Total bilirubin <math>\leq 1.5</math> x ULN.</li> <li>✓ Estimated creatinine clearance <math>\geq 30</math> mL/min.</li> </ul> </li> </ul> <p><b><u>Exclusion Criteria:</u></b></p> <ul style="list-style-type: none"> <li>• Any prior systemic treatment for CLL.</li> <li>• Known CNS lymphoma or leukemia.</li> <li>• Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.</li> <li>• Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.</li> <li>• Major surgery within 4 weeks before first dose of study drug.</li> <li>• Prior malignancy, except for adequately treated lentigo maligna melanoma, non-melanomatous skin cancer, in situ cervical carcinoma, or other malignancy treated with no evidence of active disease <math>&gt; 3</math> years before Screening and at low risk for recurrence.</li> <li>• Significant cardiovascular disease within 6 months of screening.</li> <li>• Known history of infection with HIV.</li> <li>• History of stroke or intracranial hemorrhage within 6 months before randomization.</li> <li>• Known history of a bleeding diathesis.</li> </ul>
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**Table A2 Main study characteristics ELEVATE-TN**

	Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days of first dose of study drug.
<b>Intervention</b>	<p>Arm (C) Acalabrutinib monotherapy:</p> <ul style="list-style-type: none"> <li>• Oral 100 mg twice a day until progression or unacceptable toxicity .</li> <li>• 179 received treatment and were included in the efficacy analysis</li> </ul> <p>Arm (B) Obinituzumab-Acalabrutinib:</p> <ul style="list-style-type: none"> <li>• Intravenous obinituzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1000 mg), and 15 (1000 mg) of cycle 2 and on day 1 (1000 mg) of cycles 3–7. To reduce infusion-related reactions, acalabrutinib was given for one cycle before obinituzumab.</li> <li>• 179 received treatment and were included in the efficacy analysis</li> </ul> <p>Arm (A) Obinituzumab-Chlorambucil:</p> <ul style="list-style-type: none"> <li>• Intravenous obinituzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1000 mg) and 15 (1000 mg) of cycle 1 and on day 1 (1000 mg) of cycles 2–6. Oral chlorambucil was given (0.5 mg/kg) on days 1 and 15 of each cycle.</li> <li>• 177 received treatment and were included in the efficacy analysis</li> </ul>

**Table A2 Main study characteristics ELEVATE-TN**
**Baseline characteristics**

	Number (%) of patients			Total (n = 574)
	Arm A: acalabrutinib + obinutichinib (n = 179)	Arm C: acalabrutinib (n = 179)	Arm D: chlorambucil + obinutichinib (n = 216)	
Age, years				
Mean (SD)	70.2 (8.0)	69.4 (7.9)	70.4 (7.9)	70.3 (7.9)
Median (range)	70 (41.0-88.0)	69 (40.0-87.0)	71 (40.0-91.0)	70 (41.0-91.0)
≥ 65	149 (83.2)	153 (84.9)	153 (84.4)	455 (79.3)
≥ 75	53 (29.6)	55 (31.0)	52 (29.4)	158 (27.5)
Sex (male)	113 (63.1)	119 (66.5)	108 (59.7)	340 (59.2)
Region				
North America	64 (35.8)	70 (39.1)	61 (34.7)	195 (34.1)
South America	5 (2.8)	8 (4.5)	7 (4.0)	20 (3.5)
Western Europe	20 (11.4)	22 (12.3)	52 (29.4)	142 (24.8)
Central and Eastern Europe	48 (26.8)	46 (25.7)	40 (22.7)	134 (23.3)
Australia, New Zealand	14 (7.8)	13 (7.3)	17 (9.4)	44 (7.7)
Baseline characteristics				
ECOG Performance Status				
0-1	167 (93.4)	165 (92.2)	167 (94.4)	500 (87.0)
2	12 (6.6)	14 (7.8)	12 (6.4)	36 (6.3)
Time from diagnosis to randomization, months				
Mean (SD)	47.3 (13.8)	42.3 (10.3)	46.3 (10.7)	45.3 (10.6)
Median (range)	30.3 (0.0-284.3)	26.4 (0.0-240.0)	30.7 (0.0-240.0)	27.4 (0.0-280.0)
Walter disease (≥ 3 years)	46 (25.7)	48 (26.8)	53 (29.6)	147 (25.8)
Relapse				
0	1 (0.5)	0	1 (0.4)	4 (0.7)
1	54 (30.2)	48 (26.8)	50 (28.2)	152 (26.4)
2	38 (21.2)	44 (24.6)	45 (25.5)	127 (22.1)
3	44 (24.6)	51 (28.5)	40 (22.7)	135 (23.5)
4	44 (24.6)	51 (28.5)	40 (22.7)	135 (23.5)
5	58 (32.2)	47 (26.3)	58 (32.6)	163 (28.4)
None / <i>aspartate</i> ≤ 0.5 mg/L	132 (73.7)	140 (78.2)	132 (74.4)	404 (70.3)
Cytopenia	83 (46.4)	85 (47.5)	71 (40.3)	239 (41.7)
Constitutional symptoms	36 (20.1)	39 (21.8)	39 (21.7)	114 (19.9)
Genetic markers				
del(17)	17 (9.5)	18 (10.1)	19 (10.7)	49 (8.5)
del(12)	11 (6.2)	11 (6.2)	11 (6.2)	33 (5.8)
TP53 mutation	21 (11.7)	18 (10.1)	21 (11.9)	60 (10.5)
IGHV				
Unmutated	79 (44.1)	88 (49.1)	79 (44.3)	246 (42.8)
Mutated	100 (55.9)	91 (50.9)	137 (75.7)	328 (57.2)
Undetermined	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.0)
del(17) or TP53 mutation	25 (14.0)	25 (13.9)	25 (13.6)	75 (13.0)
del(17), TP53 mutation, del(12) or unmutated IGHV	117 (65.4)	129 (71.5)	129 (71.6)	375 (65.3)

**Table A2 Main study characteristics ELEVATE-TN**

<b>Primary and secondary endpoints</b>	<p><b>Primary endpoint:</b></p> <ul style="list-style-type: none"> <li>• IRC-assessed progression-free survival, by use of iwCLL 2008 criteria, or death. Comparison of progression-free survival between arm B and arm A was the primary endpoint.</li> </ul> <p><b>Secondary endpoints:</b></p> <ul style="list-style-type: none"> <li>• IRC-assessed progression-free survival between arm C and arm A</li> <li>• IRC-assessed objective response rate (ORR) in Arm A versus Arm B and Arm A versus Arm C (the proportion of patients with complete response, complete response with incomplete bone marrow recovery, nodular partial response, or partial response)</li> <li>• Overall survival in Arm A versus Arm B and Arm A versus Arm C (defined as time from random assignment until death due to any cause)</li> <li>• Time to next treatment (TTNT) in Arm A versus Arm B and Arm A versus Arm C</li> </ul> <p>Safety was assessed by reported and observed AEs, laboratory measurements, and clinical evaluation across the treatment- emergent period. AEs were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.</p>
<b>Method of analysis</b>	<i>Se below</i>
<b>Subgroup analyses</b>	<ul style="list-style-type: none"> <li>• The effect of acalabrutinib plus obinutuzumab and acalabrutinib monotherapy (vs. chlorambucil plus obinutuzumab) on IRC-assessed PFS was investigated in predefined subgroups.</li> <li>• A post hoc analysis compared PFS between acalabrutinib plus obinutuzumab and acalabrutinib monotherapy</li> </ul>



Table A2 Main study characteristics ASCEND

Table A2 Main study characteristics ASCEND	
<b>Trial name</b>	ASCEND
<b>NCT number</b>	NCT02970318
<b>Objective</b>	The aim of phase III ASCEND study, was to compare the efficacy and safety of acalabrutinib monotherapy versus investigator's choice (Idelalisib-Rituximab or Bendamustine-Rituximab) ([I-R] or [B-R]) in patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (R/R CLL)
<b>Publications – title, author, journal, year</b>	Ghia P, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. J Clin Oncol. May. 2020 [9]
<b>Study type and design</b>	ASCEND is a phase III, randomized, multicenter, open-label study. Eligible patients, aged >18 years with R/R CLL were randomly assigned 1:1 centrally and stratified by del(17p) status, Eastern Cooperative Oncology Group performance status score (0-1 v 2), and lines of prior therapy received (1-3 v ≥ 4). Patients received acalabrutinib monotherapy or investigator's choice ([I-R] or [B-R]).
<b>Follow-up time</b>	One prespecified interim analysis was planned when approximately 79 IRC assessed PFS events (ie, 67% of the planned events for the final analysis) had occurred. On May 1, 2019, the independent data monitoring committee reviewed the interim analysis and confirmed the prespecified statistical boundary for early efficacy was crossed. Median follow-up is 16.1 months

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Men and women <math>\geq 18</math> years of age.</li> <li>• ECOG performance status of 0 to 2.</li> <li>• Received <math>\geq 1</math> prior systemic therapies for CLL.</li> <li>• Diagnosis of CLL - CD-20 positive, and meeting published criteria (Hallek, 2008).</li> <li>• Active disease meeting <math>\geq 1</math> of the IWCLL 2008 criteria for requiring treatment.</li>   <li>• Meet the following laboratory parameters: <ul style="list-style-type: none"> <li>✓ ANC <math>\geq 750</math> cells/<math>\mu</math>L or <math>\geq 500</math> cells/<math>\mu</math>L in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.</li> <li>✓ Platelet count <math>\geq 50,000</math> cells/<math>\mu</math>L or <math>\geq 30,000</math> cells/<math>\mu</math>L in subjects with documented bone marrow involvement, and without transfusion support 7 days before assessment</li> <li>✓ AST and ALT <math>\leq 2.0</math> x upper limit of normal</li> <li>✓ Total bilirubin <math>\leq 1.5</math> x ULN</li> <li>✓ Estimated creatinine clearance of <math>\geq 30</math> mL/min</li> </ul> </li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Known polymphocytic leukemia or history of, or currently suspected, Richter's syndrome. Known CNS lymphoma or leukemia.</li> <li>• Prior exposure to a BCL-2 inhibitor or B-cell receptor inhibitor.</li> <li>• Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura.</li> <li>• Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.</li> <li>• Prior radio- or toxin-conjugated antibody therapy.</li> <li>• Major surgery within 30 days of first dose of study drug.</li> <li>• Prior malignancy, except for adequately treated lentigo maligna melanoma, non-melanomatous skin cancer, carcinoma in situ or other malignancy treated with no evidence of active disease <math>&gt; 2</math> years before Screening and at low risk for recurrence.</li> <li>• Significant cardiovascular disease within 6 months of screening.</li> <li>• Known history of infection with HIV, or any uncontrolled active systemic infection.</li> <li>• Active CMV infection.</li> <li>• Serologic status reflecting active hepatitis B or C infection.</li> <li>• History of or ongoing drug-induced pneumonitis.</li> <li>• Malabsorption syndrome, or other condition that would impair absorption of oral study medication.</li> </ul>
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**Table A2 Main study characteristics ASCEND**

	<ul style="list-style-type: none"> <li>• Received a live virus vaccination within 28 days of first dose of study drug.</li> <li>• History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.</li> <li>• History of bleeding diathesis.</li> <li>• Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days of first dose of study drug</li> <li>• Requires treatment with a strong CYP3A inhibitor/inducer.</li> </ul>
<b>Intervention</b>	<p>Acalabrutinib (100 mg twice daily) was administered orally until progressive disease (PD) or unacceptable toxicity occurred</p> <p>Idelalisib (150 mg twice daily) was administered orally until PD or unacceptable toxicity in combination with rituximab (375 mg/m<sup>2</sup> intravenously [IV] on day 1 of the first cycle, followed by 500 mg/m<sup>2</sup> IV every 2 weeks for four doses and then every 4 weeks for three doses for a total of eight infusions). 119 patients were assigned.</p> <p>Bendamustine was administered at 70 mg/m<sup>2</sup> IV on days 1 and 2 of each 28-day cycle in combination with rituximab (375 mg/m<sup>2</sup> IV on day 1 of the first cycle and 500 mg/m<sup>2</sup> IV thereafter on day 1 of cycles 2 through 6). 36 patients were assigned.</p>

**Baseline characteristics**

	Number (%) of patients		
	Arm A: acalabrutinib (n = 155)	Arm B: IR or BR (n = 155)	Total (n = 310)
<b>Age, years</b>			
Mean (SD)	66.9 (9.9)	66.7 (9.8)	66.8 (9.7)
Median (range)	68 (32–89)	67 (34–90)	67 (32–90)
≥ 65	97 (62.6)	98 (63.2)	195 (62.9)
≥ 75	34 (21.9)	31 (20.0)	65 (21.0)
Sex (male)	108 (69.7)	100 (64.5)	208 (67.1)
<b>Region</b>			
North America	8 (5.2)	9 (5.8)	17 (5.5)
Australia, New Zealand	9 (5.8)	7 (4.5)	16 (5.2)
Western Europe	32 (20.6)	33 (21.3)	65 (21.0)
Central and Eastern Europe	99 (63.9)	99 (63.9)	198 (63.9)
Asia	7 (4.5)	7 (4.5)	14 (4.5)
<b>Disease characteristics</b>			
<b>ECOG Performance Status</b>			
0	58 (37.4)	55 (35.5)	113 (36.5)
1	78 (50.3)	79 (51.0)	157 (50.6)
2	19 (12.3)	21 (13.5)	40 (12.9)
<b>Time from diagnosis to randomization, months</b>			
Mean (SD)	88.5 (54.5)	87.1 (51.6)	87.8 (53.0)
Median (range)	85.3 (3.1–314.4)	79.0 (5.0–254.2)	79.0 (3.1–314.4)
Bulky disease (≥ 5 cm)	78 (49.0)	75 (48.4)	151 (48.7)
<b>Rai stage</b>			
0	2 (1.3)	4 (2.6)	6 (1.9)
I	39 (25.2)	32 (20.6)	71 (22.9)
II	49 (31.6)	54 (34.8)	103 (33.2)
III	21 (13.5)	18 (11.6)	39 (12.6)
IV	44 (28.4)	46 (29.7)	90 (28.0)
Beta-2 microglobulin > 3.5 mg/L	120 (77.4)	128 (81.3)	248 (79.4)
Cytopenia	85 (54.8)	80 (51.6)	165 (53.2)
Constitutional symptoms	91 (58.7)	97 (62.6)	188 (60.6)

**Table A2 Main study characteristics ASCEND**

	Treatment group		
	Placebo (n=149)	Acute (n=149)	Chronic (n=149)
<b>Genetic markers</b>			
Del(17p)	28 (18.1)	21 (13.5)	40 (15.8)
Del(11q)	39 (25.2)	44 (28.4)	63 (28.8)
TP53 mutation	39 (25.2)	24 (15.8)	73 (23.5)
<b>IGHV</b>			
Mutated	22 (21.3)	28 (16.8)	56 (19.0)
Unmutated	118 (76.1)	128 (80.0)	243 (79.4)
Undetermined	3 (1.8)	2 (1.3)	5 (1.0)
Del(17p) or TP53 mutation	22 (14.2%)	13 (8.4%)	35 (11.5%)
Del(17p), TP53 mutation, del(11q) or unmutated IGHV	135 (87.1)	137 (88.4)	272 (87.7)
<b>Previous treatment</b>			
Time since last previous CLL therapy to first dose, months*			
Mean (SD)	31.5 (22.0)	29.7 (27.2)	30.6 (27.6)
Median (range)	29.4 (1.0–158.9)	22.7 (1.1–158.2)	24.1 (1.0–158.9)
<b>Number of previous therapies</b>			
1	82 (52.8%)	87 (45.2%)	146 (46.1%)
2	40 (25.3%)	48 (20.7%)	88 (27.7%)
3	17 (11.0%)	24 (15.5%)	41 (13.2%)
> 4	16 (10.3%)	18 (11.0%)	34 (11.0%)
Median (range)	1 (1–8)	2 (1–10)	2 (1–10)
<b>Type of previous therapy</b>			
Purine analogues	100 (70.3)	104 (67.1)	213 (68.7)
Allylators (not bendamustine)	133 (86.6)	131 (84.3)	204 (65.2)
Bendamustine	47 (30.3)	48 (31.0)	96 (30.6)
Anti-CD20 mAbs	130 (83.9)	119 (76.8)	249 (80.3)
Stem cell transplant	1 (0.6)	1 (0.6)	2 (0.6)
Other	9 (5.8)	8 (5.2)	15 (4.6)

Table A2 Main study characteristics ASCEND

**Primary and secondary endpoints****Primary endpoints:**

- IRC-assessed PFS, defined as the time from randomization until disease progression or death from any cause, using International Workshop on Chronic Lymphocytic Leukemia 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis.

**Secondary endpoints:**

- Investigator and IRC-assessed Overall Response Rate (ORR)
- Overall survival (OS)
- Investigator and IRC-assessed Duration of response (DOR);
- Investigator-assessed PFS, ORR, and DOR; and
- Time to next CLL treatment (Data Supplement).
- Patient reported outcomes
- Safety

Safety was assessed by AEs, laboratory measurements, and clinical evaluation. Treatment-emergent AEs were defined as any event with an onset date on or after the first dose date of study drug or any ongoing event that worsened in severity after the first dose date of study drug and prior to 30 days after the date of the last dose of study drug or the first date starting new anticancer therapy. All AEs and serious AEs (SAEs) are treatment emergent, unless otherwise specified. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

**Table A2 Main study characteristics ASCEND**
**Method of analysis**

Endpoint	Analysis	Population
<b>Primary endpoint</b>		
PFS	Stratified 2-sided log rank test comparing PFS, as assessed by the IRC, between arm A and arm B Summary of distribution of PFS for each treatment arm using median and 95% CI based on Kaplan-Meier estimates HR and 95% CI estimated using a Cox proportional hazards model stratified by the randomization strata	ITT population
PFS (sensitivity analyses)	Inclusion of PFS without censoring for subsequent anti-cancer therapy Inclusion of PFS events after $\geq 2$ consecutively missed visits Exclusion of subjects with important protocol deviations Use of eCRF-recorded stratification factors	ITT population
PFS (key subgroup analyses)	Subgroups including:  age sex (male vs female) del(17p) (yes vs no) TP53 mutation (yes vs no) del(11q) (yes vs no) unmutated IGHV (yes vs no) Poor prognosis composite: <ul style="list-style-type: none"> <li>o del(17p), TP53 mutation, del(11q) or unmutated IGHV (yes vs no)</li> <li>o del(17p) and TP53 mutation (yes vs no)</li> <li>o del(17p) or TP53 mutation (yes vs no)</li> <li>o del(17p), TP53 mutation or del(11q) (yes vs no)</li> </ul> Rel stage at screening (stage 0-II vs III-IV) Bulky disease (< 5 cm vs $\geq 5$ cm) Beta-2 microglobulin at baseline ( $\leq 3.5$ mg/L vs > 3.5 mg/L) ECOG Performance Status (0, 1 vs 2) Race (white vs non-white) Geographic region Number of previous therapies (1-3 vs $\geq 4$ )	ITT population subgroups
<b>Secondary/exploratory endpoints</b>		
ORR	CMH test adjusting for randomization stratification factors Summary of number and percentage of patients, 95% CI calculated based on normal approximation	ITT population
OS, DCR, TTT and investigator-assessed PFS	Analyzed with same approach used for primary endpoint	ITT population
OS (sensitivity analysis)	Censoring of patients in Arm B who crossed over to receive acalabrutinib on day before the first dose of acalabrutinib	ITT population
FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D	Exploratory p values with no adjustment for multiple comparisons Thresholds for clinically meaningful changes were based on $\pm 1$ SD of the distribution of scores	SF population <sup>ii</sup> ITT population
<b>Safety endpoints</b>		
AEs and SAEs	Descriptive analyses by system organ class, preferred term, severity and relationship to study drug	Safety population

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**Subgroup analyses**

The effect of acalabrutinib ( vs. IR or BR) on IRC-assessed PFS was investigated in predefined subgroups.

Table A2 Main study characteristics RESONATE-2

Table A2 Main study characteristics RESONATE-2	
<b>Trial name</b>	RESONATE-2 Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
<b>NCT number</b>	NCT01722487
<b>Objective</b>	to evaluate the efficacy and safety of single-agent ibrutinib as compared with chlorambucil in patients 65 years of age or older with previously untreated CLL
<b>Publications – title, author, journal, year</b>	Jan A Burger, Alessandra Tedeschi, Paul M Barr et al., Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia, NEJM. 2015 Dec 17;373(25):2425-37 [12]



**Table A2 Main study characteristics RESONATE-2**

<b>Study type and design</b>	<p>Randomized, multicenter, open-label, Phase 3 study designed to compare the safety and efficacy of Ibrutinib versus Chlorambucil in treatment-naïve patients 65 years or older who have CLL or SLL.</p> <p>Eligible patients will be randomized in a 1:1 ratio to Treatment Arm A or B:</p> <p><b>Treatment Arm A:</b> Oral Chlorambucil 0.5 mg/kg on Days 1 and 15 of each 28-day cycle; the dose can be increased, if well tolerated, in increments of 0.1 mg/kg on Day 1 of each cycle to a maximum of 0.8 mg/kg; patients receive a minimum of 3 and a maximum of 12 cycles, in the absence of progressive disease or unacceptable toxicity.</p> <p><b>Treatment Arm B:</b> Oral Ibrutinib 420 mg/day Randomization will be stratified on Eastern Cooperative Oncology Group (ECOG) performance status (0,1 versus 2); presence of advanced Rai stage (yes/no), advanced being defined as Stages 3-4; and geographic region: US versus non-US.</p>
<b>Follow-up time</b>	<p>No interim analysis was planned. median follow-up period of 18.4 months</p>

Population (inclusion and exclusion criteria)	Criteria
	<p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Males or females of 65 years of age or greater. Patients between the ages of 65 and 70 years of age must have 1 or more of the following comorbidities that may preclude the use of frontline chemotherapy with fludarabine, cyclophosphamide, or rituximab:               <ul style="list-style-type: none"> <li>✓ creatinine clearance &lt; 70 mL/min using the Cockcroft-Gault equation</li> <li>✓ platelet count &lt; 100,000/<math>\mu</math>L or hemoglobin &lt; 10 g/dL</li> <li>✓ clinically apparent autoimmune cytopenia (autoimmune hemolytic anemia or immune thrombocytopenia)</li> <li>✓ ECOG performance score = 1 or 2</li> </ul> </li> <li>2. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008)</li> <li>3. Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment:               <ul style="list-style-type: none"> <li>✓ Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia Massive, progressive, or symptomatic splenomegaly</li> <li>✓ Massive nodes or progressive or symptomatic lymphadenopathy</li> <li>✓ Progressive lymphocytosis</li> <li>✓ Autoimmune hemolytic anemia and/or immune thrombocytopenia that is poorly responsive to corticosteroids or standard therapy</li> <li>✓ Constitutional symptoms</li> </ul> </li> <li>4. Measurable nodal disease by computed tomography (CT)</li> <li>5. ECOG performance status of 0-2</li> <li>6. Life expectancy &gt; 4 months from randomization</li> <li>7. Adequate hematologic function, defined as absolute neutrophil count (ANC) <math>\geq</math> 1,000/<math>\mu</math>L (independent of growth factor support for at least 7 days prior to screening) and platelet count <math>\geq</math> 50,000/<math>\mu</math>L (independent of transfusion and growth factor support for at least 7 days prior to screening)</li> <li>8. Adequate hepatic function, defined as serum aspartate transaminase (AST) and alanine transaminase (ALT) &lt; 2.5 x upper limit of normal (ULN), and total bilirubin <math>\leq</math> 1.5 x ULN</li> <li>9. Adequate renal function, defined as estimated creatinine clearance <math>\geq</math> 30 mL/min using the Cockcroft-Gault equation</li> <li>10. Willingness to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers study drug for the entire study</li> <li>11. Willingness of male patients, if sexually active with a female of childbearing potential, to use an effective barrier method of contraception during the study and for 3 months following the last dose of study drug</li> </ol>

12. Ability to provide written informed consent and to understand and comply with the requirements of the study

**Exclusion Criteria:**

1. Known involvement of the central nervous system by lymphoma or leukemia
2. History or current evidence of Richter's transformation or prolymphocytic leukemia
3. Documentation of deletion of the short arm of chromosome 17: del(17p13.1) in more than 20% of cells examined on any pretreatment fluorescence in situ hybridization (FISH) or cytogenetic evaluation
4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura
5. Any previous treatment (chemotherapy, radiotherapy, and/or monoclonal antibodies) intended specifically to treat CLL/SLL
6. Received any immunotherapy, vaccine, or investigational drug within 4 weeks prior to randomization
7. Corticosteroid use within 1 week prior to first dose of study drug, with the exception of inhaled, topical, or other local administrations. Patients requiring systemic steroids at daily doses > 20 mg prednisone (or corticosteroid equivalent, see Appendix N), or those who are administered steroids for leukemia control or white blood cell (WBC)-count-lowering are excluded.
8. Major surgery within 4 weeks prior to randomization
9. History of prior malignancy, with the exception of the following:
  - ✓ malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to screening and felt to be at low risk for recurrence by treating physician
  - ✓ adequately treated nonmelanomatous skin cancer or lentigo maligna melanoma without current evidence of disease
  - ✓ adequately treated cervical carcinoma in situ without current evidence of disease
10. Currently active, clinically significant cardiovascular disease or a history of myocardial infarction within 6 months prior to randomization
11. Inability to swallow capsules or tablets, or disease significantly affecting gastrointestinal function
12. Uncontrolled active systemic fungal, bacterial, viral, or other infection or requirement for intravenous (IV) antibiotics
13. Known history of infection with human immunodeficiency virus (HIV)
14. Serologic status reflecting active hepatitis B or C infection
15. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
16. Current life-threatening illness, medical condition, or organ-system dysfunction that could compromise patient safety or put the study at risk
17. Requirement for anticoagulation with warfarin

**Table A2 Main study characteristics RESONATE-2**

	18. Requirement for treatment with a strong CYP3A4/5 and/or CYP2D6 inhibitor
<b>Intervention</b>	<p>Arm A: Ibrutinib will be supplied as hard gelatin 140-mg capsules for oral (PO) administration. Ibrutinib 420 mg (3 x 140-mg capsules) is administered orally once daily.</p> <p>Arm B: Chlorambucil will be supplied as 2-mg tablets for PO administration. Chlorambucil is administered orally on Days 1 and 15 of each 28-day cycle. The starting dosage (Cycle 1) is 0.5 mg/kg. If well tolerated, the Chlorambucil dose can be increased starting at Cycle 2, with increments of 0.1 mg/kg on Day 1 of each cycle to a maximum of 0.8 mg/kg.</p>
<b>Baseline characteristics</b>	<p><a href="https://www.nejm.org/doi/full/10.1056/nejmoa1509388">https://www.nejm.org/doi/full/10.1056/nejmoa1509388</a></p> <p><i>AstraZeneca is currently checking if we have copyright for this publication. Please use link to get the information</i></p>

<p><b>Primary and secondary endpoints</b></p>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. PFS (Progression Free Survival) [ Time Frame: Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month. ]</li> </ol> <p>The primary objective of this study was to evaluate the efficacy of Ibrutinib compared with Chlorambucil based on the independent review committee (IRC) assessment of PFS</p> <p>Progressive disease according to 2008 IWCLL guidelines was defined as:</p> <p>Group A</p> <ul style="list-style-type: none"> <li>✓ Lymphadenopathy, increase <math>\geq 50\%</math></li> <li>✓ Hepatomegaly, increase <math>\geq 50\%</math></li> <li>✓ Splenomegaly, increase <math>\geq 50\%</math></li> <li>✓ Blood lymphocytes, increase <math>\geq 50\%</math> over baseline</li> </ul> <p>Group B</p> <ul style="list-style-type: none"> <li>✓ Platelets counts, decrease of <math>\geq 50\%</math> from baseline secondary to CLL</li> <li>✓ Hemoglobin, decrease of <math>&gt; 2</math> g/dL from baseline secondary to CLL</li> </ul> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Overall Survival (OS) [ Time Frame: Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month. ] <ul style="list-style-type: none"> <li>✓ OS is calculated for all randomized subjects as the duration of time from the date of randomization to the date of death due to any cause or the date last known alive for subjects who were not known to have died at study closure.</li> </ul> </li> <li>2. ORR (Overall Response Rate) [ Time Frame: Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month. ] <ul style="list-style-type: none"> <li>✓ ORR is defined as the proportion of subjects who achieved complete response (CR), complete response with incomplete marrow recovery (CRi), nodule partial response (nPR) or PR per IRC assessment. Response criteria are as outlined in the International Workshop on CLL (iwCLL) 2008 criteria with the 2012 iwCLL modification</li> </ul> </li> </ol>
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**Table A2 Main study characteristics RESONATE-2**

	<p>stating that treatment-related lymphocytosis in the setting of improvement in other parameters was not considered as PD and the 2013 iwCLL clarification of criteria for a partial response to therapy.</p> <ol style="list-style-type: none"> <li>3. Proportion of Sustained Hemoglobin Improvement [ Time Frame: Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month. ]</li> <li>4. Proportion of Sustained Hemoglobin Improvement in Subjects With Baseline Anemia [ Time Frame: Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month. ]</li> <li>5. Proportion of Sustained Platelet Improvement [ Time Frame: Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month. ]</li> </ol> <p>Proportion of Sustained Platelet Improvement in Subjects With Baseline Thrombocytopenia [ Time Frame: Analysis was conducted when 15 months had elapsed after the last subject was randomized with cutoff date of 4 May 2015. The median follow-up time is 18 month. ]</p>
<b>Method of analysis</b>	<p>The study was powered on the basis of the primary end point, progression-free survival. We calculated that the occurrence of 81 events of death or disease progression would provide the study with approximately 85% power to detect a hazard ratio for progression or death of 0.50 with ibrutinib as compared with chlorambucil, with the use of a one-sided log-rank test at an alpha level of 0.025. No interim analysis was planned. The type I error was controlled with the use of a hierarchical closed-testing procedure for the primary end point and ordered secondary end points including, in order, overall response rate, overall survival, and sustained hematologic improvement.</p>
<b>Subgroup analyses</b>	<p>The primary analysis was a two-sided log-rank test stratified according to two randomization factors: ECOG performance-status score (0 or 1 vs. 2) and disease stage (Rai stage ≤II vs. III or IV). The overall response rate was analyzed by means of the Cochran–Mantel–Haenszel chi-square test, stratified according to the two randomization factors. Overall survival was analyzed with the use of an unstratified log-rank test, owing to small event numbers. The rate of sustained hematologic improvement was compared by a chi-square test for treatment effect.</p>

Table A2 Main study characteristics Alliance

Table A2 Main study characteristics ALLIANCE	
<b>Trial name</b>	<b>ALLIANCE -A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients (≥65 Years of Age) With Chronic Lymphocytic Leukemia (CLL)</b>
<b>NCT number</b>	NCT01886872
<b>Objective</b>	Randomized open label phase III trial to study rituximab with bendamustine hydrochloride or ibrutinib to see how well they work compared to ibrutinib alone in treating older patients with previously untreated chronic lymphocytic leukemia
<b>Publications – title, author, journal, year</b>	Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, Bartlett NL, Brander DM, Barr PM, Rogers KA, Parikh SA, Coutre S, Hurria A, Brown JR, Lozanski G, Blachly JS, Ozer HG, Major-Elechi B, Fruth B, Nattam S, Larson RA, Erba H, Litzow M, Owen C, Kuzma C, Abramson JS, Little RF, Smith SE, Stone RM, Mandrekar SJ, Byrd JC. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018 Dec 27;379(26):2517-2528.. [15]
<b>Study type and design</b>	Open label, randomized, Phase III study to study rituximab with bendamustine hydrochloride or ibrutinib to see how well they work compared to ibrutinib alone in treating older patients with previously untreated chronic lymphocytic leukemia
<b>Follow-up time</b>	38 months
<b>Population (inclusion and exclusion criteria)</b>	<p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Patients must be diagnosed with CLL in accordance with International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria that includes all of the following: <ul style="list-style-type: none"> <li>○ <math>\geq 5 \times 10^9</math> B lymphocytes (5000/uL) in the peripheral blood</li> <li>○ On morphologic review, the leukemic cells must be small mature lymphocytes, and prolymphocytes must not exceed 55% of the blood lymphocytes</li> <li>○ CLL cells on immunophenotype (performed locally) must reveal a clonal B-cell population, which express the B cell surface markers of cluster of differentiation (CD)19 and CD20, as well as the T-cell antigen CD5; patients with bright surface immunoglobulin expression or lack of CD23 expression in &gt; 10% of cells must lack t(11;14) translocation by interphase cytogenetics</li> </ul> </li> </ul>

**Table A2 Main study characteristics ALLIANCE**

- Patients must be intermediate or high-risk Rai stage CLL
  - Intermediate risk (formerly Rai stage I/II) is defined by lymphocytosis plus enlarged lymph nodes at any site, with or without hepatomegaly or splenomegaly
  - High risk (formerly Rai stage III/IV) is defined by lymphocytosis with or without enlarged nodes and spleen plus disease-related anemia (hemoglobin < 11 g/dL) or thrombocytopenia (platelet count < 100 x 10<sup>9</sup>/L) that is not attributable to autoimmune hemolytic anemia or thrombocytopenia
- Patients must meet criteria for treatment as defined by IWCLL 2008 guidelines which includes at least one of the following criteria:
  - Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia)
  - Massive (>= 6 cm below the costal margin), progressive or symptomatic splenomegaly
  - Massive nodes (>= 10 cm) or progressive or symptomatic lymphadenopathy
  - Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy
  - Constitutional symptoms, which include any of the following:
    - Unintentional weight loss of 10% or more within 6 months
    - Significant fatigue
    - Fevers > 100.5 degrees F for 2 weeks or more without evidence of infection
    - Night sweats > 1 month without evidence of infection
- Prior treatment
  - Patients must not have had prior therapy for CLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab or steroids)
  - Treatment with rituximab and/or high dose corticosteroids for autoimmune complications of CLL must be complete at least 4 weeks prior to enrollment; palliative steroids must be at a dose not higher than 20 mg/day of prednisone or equivalent corticosteroid at the time of registration
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Patients with active hepatitis B defined by hepatitis B surface antigen positivity or core antibody positivity in the presence of hepatitis B DNA are not eligible for this study; patients with a positive hepatitis B core antibody but with negative hepatitis B DNA may participate, but must have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician
- Intravenous immunoglobulin (IVIG) can cause a false positive hepatitis B serology; if patients receiving routine IVIG have core antibody or surface antigen positivity without evidence of active viremia (negative hepatitis B



**Table A2 Main study characteristics ALLIANCE**

DNA) they may still participate in the study, but should have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician

- Patients must not be receiving active systemic anticoagulation with heparin or warfarin; patients must be off warfarin therapy for at least 30 days prior to enrollment
- Patients with class III or class IV heart failure by New York Heart Association, those with unstable angina, and those with uncontrolled arrhythmia are not eligible
- Patients who have had a myocardial infarction, intracranial bleed, or stroke within the past 6 months are not eligible
- Patients with human immunodeficiency virus (HIV) are eligible if their CD4 count is  $\geq 350$  cells/mm<sup>3</sup> and if they are not taking prohibited cytochrome (CYP)-interacting medications
- Patients must not have any history of Richter's transformation or polymphocytic leukemia (polymphocytes in blood  $> 55\%$ )
- Patients must not require more than 20 mg prednisone or equivalent corticosteroid daily
- Patients must not have uncontrolled active systemic infection requiring intravenous antibiotics
- Patients must not have continued requirement for therapy with a strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitor or inducer
- Patients must not have a known allergy to mannitol
- Patients must not have prior significant hypersensitivity to rituximab (not including infusion reactions)
- Patients may not have had major surgery within 10 days of enrollment, or minor surgery within 7 days of enrollment; examples of minor surgery include dental surgery, insertion of a venous access device, skin biopsy, or aspiration of a joint; the decision about whether a surgery is major or minor can be made at the discretion of the treating physician
- Absolute neutrophil count (ANC)  $\geq 1,000$ /uL unless due to bone marrow involvement
- Aspartate aminotransferase (AST) or alanine aminotransferase (AST)  $\leq 2.5$  x upper limits of normal except if due to disease infiltration of the liver
- Bilirubin  $\leq 1.5$  x upper limits of normal (unless due to liver involvement, hemolysis, or Gilbert's disease)
- Creatinine clearance  $\geq 40$  mL/min
- To be calculated by modified Cockcroft-Gault formula
- Platelet count (untransfused)  $\geq 30,000$ /uL

**Table A2 Main study characteristics ALLIANCE**

**Intervention**

**Active Comparator: Arm I (rituximab, bendamustine hydrochloride)**

Patients receive rituximab IV on day 1 (day 0 course 1) and bendamustine hydrochloride IV over 30 minutes on days 1-2. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity. Patients experiencing disease progression may crossover to Arm II.

**Experimental: Arm II (ibrutinib)**

Patients receive ibrutinib PO daily. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity.

**Experimental: Arm III (ibrutinib, rituximab)**

Patients receive ibrutinib as in Arm II. Patients receive rituximab IV on days 1, 8, 15, and 22 of course 2 and on day 1 of courses 3-6. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity.

**Baseline characteristics**

**Table 1. Characteristics of the Patients at Baseline.**

Characteristic	All Patients (N=547)	Bendamustine+ Rituximab (N=183)	Ibrutinib (N=162)	Ibrutinib+ Rituximab (N=182)	P Value <sup>a</sup>
Age — yr					0.53
Median	73	70	71	71	
Range	65-89	62-96	65-89	66-84	
Male sex — no. (%)	467 (85)	159 (87)	123 (76)	165 (91)	0.75
High risk disease according to modified bin stage — no. (%)	296 (54)	99 (54)	99 (61)	98 (54)	0.99
ECOG performance-status score — no. (%)					0.08
0	271 (50)	98 (54)	87 (54)	88 (49)	
1	259 (47)	75 (41)	80 (49)	84 (47)	
2	17 (3)	10 (6)	5 (3)	7 (4)	
TISH analysis according to hierarchical classification of Dillman et al. — no./total no. (%)					0.95
Del(17p11.1)	84/342 (25)	34/141 (24)	47/181 (26)	13/180 (7)	
Del(13q32.3)	305/342 (89)	33/141 (23)	15/181 (8)	32/180 (18)	
Trisomy 12	118/342 (34)	40/141 (28)	40/181 (22)	38/180 (21)	
None	30/342 (9)	28/141 (20)	32/181 (18)	7/180 (4)	
Del(13q14.3)	289/342 (84)	83/141 (59)	63/181 (35)	64/180 (36)	
Mutated FISH — no./total no. (%)	31/310 (10)	16/174 (9)	13/168 (8)	7/168 (4)	0.60
Complex karyotype — no./total no. (%)	143/499 (29)	44/146 (30)	34/168 (20)	60/168 (36)	0.04
Unmethylated ZAP70 — no./total no. (%)	287/348 (83)	85/142 (60)	46/182 (25)	66/182 (36)	0.09
Unmutated IgVH gene — no./total no. (%)	218/360 (61)	72/123 (58)	77/122 (63)	70/110 (64)	0.60

<sup>a</sup> All P values are for comparisons across all three treatment groups and are two-sided. P values for continuous variables were calculated with the use of the Kruskal-Wallis test, and P values for categorical variables were calculated with the use of the chi-square test or Fisher's exact test.  
<sup>b</sup> Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 3, with higher scores indicating greater disability.  
<sup>c</sup> Central Fluorescence in situ Hybridization (FISH) analysis was performed with the use of the hierarchical classification method established by Dillman et al.

**Primary and secondary endpoints**

**Table A2 Main study characteristics ALLIANCE**
**Primary Outcome Measures :**

1. Progression Free Survival (PFS) [ Time Frame: Time from study entry to the time of documented disease progression or death. The analysis was event driven, performed at 2.5 years after the last patient enrolled; up to 4 years. ]

The Kaplan-Meier method will be used to estimate the progression free survival distributions for each arm, with median estimates provided. Progression is defined as any one of the following: an increase in number of blood lymphocytes by  $\geq 50\%$  with  $\geq 5000$  B lymphocytes/mL in patients on Arm A or those on Arms 2 or 3 no longer receiving ibrutinib,  $\geq 50\%$  increase in the products of at least 2 lymph nodes on 2 consecutive determination 2 weeks apart,  $\geq 50\%$  increase in the size of the liver/spleen, transformation to a more aggressive histology, progression of any cytopenia (i.e. decrease of Hb levels  $> 2\text{g/dL}$ ). Progression free survival time will be the time to either progression or death whichever occurs first.

**Secondary Outcome Measures :**

1. Progression Free Survival (PFS) Rate at 2 Years [ Time Frame: Time from study entry to the time of documented disease progression or death, assessed up to 2 years ]

The Kaplan-Meier method will be used to estimate the rate of progression free survival at 2 years in each treatment arm. Progression is defined as any one of the following: an increase in number of blood lymphocytes by  $\geq 50\%$ ,  $\geq 50\%$  increase in the products of at least 2 lymph nodes on 2 consecutive determination 2 weeks apart,  $\geq 50\%$  increase in the size of the liver/spleen, transformation to a more aggressive histology, progression of any cytopenia (i.e. decrease of Hb levels  $> 2\text{g/dL}$ ). Progression free survival time will be the time to either progression or death whichever occurs first.

2. Overall Survival (OS) at 2 Years [ Time Frame: From the date of registration to the date of death, assessed up to 2 years ]

The Kaplan-Meier method will be used to estimate the rate of overall survival at 2 years in each treatment arm. OS will be measured from the date of registration to the date of the event (i.e., death) or the date of last follow-up to evaluate that event. Patients who are event-free at their last follow-up evaluation will be censored at that time point.

3. Duration of Response (DOR) (Complete Response [CR], CCR, Nodular Partial Response [nPR], Partial Response [PR], and PRL) [ Time Frame: From the date of first response until progression or death, performed at 2.5 years after the last patient enrolled; up to 4 years. ]

**Table A2 Main study characteristics ALLIANCE**

The Kaplan-Meier method will be used to estimate median DOR. DOR is the time from first objective status to progression or death. CR requires all of the following: absence of lymphadenopathy > 1.5 cm on physical exam/CT scan, no hepatomegaly/splenomegaly on physical exam, no clonal B-cells in the blood, Normal CBC, bone marrow aspirate & biopsy must be normocellular for age. PR requires  $\geq 50\%$  decrease in peripheral lymphocyte count from pre-treatment value,  $\geq 50\%$  reduction in lymphadenopathy, and/or  $\geq 50\%$  reduction in splenomegaly/hepatomegaly. CR with exception of having bone marrow lymphoid CLL nodules will be considered a nodular PR (nPR). CR with exception of not having a bone marrow biopsy performed will be considered a clinical CR (CCR). PR with the exception of having less than a 50% reduction in peripheral lymphocyte count will be considered a PR except persistent lymphocytosis (PRL).

4. Percentage of Patients Achieving Any Response to Treatment (Overall Response Rate [ORR] [Complete Response [CR], CCR, Nodular Partial Response [nPR], Partial Response [PR], and PRL]) [ Time Frame: Performed at 2.5 years after the last patient enrolled; up to 4 years. ]

Complete response (CR) requires all of the following: absence of lymphadenopathy >1.5 cm on physical exam/CT scan, no hepatomegaly/splenomegaly on physical exam, no clonal B-cells in the blood, Normal CBC, bone marrow aspirate & biopsy must be normocellular for age. Partial response (PR) requires  $\geq 50\%$  decrease in peripheral lymphocyte count from pre-treatment value,  $\geq 50\%$  reduction in lymphadenopathy, and/or  $\geq 50\%$  reduction in splenomegaly/hepatomegaly. CR with exception of having bone marrow lymphoid CLL nodules will be considered a nodular PR (nPR). CR with exception of not having a bone marrow biopsy performed will be considered a clinical CR (CCR). PR with the exception of having less than a 50% reduction in peripheral lymphocyte count will be considered a PR except persistent lymphocytosis (PRL). Overall response rate and corresponding exact binomial 95% CI provided.

5. Percentage of Patients Achieving a Biopsy-proven Complete Response (CR) [ Time Frame: Performed at 2.5 years after the last patient enrolled; up to 4 years. ]

Complete response (CR) requires all of the following: absence of lymphadenopathy > 1.5 cm on physical exam/CT scan, no hepatomegaly or splenomegaly on physical exam, no clonal B-cells in the blood, Normal CBC, bone marrow aspirate and biopsy must be normocellular for age. Complete response rate and corresponding exact binomial 95% confidence intervals provided.

6. Percentage of Patients Achieving Complete (CR and CCR) or Nodular Partial Response (nPR) [ Time Frame: Performed at 2.5 years after the last patient enrolled; up to 4 years. ]

Complete response (CR) requires all of the following: absence of lymphadenopathy > 1.5 cm on physical exam/CT scan, no hepatomegaly or splenomegaly on physical exam, no clonal B-cells in the blood, Normal CBC, bone marrow aspirate and biopsy must be normocellular for age. CR with exception of having bone marrow lymphoid CLL nodules will be considered a nodular PR (nPR). CR with exception of not having a

**Table A2 Main study characteristics ALLIANCE**

bone marrow biopsy performed will be considered a clinical CR (CCR). Response rate and corresponding exact binomial 95% confidence intervals provided.

7. Percentage of Patients Who Attain Minimal Residual Disease (MRD) Negative Status [ Time Frame: Cycle 9 Day 1 Evaluation ]

Estimated using the number of patients who achieve minimal residual disease divided by the total number randomized to that treatment arm. Corresponding exact binomial 95% confidence intervals for MRD rates will be calculated.

8. The Rate of Grade 3, 4, or 5 Treatment-related Non-hematologic Adverse Events (Toxicities) [ Time Frame: Performed at 2.5 years after the last patient enrolled; up to 4 years. ]

The rate of grade 3, 4, or 5 treatment-related non-hematologic adverse events (toxicities) by arm; excludes adverse events occurring post-crossover for patients in Arm A

**Other Outcome Measures:**

1. Geriatric Functional Status (Optional) [ Time Frame: Performed at 2.5 years after the last patient enrolled ]

Assessed using the Older Americans' Resources and Services Multidimensional Functional Assessment Questionnaire, Activities of Daily Living, Medical Outcomes Study physical functioning, Karnofsky performance status rated by a health care professional, Karnofsky performance status rated by the patient, timed "Up and Go", and number of falls in the last six months.

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**Method of analysis**

Chi-square or Fisher's exact tests were used to compare categorical baseline characteristics, patterns of adverse events (AEs), and best response rates among the treatment groups. Kruskal-Wallis tests were used to compare continuous baseline characteristics among the treatment groups. PFS and OS curves were estimated using the method of Kaplan-Meier for the intent-to-treat population and compared between treatment groups using log-rank tests. Forest plots were used to illustrate the comparisons between the arms within subgroups defined by the stratification factors. Univariable and multivariable Cox proportional hazards models for the primary end point of PFS were fit (using patients who had complete data on all predictors) to understand the impact of treatment, age, gender, baseline Rai stage, ECOG performance status, white blood cell counts, elevated beta-2 microglobulin, elevated lactate dehydrogenase, splenomegaly, Zap-70 methylation, high-risk FISH abnormalities (del(17p) or del(11q)), TP53 mutations, and complex karyotype on outcome.

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**Subgroup analyses**

Subgroup analysis was performed in the intention-to treat population. Hazard ratios were calculated with univariable Cox proportional-hazards models. Univariable and multivariable Cox proportional hazards models for the primary end point of PFS were fit (using patients who had complete data on all predictors) to understand the impact of treatment, age,

**Table A2 Main study characteristics ALLIANCE**

gender, baseline Rai stage, ECOG performance status, white blood cell counts, elevated beta-2 microglobulin, elevated lactate dehydrogenase, splenomegaly, Zap-70 methylation, high-risk FISH abnormalities (del(17p) or del(11q)), TP53 mutations, and complex karyotype on outcome

**Table A2 Main study characteristics Ahn et al.**
**Table A2 Main study characteristics Ahn**

<b>Trial name</b>	A Phase II Study of PCI-32765 for Patients With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Need Therapy and Are Older Than 65 or Have a 17p Deletion
<b>NCT number</b>	NCT01500733
<b>Objective</b>	To evaluate the efficacy and safety of single-agent ibrutinib as compared with chlorambucil in patients 65 years of age or older with previously untreated CLL
<b>Publications – title, author, journal, year</b>	Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study, Ahn IE, Farooqui MZH, Tian X, Valdez J, Sun C, Soto S, Lotter J, Housel S, Stetler-Stevenson M, Yuan CM, Maric I, Calvo KR, Nierman P, Hughes TE, Saba NS, Marti GE, Pittaluga S, Herman SEM, Niemann CU, Pedersen LB, Geisler CH, Childs R, Aue G, Wiestner A, Blood. 2018 May 24;131(21):2357-2366 [16]

**Table A2 Main study characteristics Ahn**

<b>Study type and design</b>	<p>Open label, non-randomized, Phase 2 study for Patients With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Need Therapy and Are Older Than 65 or Have a 17p Deletion</p> <p>Eligibility:</p> <ul style="list-style-type: none"> <li>• Individuals over 65 years of age who have CLL/SLL.</li> <li>• Individuals at least 18 years of age who have CLL/SLL and 17p deletion.</li> </ul> <p>Design:</p> <ul style="list-style-type: none"> <li>• Participants will take PCI-32765 capsules every day for 28 days (one cycle of treatment). Treatment will be monitored with frequent blood tests and clinic visits.</li> <li>• PCI-32765 will be given for six cycles of treatment. Those who benefit from the drug will continue to take it as long as there are no side effects and the disease does not progress. Those who do not benefit will stop treatment and have regular followup exams.</li> </ul> <p>Eligible patients will be randomized in a 1:1 ratio to Treatment Arm A or B:</p> <ul style="list-style-type: none"> <li>• Experimental: Elderly greater than 65</li> </ul> <p>Intervention: Drug: PCI 32765</p> <ul style="list-style-type: none"> <li>• Experimental: 17p Deletioin</li> </ul> <p>Intervention: Drug: PCI 32765</p> <p>Drug: PCI 32765. 420 mg daily</p>
<b>Follow-up time</b>	<p>5 year follow-up</p>

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p><b>INCLUSION CRITERIA:</b></p> <ol style="list-style-type: none"> <li>1. Cohort 1: Treated and untreated patients age 65 or older and need for therapy  Cohort 2: Treated (maximum accrual n=16) and untreated (n=27, evaluable) patients at least 18 years old with 17p deletion or p53 expression by immunohistochemistry or p53 mutation by sequencing analysis.</li> <li>2. Men and women with histologically confirmed disease as defined by the following: <ul style="list-style-type: none"> <li>• B-lymphocytosis greater than 5000 cells/microL (may be less than 5000 cells/microL if lymphadenopathy is present with histologic confirmation of lymph node involvement by SLL)</li> <li>• Immunophenotypic profile read by an expert pathologist as consistent with CLL. This will include CD5, CD19, and CD20 expression by the CLL cells typically also with CD23 expression, but CD23 negative cases may be included if there is no t11;14 translocation present.</li> </ul> </li> <li>3. Active disease as defined by at least one of the following: <ul style="list-style-type: none"> <li>• Weight loss greater than or equal to 10% within the previous 6 months</li> <li>• Extreme fatigue</li> <li>• Fevers of greater than 100.5 degrees F for greater than or equal to 2 weeks without evidence of infection</li> <li>• Night sweats for more than one month without evidence of infection</li> <li>• Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia</li> <li>• Massive or progressive splenomegaly</li> <li>• Massive nodes or clusters or progressive lymphadenopathy</li> <li>• Progressive lymphocytosis with an increase of greater than 50% over a 2 month period, or an anticipated doubling time of less than 6 months</li> <li>• Compensated autoimmune hemolysis</li> </ul> </li> <li>4. Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2</li> <li>5. ANC greater than 500/microL, platelets greater than 30,000/microL</li> <li>6. Agreement to use contraception during the study and for 90 days after the last dose of study drug if sexually active and able to bear children</li> <li>7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty</li> </ol>
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8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

**EXCLUSION CRITERIA:**

1. Previous radiotherapy, radioimmunotherapy, biological therapy, chemotherapy, or treatment with an investigational product for CLL treatment in the last 4 weeks (i.e. intravenous immunoglobulin).
2. Transformed CLL
3. Autoimmune hemolytic anemia or thrombocytopenia requiring steroid therapy
4. Impaired hepatic function: Total bilirubin greater than or equal to 1.5 times upper limit of normal unless due to Gilbert's disease, AST/ ALT greater than or equal to 2.5 times institutional upper limit of normal unless due to infiltration of the liver.
5. Impaired renal function: Creatinine greater than or equal to 2.0 mg/dL or GFR less than or equal to 50ml/min
6. Life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of PCI-32765 PO, or put the study outcomes at undue risk
7. Concomitant immunotherapy, chemotherapy, radiotherapy, corticosteroids (at dosages equivalent to prednisone > 20 mg/day), or experimental therapy
8. Active Hepatitis B infection
9. HIV infection
10. Female patients: Current pregnancy or unwilling to take oral contraceptives or refrain from pregnancy if of childbearing potential or currently breastfeeding. Male patients who are unwilling to follow the contraception requirements described in this protocol.
11. Psychiatric illness/social situations that would limit the patient's ability to tolerate and/or comply with study requirements.
12. Unable to understand the investigational nature of the study or give informed consent.
13. Individuals < 18 yrs old
14. Known hypersensitivity to any component of PCI-32765
15. Any prior therapy with PCI 32765 or any other BTK inhibitors.
16. Requires anticoagulation with warfarin.

**Table A2 Main study characteristics Ahn**

	Requires treatment with strong CY3A4/5 and/or CYP2D6 inhibitors (unless no alternative is available).
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• Experimental: Elderly greater than 65 Intervention: Drug: PCI 32765</li> <li>• Experimental: 17p Deletion Intervention: Drug: PCI 32765</li> </ul> <p>Drug: PCI 32765 420 mg daily</p> <p>Patients received ibrutinib 420 mg administered orally once daily on a continuous schedule until disease progression or toxicity necessitated drug discontinuation.</p> <p>Each cycle was 28 days (give or take 4 days).</p>
<b>Baseline characteristics</b>	<i>AstraZeneca is currently checking if we have copyright for this publication. Please use link to get the information</i>

**Table A2 Main study characteristics Ahn**

<b>Primary and secondary endpoints</b>	<p>The primary endpoint was response after 6 cycles of therapy.</p> <p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>Overall Response Rate at 6 Months [ Time Frame: 6 months ]</li> </ol> <p>The primary endpoint was response after 6 cycles of therapy. Overall response rate was calculated as complete response plus partial response, based on the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria.as follows:</p> <p>Complete response (CR): all group A and group B criteria are met</p> <ul style="list-style-type: none"> <li>Group A criteria: resolution of enlarged lymph nodes, normal size spleen and liver, absolute lymphocyte count &lt; 4,000/uL, normocellular bone marrow with &lt; 30% lymphocytes without nodules</li> <li>Group B criteria: improved blood count (platelet count &gt; 100,000/uL, hemoglobin &gt; 11.0 g/dL, neutrophils &gt; 1,500/uL)</li> </ul> <p>Partial response (PR): at least 2 of the group A criteria plus one of the group B criteria are met</p> <ul style="list-style-type: none"> <li>Group A criteria: &gt;=50% decrease in target lymph nodes, &gt;=50% decrease in spleen size, &gt;=50% decrease in liver size, 50% reduction in marrow infiltrates</li> <li>Group B criteria: platelet count &gt; 100,000/uL, hemoglobin &gt; 11.0 g/dL, neutrophils &gt; 1,500/uL</li> </ul> <p>Secondary endpoints included safety, tolerability, overall survival (OS), PFS, and best response</p>
<b>Method of analysis and subgroup analyses</b>	<p>Duration of follow-up was calculated for surviving patients. OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test. Response rates were estimated by the proportions for all patients and subgroups, and their 95% confidence intervals (CIs) were computed and compared between subgroups by Fisher's exact test. In September 2012, the study was amended to allow enrollment of up to 35 patients with TN-CLL in the TP53 cohort, adding to 16 patients with RR-CLL. The total for the TP53 cohort was 51 patients; 35 patients were enrolled in the elderly cohort.</p>

Table A2 Main study characteristics RESONATE

Table A2 Main study characteristics RESONATE	
<b>Trial name</b>	RESONATE-A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
<b>NCT number</b>	NCT01578707
<b>Objective</b>	The purpose of the study is to evaluate whether treatment with ibrutinib as a monotherapy results in a clinically significant improvement in progression free survival (PFS) as compared to treatment with ofatumumab in patients with relapsed or refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)
<b>Publications – title, author, journal, year</b>	John C. Byrd, Jennifer R. Brown, Susan O'Brien et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia, N Engl J Med 2014; 371:213-223 [18]
<b>Study type and design</b>	<p>Study PCYC-1112-CA is a randomized, multicenter, open-label, phase 3 study of the Bruton's Tyrosine Kinase (BTK) inhibitor Ibrutinib (PCI-32765) versus Ofatumumab in patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.</p> <p>Patients randomized to the ofatumumab arm may be considered to receive next subsequent therapy with ibrutinib.</p> <p>Patients were stratified according to whether they had resistance to purine analogue chemoimmunotherapy (defined as no response or a relapse within 12 months after the last dose of a purine analogue) and whether they had a chromosome 17p13.1 deletion.</p>
<b>Follow-up time</b>	Median follow-up of 9.4 months

**Table A2 Main study characteristics RESONATE**
**Population (inclusion and exclusion criteria)**
**Inclusion Criteria:**

- ✓ ECOG performance status of 0-1.
- ✓ Diagnosis of CLL or SLL that meets IWCLL 2008 criteria.
- ✓ Active disease meeting at least 1 of the IWCLL 2008 criteria for requiring treatment.
- ✓ Must have received at least one prior therapy for CLL/SLL.
- ✓ Considered not appropriate for treatment or retreatment with purine analog based therapy.
- ✓ Measurable nodal disease by CT.
- ✓ Patients must be able to receive outpatient treatment and laboratory monitoring at the institution that administers study drug for the entire study.

**Exclusion Criteria:**

- ✓ Known CNS lymphoma or leukemia.
- ✓ No documentation of cytogenetic and/or FISH in patient records prior to first dose of study drug.
- ✓ Any history of Richter's transformation or prolymphocytic leukemia.
- ✓ Uncontrolled Autoimmune Hemolytic Anemia (AIHA) or idiopathic thrombocytopenia purpura (ITP).
- ✓ Prior exposure to ofatumumab or to ibrutinib.
- ✓ Prior autologous transplant within 6 months prior to first dose of study drug.
- ✓ Prior allogeneic stem cell transplant within 6 months or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug.
- ✓ History of prior malignancy, with the exception of certain skin cancers and malignancies treated with curative intent and with no evidence of active disease for more than 3 years.
- ✓ Serologic status reflecting active hepatitis B or C infection.
- ✓ Unable to swallow capsules or disease significantly affecting gastrointestinal function.
- ✓ Uncontrolled active systemic fungal, bacterial, viral, or other infection.
- ✓ History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug.
- ✓ Requires anticoagulation with warfarin.

**Table A2 Main study characteristics RESONATE**

<b>Intervention</b>	<p>Arm A: Ofatumumab. An anti-CD20 monoclonal antibody. The ofatumumab (IV) dosage and schedule is 12 doses administered over 24 weeks or until disease progression, unacceptable toxicity. Week 1: 300 mg initial dose Week 2 through 8: 2,000 mg (once weekly) Week 12, 16, 20 and 24: 2,000 mg (every 4 weeks)</p> <p>Arm B: ibrutinib 420 mg (3 x 140-mg capsules) will be administered orally once daily until disease progression or unacceptable toxicity</p>
<b>Baseline characteristics</b>	<p><a href="https://www.nejm.org/doi/pdf/10.1056/NEJMoa1400376?articleTools=true">https://www.nejm.org/doi/pdf/10.1056/NEJMoa1400376?articleTools=true</a></p> <p><i>AstraZeneca is currently checking if we have copyright for this publication. Please use link to get the information</i></p>
<b>Primary and secondary endpoints</b>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. PFS (Progression Free Survival) by Independent Review Committee (IRC), Limited to the Time of Primary Analysis 06 November 2013 [ Time Frame: Analysis was conducted after observing approximately 117 PFS events, which occurred about 18 months after the first subject was enrolled. ]</li> </ol> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Overall Response Rate (ORR) by Independent Review Committee (IRC) [ Time Frame: About 18 months after the first subject was enrolled ]</li> <li>2. OS (Overall Survival) [ Time Frame: OS analysis was conducted at the time of study closure, including up to 6 years of study follow-up ]</li> <li>3. Rate of Sustained Hemoglobin and Platelet Improvement [ Time Frame: From study initiation to study closure, including up to 6 years of study follow-up ]</li> </ol> <p>Other Outcome Measures:</p> <ol style="list-style-type: none"> <li>1. Progression Free Survival (PFS) by Investigator With up to 6 Years of Study Follow-up [ Time Frame: From study initiation to study closure, including up to 6 years of study follow-up ]</li> </ol> <p>Overall Response Rate (ORR) by Investigator [ Time Frame: From study initiation to study closure, including up to 6 years of study follow-up ]</p>

**Table A2 Main study characteristics RESONATE**

<b>Method of analysis</b>	<p>The primary end point, progression-free survival, was used in the calculation of the study sample size. The number of required events was based on a target hazard ratio for progression or death of 0.60, as calculated with the use of a two-sided log-rank test at an alpha level of 0.05, with a study power of at least 90%. The efficacy boundary (two-sided <math>P &lt; 0.028</math>)</p>
<b>Subgroup analyses</b>	<p>The primary analysis was a two-sided log-rank test stratified according to the presence or absence of the chromosome 17p13.1 deletion and the disease refractory status at randomization. The type I error was controlled through adjustment of the significance level with the use of the O'Brien–Fleming boundary<sup>21</sup> for the interim analysis and with the use of a hierarchical closed-testing procedure for primary and ordered secondary end points.</p> <p>The hazard ratio (ibrutinib/ofatumumab) with its 95% confidence interval will be calculated based on an unstratified Cox regression model for each subgroup. The hazard ratio and their 95% confidence intervals will be displayed for all subgroups graphically in a forest plot.</p>

**Table A2 Main study characteristics COMPLEMENT-1**
**Table A2 Main study characteristics COMPLEMENT1**

<b>Trial name</b>	<p>A Phase III, Open Label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil Versus Chlorambucil Monotherapy in Previously Untreated Patients With Chronic Lymphocytic Leukemia</p>
<b>NCT number</b>	<p>NCT00748189</p>
<b>Objective</b>	<p>The objective of this study was to evaluate progression-free survival (PFS), overall response and overall survival in subjects with previously untreated CLL with ofatumumab added to chlorambucil versus chlorambucil.</p>

**Table A2 Main study characteristics COMPLEMENT1**

<b>Publications – title, author, journal, year</b>	<p>Hillmen P, Robak T, Janssens A, Babu KG, Kloczko J, Grosicki S, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. <i>Lancet</i> (London, England). 2015;385(9980):1873-83. [22]</p>
<b>Study type and design</b>	<p>Phase III, Open Label, Randomized, Multicenter Trial</p> <p>Included patients who had active disease needing treatment, but in whom fludarabine-based treatment was not possible. Patients were randomly assigned (1:1) to receive oral chlorambucil (10 mg/m<sup>2</sup>) on days 1–7 of a 28 day treatment course or to receive chlorambucil by this schedule plus intravenous ofatumumab (cycle 1: 300 mg on day 1 and 1000 mg on day 8; subsequent cycles: 1000 mg on day 1) for three to 12 cycles. Assignment was done with a randomisation list that was computer generated at GlaxoSmithKline, and was stratified, in a block size of two, by age, disease stage, and performance status</p>
<b>Follow-up time</b>	<p>28.9 months</p>



**Table A2 Main study characteristics COMPLEMENT1**

<b>Population (inclusion and exclusion criteria)</b>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>confirmed CLL diagnosis and active CLL requiring treatment</li> <li>considered inappropriate for fludarabine-based therapy</li> <li>not been treated for CLL before</li> <li>fully active at a minimum or fully capable of selfcare and up and about more than 50% of waking hours</li> <li>age 18yrs or older</li> <li>signed written informed consent</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>prior CLL therapy</li> <li>abnormal/inadequate blood values, liver, and kidney function</li> <li>certain heart problems, active or chronic infections, serious significant diseases, active autoimmune hemolytic anemia (AIHA) requiring treatment, other current cancer or within last 5 years</li> <li>CLL transformation</li> <li>CLL central nervous system involvement</li> <li>current participation in other clinical study</li> <li>inability to comply with the protocol activities</li> <li>lactating or pregnant women or female patients of child-bearing potential (or male patients with such partners) not willing to use adequate contraception</li> </ul>
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**Table A2 Main study characteristics COMPLEMENT1**

<b>Intervention</b>	<p>Experimental: ofatumumab + chlorambucil</p> <p>ofatumumab dose: cycle 1 300mg day 1 and 1000mg day 8, subsequent cycles: 1000mg at day 1 every 28 days; chlorambucil dose: 10mg/m<sup>2</sup> PO at days 1-7 every 28 days; duration: minimum of 3 cycles until best response or maximum of 12 treatment cycles</p> <p>Active Comparator: chlorambucil</p> <p>chlorambucil dose: 10mg/m<sup>2</sup> PO at days 1-7 every 28 days; duration: minimum of 3 cycles until best response or maximum of 12 cycles</p>
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**Baseline characteristics**

	Group assigned to chlorambucil (n=226)	Group assigned to chlorambucil plus ofatumumab (n=221)	All patients (n=447)
Median age (years)	70 (36-91)	69 (35-92)	69 (35-92)
<65 years	71 (31%)	69 (31%)	140 (31%)
>65 years	155 (69%)	152 (69%)	307 (69%)
>70 years	117 (52%)	104 (47%)	221 (49%)
>75 years	61 (28%)	56 (25%)	119 (27%)
Men	140 (62%)	142 (64%)	282 (63%)
Binet stage			
A	70 (31%)	77 (35%)	147 (33%)
B	87 (38%)	74 (33%)	161 (36%)
C	69 (31%)	70 (32%)	139 (31%)
ECOG performance status			
0	84/224 (38%)	86/221 (39%)	170/445 (38%)
1	124/224 (54%)	118/221 (53%)	239/445 (54%)
2	19/224 (8%)	17/221 (8%)	36/445 (8%)
>3	0	0	0
B symptoms	120 (53%)	118 (53%)	238 (53%)
>2 comorbidities	159 (70%)	162 (73%)	321 (72%)
Creatinine clearance <70 ml per min	115 (51%)	99 (45%)	214 (48%)
Age > 65 years or > 2 comorbidities or creatinine clearance <70 ml per min	197 (87%)	192 (87%)	389 (87%)
CRS-G	8 (4-19)	9 (4-21)	9 (4-21)
β <sub>2</sub> -microglobulin > 3500 mg/L	169/217 (78%)	153/214 (71%)	322/431 (75%)
Unmutated IGHV	113/203 (56%)	114/201 (57%)	227/404 (56%)
Chromosomal abnormality			
17p deletion	17/216 (8%)	10/209 (5%)	27/425 (6%)
11q deletion (no 17p deletion)	24/216 (11%)	39/209 (19%)	63/425 (15%)
12q or 13q deletion or 6q deletion (no 17p or 11q deletion)	111/216 (51%)	119/209 (57%)	230/425 (54%)
ZAP70			
B-cell positive	110/213 (52%)	100/208 (48%)	210/421 (50%)
Positive B-cell:T-cell ratio	135/213 (63%)	137/208 (66%)	272/421 (65%)
B-cell positive and positive B-cell:T-cell ratio	80/213 (38%)	81/208 (39%)	161/421 (38%)
B-cell negative and negative B-cell:T-cell ratio	48/213 (23%)	52/208 (25%)	100/421 (24%)
B-cell positive or positive B-cell:T-cell ratio (intermediate)	85/213 (40%)	75/208 (36%)	160/421 (38%)

Data are median (range), n (%), or n/number assessed (%), unless otherwise stated. B-cell/ZAP70 positive is defined as greater than 120 molecules of equivalent soluble fluorochrome per cell. B-cell:T-cell positive ratio is defined as a ratio of more than 0.14. ECOG=Eastern Cooperative Oncology Group. IGHV=immunoglobulin heavy chain. CRS-G=Cumulative Illness Rating Scale for Geriatrics.

**Table 1 - Baseline characteristics**

**Primary and secondary endpoints**

Primary Outcome Measures :

1. Progression-Free Survival (PFS), as Assessed by the Independent Review Committee (IRC)  
[ Time Frame: From randomization to the date of first documented disease progression or death due to any cause, whichever occurred first, reported between day of first patient randomized up to about 49 months ]

PFS is defined as the interval of time between the date of randomization and the earlier of the date of disease progression (PD) and the date of death due to any cause. PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlarged lymph nodes (>1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia. Par. who were alive and had not progressed at the time of analysis or if a progression event or death occurred after extensive lost-to-follow-up time or if new anti-cancer therapy was started were censored at the date of the last visit with adequate assessment.

Secondary Outcome Measures :

1. Number of Participants With the Best Overall Response (OR), as Assessed by the IRC  
[ Time Frame: From randomization until the 259th PFS event occurred, up to about 49 months ]

OR is defined as the number of participants achieving an objective response (complete response [CR], CR with incomplete bone marrow recovery [CRi], partial response [PR], and nodular PR [nPR]). CR (all the criteria at least 2 months after last treatment): no lymphadenopathy (Ly) > 1.5 cm/ hepatomegaly/ splenomegaly/ constitutional symptoms; neutrophils >1500 per microliter ( $\mu\text{L}$ ), platelets (PL) >100,000/ $\mu\text{L}$ , hemoglobin (Hb) >11 grams/deciliter (g/dL), lymphocytes (LC) <4000/ $\mu\text{L}$ , bone marrow (BM) sample must be normocellular for age, <30% LC, no lymphoid nodule. CRi: CR criteria, persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. PR:  $\geq$ 50% decrease in LC, Ly, size of liver and spleen and at least one of the following results: PL >100,000/ $\mu\text{L}$  or 50% improvement over Baseline (BL), Hb >11 g/dL or 50% improvement over BL. nPR: persistent nodules BM.

	<p>2. Number of Participants Who Were Negative for Minimal Residual Disease (MRD) [ Time Frame: From randomization until the 259th PFS event occurred (Median follow-up approximately 28.9 months) ]</p> <p>MRD was performed by flow cytometry on a bone marrow or peripheral blood sample taken at least 2 months after final treatment. MRD negative was defined as less than one CLL cell per 10000 leukocytes.</p> <p>3. Overall Survival [ Time Frame: From randomization up to about 111 months ]</p> <p>Overall survival is defined as the time from randomization to death due to any cause. Each participant was followed at the time when the total IRC-assessed PFS events occurred. Participants who had not died were censored at the date of last contact.</p> <p>4. Time to Response, as Assessed by the IRC [ Time Frame: From randomization up to about 27 months ]</p> <p>Time to response is defined as the time from randomization to the first response (CR, CRi, nPR, or PR). CR (all the criteria at least 2 months after last treatment): no lymphadenopathy (Ly) &gt; 1.5 cm/ hepatomegaly/ splenomegaly/ constitutional symptoms; neutrophils &gt;1500 per microliter (<math>\mu\text{L}</math>), platelets (PL) &gt;100,000/<math>\mu\text{L}</math>, hemoglobin (Hb) &gt;11 grams/deciliter (g/dL), lymphocytes (LC) &lt;4000/<math>\mu\text{L}</math>, bone marrow (BM) sample must be normocellular for age, &lt;30% LC, no lymphoid nodule. CRi: CR criteria, persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. PR: <math>\geq</math>50% decrease in LC, Ly, size of liver and spleen and at least one of the following results: PL &gt;100,000/<math>\mu\text{L}</math> or 50% improvement over Baseline (BL), Hb &gt;11 g/dL or 50% improvement over BL. nPR: persistent nodules BM. Participants with unknown or missing responses were considered as non-responders. Only responders (CR, CRi, PR, nPR) were included in the analysis.</p> <p>5. Duration of Response (DOR), as Assessed by the IRC [ Time Frame: From randomization up to about 43 months ]</p> <p>DOR is defined as the time from the initial response (CR, CRi, nPR, or PR) to the first documented sign of PD or death due to any cause. PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlarged lymph nodes (&gt;1.5 cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or</p>
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	<p>spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia. Par. who were alive and had not progressed at the time of analysis or if a progression event occurred after extensive lost-to-follow-up time (<math>\geq 12</math> weeks) were censored at the date of the last visit with adequate assessment. Par. with unknown or missing responses were considered as non-responders.</p> <p>6. Time to Progression, as Assessed by the IRC [ Time Frame: From randomization up to about 49 months ]</p> <p>Time to progression is defined as the time from the date of randomization to disease progression (PD). PD requires at least one of the following: lymphadenopathy, appearance of any new lesion such as enlarged lymph nodes (<math>&gt;1.5</math> cm) spleen or liver or other infiltrates or an increase by 50% or more in the greatest diameter of any previous site; an increase by 50% or more in the previously noted enlargement of the liver or spleen, an increase by 50% or more in the numbers of blood lymphocytes with at least 5000 lymphocytes per microliter, transformation to a more aggressive histology, or occurrence of cytopenia attributable to chronic lymphocytic leukaemia. Participants who were alive and had not progressed at the time of analysis or if a progression event occurred after extensive lost-to-follow-up time were censored at the date of the last visit with adequate assessment.</p> <p>7. Time to Next Therapy [ Time Frame: From randomization up to about 49 months ]</p> <p>Time to next therapy is defined as the time from randomization until the start of the next-line of treatment.</p> <p>8. Number of Participants With Improvement in ECOG Performance Status of 0 or 1 [ Time Frame: Baseline, Cycle 3 Day 1, 1 month Follow-up ]</p> <p>The ECOG performance status scales and criteria are used by doctors and researchers to assess how a participant's disease is progressing, how the disease affects the daily living, and determines appropriate treatment and prognosis. Grade 0, fully active, able to carry on all pre-disease performance without restriction. Grade 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. Grade 2, ambulatory and capable of all selfcare, but unable to carry out any work activities; up and about more than 50% of waking hours. Grade 3, capable of only limited selfcare; confined to bed or chair more than 50% of waking hours. Grade 4, completely disabled;</p>
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	<p>cannot carry on any selfcare; totally confined to bed or chair. Grade 5, dead. Participants with an ECOG performance status of 0 or 1 are shown</p> <p>9. Number of Participants With Improvement in Constitutional Symptoms (CS) [ Time Frame: Baseline, Cycle 3 Day 1, and 1 month Follow-up ]</p> <p>Assessment for the presence of the following symptoms were performed at Screening, Day 1 of each treatment cycle and at every Follow-up visit: night sweats (without signs of infection); unexplained, unintentional weight loss <math>\geq 10\%</math> within the previous 6 months; recurrent, unexplained fever of greater than 38 degrees celsius or 100.5 degrees fahrenheit for 2 weeks; and extreme fatigue. The best response refers to overall best response in terms of CR, CRi, PR or nPR. Data are presented for constitutional response= yes and no.</p> <p>10. Number of Participants With a Human Anti-human Antibody (HAHA) Positive Result [ Time Frame: Baseline, Cycle 4 Day 1, 1 Month Follow-up, and 6 Month Follow-up ]</p> <p>Serum samples for analysis of HAHA were collected at Baseline (Screening), Cycle 4 Day 1 (after 3 months of treatment), and at 1 month and 6 months post last dose of ofatumumab. All samples were first tested in a screening step; positive samples from the screening were further evaluated in a confirmation test. The confirmed positive samples were reported as HAHA-positive and further evaluated in the titration test to obtain a titer of HAHA.</p> <p>11. Cmax and Ctough of Ofatumumab [ Time Frame: Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, and Cycle 9 Day 1 ]</p> <p>Blood samples were collected to assess the plasma concentration of ofatumumab. Maximum concentration (Cmax) and observed drug concentration prior to the next dose (Ctough) were determined. Blood samples were collected from participants who received ofatumumab plus chlorambucil at pre-dose and 0.5 hours after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on the duration of treatment.</p> <p>12. Total Plasma Clearance (CL) of Ofatumumab [ Time Frame: Cycle 4 Day 1 ]</p> <p>Plasma clearance is defined as the plasma volume which is totally cleared of drug per unit of time. Blood samples were collected from participants who received ofatumumab plus</p>
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chlorambucil at pre-dose and 0.5 hours after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to the ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on duration of treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.

13. AUC(0-tau) of Ofatumumab [ Time Frame: Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 4 Day 1 ]

Area under the concentration time curve over the dosing interval [AUC(0-tau)] is a measure of drug exposure over time. AUC(0-tau) is defined as the area under the ofatumumab plasma concentration-time curve from dosing to time tau, where tau is the length of the dosing interval of ofatumumab. For estimation of AUC(0-tau), blood samples were collected from participants who received ofatumumab plus chlorambucil at pre-dose and 0.5 hours after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to the ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on duration of treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.

14. Volume of Distribution at Steady State (V<sub>ss</sub>) of Ofatumumab [ Time Frame: Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 4 Day 1 ]

Volume of distribution at steady state (V<sub>ss</sub>) is defined as the distribution of a drug between plasma and the rest of the body at steady state. Blood samples were collected from participants who received ofatumumab plus chlorambucil at predose and 0.5 hour after the end of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on the duration of the treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.

15. Plasma Half Life (t<sub>1/2</sub>) of Ofatumumab [ Time Frame: Cycle 4 Day 1 ]

The terminal half-life (t<sub>1/2</sub>) of ofatumumab is defined as the time required for the plasma concentration of ofatumumab to reach half of its original concentration. Blood samples were collected to assess the plasma half-life of ofatumumab. Blood samples were collected from participants who received ofatumumab plus chlorambucil pre-dose and 0.5 hours after the end



	<p>of the ofatumumab infusion at treatment Cycle 1 and Cycle 4 (Days 1, 8, and 85). In addition, pre-dose samples were collected prior to ofatumumab administration at Cycles 2, 3, 5, 6, 9 and 12 (Days 29, 57, 113, 141, 225 and 309), depending on the duration of the treatment. Samples were also collected during clinic visits on Day 15 (during Cycle 1) and Day 43 (during Cycle 2) and at 1, 3, and 6 months post-treatment.</p> <p>16. Dose-normalized Cmax of Chlorambucil and Phenylacetic Acid Mustard (PAAM) [ Time Frame: Cycle 3 Day 1 ]</p> <p>Blood samples for the determination of serum concentrations of chlorambucil and its metabolite PAAM were collected from participants in a substudy on Cycle 3 Day 1. The maximum observed concentration (Cmax) of chlorambucil and PAAM normalized to the administered dose was determined as a measure of exposure and compared to reference data from a prior study (LEUA1001) [No NCT number available for this study; GlaxoSmithKline Document Number RM1998/00449/00]</p> <p>17. Dose-normalized AUC(0-6) and AUC(0-inf) of Chlorambucil and Dose-normalized AUC(0-6) of Phenylacetic Acid Mustard (PAAM) [ Time Frame: Cycle 3 Day 1 ]</p> <p>Blood samples for the determination of serum concentrations of chlorambucil and its metabolite PAAM were collected from participants in a substudy on Cycle 3 Day 1. The area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-inf]) and over 6 hours (AUC[0-6]) of chlorambucil and AUC(0-6) of PAAM normalized to the administered dose was determined as a measure of exposure and compared to reference data from a prior study (LEUA1001) [No NCT number available for this study; GlaxoSmithKline Document Number RM1998/00449/00]</p> <p>18. Change From Baseline in Health Related Quality of Life (HRQOL) [ Time Frame: Baseline, Cycle 4 day 1, cycle 7 day 1, 1 month follow-up, 6 month follow-up, 12 month follow-up ]</p> <p>HRQOL was assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTCQLQC30), Chronic Lymphocytic Leukemia module (EORTC QLQ-CLL16), EuorQoL-Five Dimension (EQ-5D), and HCQ. Period (P)1 (Day 85, Day 169, Day 253) and P2 (scheduled follow-up (FU) and withdrawal visits) analysis were considered. Baseline (BL) for P1 was defined as score from screening visit and BL for P2 was defined as the last on-treatment score. The 2 principal QoL outcomes were pre-specified as the Global Health scale (GHS/QOL) of the EORTC QLQ-C30 and fatigue scale of the EORTC QLQ-CLL16. For EORTC QLQ-</p>
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C30,GHS/QoL, the possible scale range was 0-100 (with 100 being 'best') and a positive difference from BL is indicative of better functioning (range -100 to +100). For the EORTC QLQ-CLL16 fatigue scale, the possible scale range was 0-100 (with 0 being 'best') and a negative difference from BL represents an improvement in fatigue (range -100 to +100).

19. Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE)

[ Time Frame: From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy, up to approximately 111 months. ] An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Refer to the general Adverse AE/SAE module for a complete list of AEs and SAEs.

20. Number of Participants With AEs and SAEs of Maximum Severity of Grade 3 or Higher

[ Time Frame: From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy, up to approximately 111 months. ] An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Refer to the general Adverse AE/SAE module for a complete list of AEs and SAEs. Maximum severity grades were evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (1, mild; 2, moderate; 3, severe; 4, life-threatening/disabling; 5, death).

21. Number of Participants With at Least One Grade 3/Grade 4 Myelosuppression (Anemia, Neutropenia, and Thrombocytopenia)

[ Time Frame: From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy, up to approximately 111 months. Participants with a Grade 3 or Grade 4 myelosuppression (anemia, neutropenia, and thrombocytopenia) are presented by treatment cycle. Myelosuppression is defined as the decrease in the ability of the bone marrow to produce blood cells. AEs were graded according to NCI common terminology criteria for adverse events (CTCAE) grade, version 3.0 (1, mild; 2, moderate; 3, severe; 4, life-threatening/disabling; 5, death).

**Table A2 Main study characteristics COMPLEMENT1**

	<p>22. Number of Participants With Autoimmune Hemolytic Anaemia (AIHA) Disease [ Time Frame: From the first dose of study medication to 60 days after the last dose of study medication and until follow-up for SAEs unless initiation of subsequent anti-CLL therapy, up to approximately 111 months. AIHA is a disease where the body's immune system fails to recognize red blood cells as "self" and begins destroying these red blood cells. The number of participants diagnosed with AIHA are presented.</p> <p>23. Number of Participants Who Received no Transfusion or at Least One Transfusion During the Study [ Time Frame: From start of treatment to the last study visit/withdrawal visit (Median follow-up approximately 28.9 months) Participants who received no transfusion and at least one transfusion during the study are presented. Participants who took any blood products are counted in this table.</p> <p>24. Mean Change From Baseline in the Immunoglobulin (Ig) Antibodies IgA, IgG, and IgM [ Time Frame: From start of treatment up to 30 days after last treatment ]Immunoglobulins, or antibodies, are large proteins used by the immune system to identify and neutralize foreign particles such as bacteria and viruses. Their normal blood levels indicate proper immune status. Low levels indicate immuno-suppression. IgA, IgG, and IgM were measured in the blood samples of the participants. Baseline IgA, IgG, and IgM values are the last pre-dose assessment values performed on Cycle 1 Day 1. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.</p>
<b>Method of analysis</b>	<p>For our analysis of endpoints, progression-free survival was summarized in Kaplan-Meier curves and compared treatment groups with a stratified log-rank test adjusted for randomisation stratification factors.</p> <p>Progression-free survival was censored for patients with two or more missing visits or start of alternative chronic lymphocytic leukaemia treatment before progression or death. Secondary time-to-event endpoint analyses was done with Kaplan-Meier estimates. Response rates were compared between the treatment groups with use of a Mantel-Haenszel test that was adjusted for stratification factors.</p>

**Table A2 Main study characteristics COMPLEMENT1**

<b>Subgroup analyses</b>	For the demographic and efficacy analyses, we included all patients enrolled and grouped patients by treatment to which the patient was randomised to, irrespective of actual treatment received (intention-to-treat analysis).
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**Table A2 Main study characteristics CAM307**

<b>Table A2 Main study characteristics CAM307</b>	
<b>Trial name</b>	A Phase III Study to Evaluate the Efficacy and Safety of Front-Line Therapy With Alemtuzumab (Campath, MabCampath) vs Chlorambucil in Patients With Progressive B-Cell Chronic Lymphocytic Leukemia
<b>NCT number</b>	NCT00046683
<b>Objective</b>	To evaluate the efficacy and safety of intravenous alemtuzumab compared with chlorambucil in first-line treatment of chronic lymphocytic leukemia (CLL).
<b>Publications – title, author, journal, year</b>	Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. <i>Journal of clinical oncology : official journal of the American Society of Clinical Oncology</i> . 2007;25(35):5616-23. [23]
<b>Study type and design</b>	Patients received alemtuzumab (30 mg three times per week, for up to 12 weeks) or chlorambucil (40 mg/m <sup>2</sup> every 28 days, for up to 12 months). Phase III, open-label, multicenter, randomized, comparative study of Campath versus chlorambucil as front line therapy in patients with progressive B-Cell Lymphocytic Leukemia (B-CLL). Eligible patients must have previously untreated, Rai stage I-IV disease, and be experiencing progression of their B-CLL requiring treatment. Patients who meet all eligibility criteria may be randomized on a 1:1 basis to receive either Campath or chlorambucil. An estimated 284 patients (142 per treatment arm) from approximately 40 or more investigational sites will be randomized to one of the two treatment arms.
<b>Follow-up time</b>	24.6 months

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Histopathologically confirmed diagnosis of B-CLL with CD5, CD19, or CD23 positive clone.</li> <li>• Rai Stage I through IV disease with evidence of progression as evidenced by the presence of one or more of the following: 1. Disease-related B symptoms (fever of greater than 38 celsius (100.5 F) for greater than or equal to 2 weeks without evidence of infection, night sweats without evidence of infection, weight loss &gt;10% within previous 6 months. 2. Evidence of progression marrow failure as manifested by: a. decrease in hemoglobin to &lt;11g/dL or b. decrease in platelet count to &lt;100x10 to the ninth/L within the previous 6 months or c. decrease in absolute neutrophil count (ANC) to &lt;1.0x10 to the ninth/L within the previous 6 months. 3. Progressive splenomegaly to &gt;2 cm below the left costal margin or other organomegaly with progressive increase over 2 consecutive clinic visits greater than or equal to 2 weeks apart. 4. Progressive lymphadenopathy with at least 5 sites of involvement with either two nodes at least 2cm in longest diameter or one node greater than or equal to 5cm in longest diameter with progressive increase over 2 consecutive visits greater than or equal to weeks apart. 5. Progressive lymphocytes with an increase of &gt;50% over a 2-month period, or an anticipated doubling time of less than 6 months.</li> <li>• Received no previous chemotherapy for B-CLL.</li> <li>• Life expectancy of at least 12 weeks.</li> <li>• WHO performance status of 0, 1, or 2.</li> <li>• Serum creatinine less or equal to 2.0 times the institutional upper limit of normal (ULN) value.</li> <li>• Adequate liver function as indicated by a total bilirubin, AST, and ALT less or equal to 2 times the institutional ULN value, unless directly attributable to the disease.</li> <li>• Female patients with childbearing potential must have a negative serum pregnancy test within 2 weeks prior to randomization. Male and female patients must agree to use an effective contraceptive method while on study treatment, if appropriate, and for a minimum of 6 months after study therapy.</li> <li>• Signed, written informed consent.</li> <li>• 18 years of age or older.</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• ANC less than 500 million per liter or platelet count less than 10 billion per liter.</li> <li>• Medical condition requiring chronic use of oral corticosteroids.</li> <li>• Autoimmune thrombocytopenia.</li> <li>• Previous bone marrow transplant.</li> </ul>
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**Table A2 Main study characteristics CAM307**

	<ul style="list-style-type: none"> <li>• Use of investigational agents within previous 30 days.</li> <li>• Positive for HIV.</li> <li>• Past history of anaphylaxis following exposure to rat or mouse-derived complementary determining region (CDR) grafted humanized monoclonal antibodies.</li> <li>• Active infection.</li> <li>• Serious cardiac or pulmonary disease that could interfere with their ability to participate in the study.</li> <li>• Recent documented (with in 2 years) of active tuberculosis (TB), current active TB, or currently receiving anti-tuberculosis medication.</li> <li>• Active secondary malignancy.</li> <li>• Central nervous system involvement with CLL.</li> <li>• Positive quantitative CMV by PCR assay (using the laboratory normal ranges).</li> <li>• A diagnosis of mantle cell lymphoma.</li> <li>• Other severe, concurrent diseases or mental disorders.</li> <li>• Pregnant or lactating women.</li> </ul>
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**Table A2 Main study characteristics CAM307**

<b>Intervention</b>	<p>Patients were randomly assigned to alemtuzumab or chlorambucil . Treatment arm assignment was balanced by study center, Raistage (I to II v III/IV), performance status (0 to 1 v 2), age (&lt;_65 v_65 years), sex and maximum lymph node size (none palpable or_5 v_5 cm).</p> <p><b>Alemtuzumab</b> was escalated daily (3, 10, and 30 mg) until tolerated at an intravenous (IV) dose of 30 mg over 2 hours. Subsequently, patients received alemtuzumab 30 mg three times a week for no more than 12 weeks, including the dose-escalation phase. Premedication for alemtuzumab consisted of diphenhydramine and acetaminophen or paracetamol orally (PO) 30 minutes before dosing, with optional IV meperidine or hydrocortisone when warranted. During the first month of treatment, patients received allopurinol days_1 to 13. Patients received prophylactic trimethoprim/ sulfamethoxazole DS and famciclovir (or equivalents) during therapy and for at least 2 months after the last alemtuzumab dose or until CD4_ counts were 200 cells/_L or higher.</p> <p>Patients in the <b>chlorambucil</b> arm received 40 mg/m<sup>2</sup>POq 28 days for no more than 12 cycles with allopurinol PO days_1 to 8 for the first three cycles.</p> <p>Prophylactic antibiotics were not required.</p>
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**Table A2 Main study characteristics CAM307**

Baseline characteristics	Table 1. Baseline Patient Characteristics and Cytogenetics			
	Acalabrutinib (n = 142)		Chlorambucil (n = 142)	
Characteristic	No. of Patients	%	No. of Patients	%
Age, years				
Median	59.0		60.0	
Range	25-86		26-92	
Sex				
Male	106	71.1	107	72.2
Female	43	29.9	41	27.7
Rai stage group (IRSP)				
0 or missing*	6	4.0	3	2.0
I-II	83	62.4	96	64.9
III-IV	50	33.6	49	33.1
Time since initial diagnosis to random assignment, months				
Median	9.38		7.86	
Range	-0.5-167.41		0.1-224.8	
Maximum lymph node size, cm				
< 5	107	71.8	104	70.3
≥ 5	33	22.1	34	22.0
No enlarged lymph nodes	8	5.4	10	6.8
Palpable hepatomegaly	43	29.9	37	25.2
Palpable splenomegaly	53	35.6	56	37.8
WHO performance status				
0-1	143		140	
2	5	3.4	5	3.4
Night sweats	64	42.0	69	46.6
Weight loss > 10%	9	6.0	16	10.8
Fever	9	5.7	2	1.4
Hierarchical cytogenetic subgroups†				
17p11.1 (p53)	11	7.7	10	7.2
Any del 11q	23	16.1	31	22.3
Trisomy 12 (no 11p or 17p del)	24	16.8	10	7.2
Normal	26	17.5	26	18.7
Solo del 12q	23	13.1	34	24.5
Various other combinations	27	18.9	29	20.1

Abbreviations: IRSP, independent response review panel; CLL, chronic lymphocytic leukemia; del, deletion.  
 \*These patients were assessed as Rai stage 0 (n = 5) and unconfirmed for Rai stage CLL diagnosis (n = 4) by the IRSP.  
 †One patient was inadvertently randomly assigned prior to completion of CLL diagnosis.  
 ‡According to the hierarchical Döhner et al<sup>3</sup> method, n = 143 for the acalabrutinib group and n = 139 for the chlorambucil group.

**Primary and secondary endpoints**

The primary end point was progression-free survival (PFS). Secondary end points included overall response rate (ORR), complete response (CR), time to alternative therapy, safety, and overall survival

**Method of analysis**

The planned sample size was 284 patients (142 per arm) to allow detection of a 50% increase in median PFS in either arm (hazard ratio[HR] = 0.667), with 80% power and .05 (two-sided). A preplanned interim analysis was performed after 95 progressions, and the final analysis was performed at a significance level of .048 using the O'Brien-Fleming methodology to ensure the overall significance level of alpha = 0.05. All randomly assigned patients were included in the efficacy analysis per the intent-to-treat principle.



**Table A2 Main study characteristics CAM307**

<b>Subgroup analyses</b>	<p>All time-to-event distributions were calculated using Kaplan-Meier method, reported in months, and compared using stratified (Rai stage I to II v III to IV) log-rank test. HRs were calculated using Cox model stratified for Rai stage.</p> <p>Response rates were compared using X<sup>2</sup> test or Fisher's exact test, as appropriate. PFS was defined from the date of random assignment to first objective documentation of disease progression or death, whichever was earlier. Time to alternative treatment was defined from date of random assignment to the date of first alternative treatment or death resulting from any cause.</p> <p>A total of 191 disease progression or death events in the alemtuzumabarmand in the chlorambucil arm) were used for the final analysis of PFS.</p>
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**Table A2 Main study characteristics CLL11**
**Table A2 Main study characteristics CLL11**

<b>Trial name</b>	An Open-label, Multi-center, Three Arm Randomized Study to Investigate the Safety and Efficacy on Progression-free Survival of RO5072759 + Chlorambucil (GClb) Compared to Rituximab + Chlorambucil (RClb) or Chlorambucil (Clb) Alone in Previously Untreated CLL Patients With Comorbidities.
<b>NCT number</b>	NCT01010061
<b>Objective</b>	To investigated the benefit of the type 2, glycoengineered antibody Obinutuzumab (also known as GA101) as compared with that of rituximab, each combined with chlorambucil, in patients with previously untreated CLL and coexisting conditions
<b>Publications – title, author, journal, year</b>	Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. The New England journal of medicine. 2014;370(12):1101-10. [24]

**Table A2 Main study characteristics CLL11**

<b>Study type and design</b>	<p>This open-label, randomized, 3-arm study will evaluate the efficacy and safety of obinutuzumab (RO5072759) in combination with chlorambucil as compared to rituximab plus chlorambucil or chlorambucil alone in patients with previously untreated chronic lymphocytic leukemia (CLL). Patients will be randomized 2:2:1 to receive a maximum of six 28-day cycles of either RO5072759 (1000 mg intravenous (iv) infusion, on days 1, 8 and 15 of cycle 1 and day 1 of cycles 2-6) plus chlorambucil (0.5 mg/kg orally, days 1 and 15 of cycles 1-6), or rituximab (iv infusion day 1, 375 mg/m<sup>2</sup> cycle 1, 500 mg/m<sup>2</sup> cycles 2-6) plus chlorambucil, or chlorambucil alone. Anticipated time on study treatment is &gt;6 months and follow-up for disease-progression and safety will be at least 5 years. In the US, this trial is sponsored/managed by Genentech.</p>
<b>Follow-up time</b>	<p>The primary analyses for the comparisons of the obinutuzumab–chlorambucil group and the rituximab–chlorambucil group with the chlorambucil-alone group were conducted in July 2012 and August 2012, respectively, and were updated in May 2013, when the primary analysis of the comparison between the obinutuzumab–chlorambucil group and the rituximab–chlorambucil group was performed. The efficacy boundary was crossed at a preplanned interim analysis. All results presented are from the analyses of May 2013</p>

**Table A2 Main study characteristics CLL11**

<b>Population (inclusion and exclusion criteria)</b>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Adults <math>\geq 18</math> years</li> <li>• Documented Cluster of Differentiation Antigen 20 (CD20) + B-Cell Chronic Lymphocytic Lymphoma (B-CLL)</li> <li>• Previously untreated Chronic Lymphocytic Leukemia (CLL) requiring treatment according to the National Cancer Institute (NCI) criteria</li> <li>• Total Cumulative Illness Rating Scale (CIRS) <math>&gt; 6</math> and/or creatinine clearance <math>&lt; 70</math> ml/min</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Prior CLL therapy</li> <li>• Transformation of CLL to aggressive Non-Hodgkin's Lymphoma (NHL) (Richter's transformation)</li> <li>• History of other malignancy unless the malignancy has been in remission without treatment for <math>\geq 2</math> years prior to enrolment, and except for carcinoma in situ of the cervix, basal or squamous cell skin cancer, surgically treated low-grade prostate cancer, or ductal carcinoma in situ (DCIS) of the breast treated with lymphectomy alone</li> <li>• Positive hepatitis serology (HBV, HCV) or positive HIV or Human T Cell Leukemia Virus (HTLV) testing</li> <li>• Patients with active infection requiring systemic treatment</li> </ul>
<b>Intervention</b>	<p>Experimental: obinutuzumab + chlorambucil (GClb)</p> <p>Participants received 1000 mg obinutuzumab intravenous (IV) infusion, on Days 1 [first infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 in Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles).</p> <p>Active Comparator: rituximab + chlorambucil (RCIb)</p> <p>Participants received 375 mg/m<sup>2</sup> rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m<sup>2</sup> IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).</p>

**Table A2 Main study characteristics CLL11**
**Baseline characteristics**

**Table 1. Baseline Characteristics, Intention-to-Treat Population.<sup>a</sup>**

Characteristic	Obinutuzumab-Chlorambucil vs. Chlorambucil Alone		Rituximab-Chlorambucil vs. Chlorambucil Alone		Obinutuzumab-Chlorambucil vs. Rituximab-Chlorambucil	
	Obinutuzumab-Chlorambucil (N=238)	Chlorambucil Alone (N=118)	Rituximab-Chlorambucil (N=233)	Chlorambucil Alone (N=118)	Obinutuzumab-Chlorambucil (N=333)	Rituximab-Chlorambucil (N=330)
Age — yr						
Median	74	72	73	72	74	73
Range	39–88	43–87	40–90	43–87	39–89	40–90
Cumulative Illness Rating Scale†						
Score — median (range)	8 (1–20)	8 (0–18)	8 (0–18)	8 (0–18)	8 (0–22)	8 (0–18)
Affected organ system or disorder — no. (%)						
Cardiac	120 (50)	62 (53)	111 (48)	62 (53)	171 (51)	165 (50)
Hypertension	168 (71)	88 (75)	155 (67)	88 (75)	228 (68)	225 (68)
Vascular	91 (38)	34 (29)	68 (29)	34 (29)	114 (34)	95 (29)
Respiratory	85 (36)	43 (36)	85 (36)	43 (36)	121 (36)	127 (38)
Eye, ear, throat, or larynx	86 (36)	53 (45)	102 (44)	53 (45)	131 (39)	141 (43)
Upper gastrointestinal	80 (34)	39 (33)	70 (30)	39 (33)	104 (31)	102 (31)
Lower gastrointestinal	50 (21)	25 (21)	38 (16)	25 (21)	68 (20)	55 (17)
Hepatic or biliary	39 (16)	21 (18)	40 (17)	21 (18)	56 (17)	66 (20)
Renal	104 (44)	45 (38)	111 (48)	45 (38)	137 (41)	145 (44)
Genitourinary	83 (35)	44 (37)	76 (33)	44 (37)	114 (34)	114 (35)
Musculoskeletal	106 (45)	45 (38)	96 (41)	45 (38)	148 (44)	135 (41)
Endocrine or metabolic	127 (53)	64 (54)	117 (50)	64 (54)	183 (55)	161 (49)
Neurologic	46 (19)	33 (28)	48 (21)	33 (28)	72 (22)	72 (22)
Psychiatric	39 (16)	11 (9)	36 (15)	11 (9)	59 (18)	49 (15)
Median calculated creatinine clearance — ml/min	61.4	63.8	61.8	63.8	62.5	62.6
Binet stage — no. (%)						
A	55 (23)	24 (20)	49 (21)	24 (20)	74 (22)	74 (22)
B	98 (41)	50 (42)	100 (43)	50 (42)	142 (43)	135 (41)
C	85 (36)	44 (37)	84 (36)	44 (37)	117 (35)	121 (37)
Unmutated IGHV — no./total no. (%)	129/210 (61)	58/99 (59)	126/204 (62)	58/100 (58)	188/305 (62)	182/298 (61)
del(17p) on FISH — no./total no. (%)	16/203 (8)	10/96 (10)	9/196 (5)	10/97 (10)	22/295 (7)	20/287 (7)

<sup>a</sup> The intention-to-treat population included all patients randomly assigned to a treatment group. There were no significant differences in the listed baseline characteristics between groups in the three pairwise comparisons. Pairwise comparisons of the three treatment groups were performed in different study cohorts and therefore are always displayed side by side. FISH denotes fluorescence in situ hybridization, and IGHV, the immunoglobulin heavy-chain variable-region gene.

<sup>†</sup> Scores on the Cumulative Illness Rating Scale range from 0 to 36, with higher scores indicating worse health status.

<p><b>Primary and secondary endpoints</b></p>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression-free Survival (PFS) [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ] PFS was defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. Progressive disease (PD) required at least one of the following: <math>\geq 50\%</math> increase in the absolute number of lymphocytes, appearance of new palpable lymph nodes (<math>&gt;15</math> mm in longest diameter) or any new extra nodal lesion, <math>\geq 50\%</math> increase in the longest diameter of any previous site of clinically significant lymphadenopathy, <math>\geq 50\%</math> increase in the enlargement of the liver and/or spleen, Transformation to a more aggressive histology or After treatment, the progression of any cytopenia (a decrease of hemoglobin levels <math>&gt;20</math> g/L or <math>&lt;10</math> g/dL or a decrease of platelet counts <math>&gt;50\%</math> or <math>&lt;100 \times 10^9/L</math> or by a decrease of neutrophil counts <math>&gt;50\%</math> or <math>&lt;1.0 \times 10^9/L</math>).</li> <li>2. Percentage of Participants With Progression Free Survival Events [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ]</li> </ol> <p style="padding-left: 40px;">Percentage of Participants with Progression Free Survival Events: disease progression, relapse, or death.</p> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression Free Survival Based on Independent Review Committee (IRC) Data [ Time Frame: Randomization to clinical cutoff date of 9 May 2013 (median observation 22.8 months) ] PFS was defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by Independent Review Committee. Progressive disease required at least one of the following: <math>\geq 50\%</math> increase in the absolute number of lymphocytes, appearance of new palpable lymph nodes (<math>&gt;15</math> mm in longest diameter) or any new extra nodal lesion, <math>\geq 50\%</math> increase in the longest diameter of any previous site of clinically significant lymphadenopathy, <math>\geq 50\%</math> increase in the enlargement of the liver and/or spleen, Transformation to a more aggressive histology or After treatment, the progression of any cytopenia (a decrease of hemoglobin levels <math>&gt;20</math> g/L or <math>&lt;10</math> g/dL or a decrease of platelet counts <math>&gt;50\%</math> or <math>&lt;100 \times 10^9/L</math> or by a decrease of neutrophil counts <math>&gt;50\%</math> or <math>&lt;1.0 \times 10^9/L</math>).</li> <li>2. Percentage of Participants With Progression Free Survival Events Based on Independent Review Committee (IRC) Data [ Time Frame: Randomization to clinical cutoff date of 9 May 2013 (median observation 22.8 months) ] Percentage of Participants with Progression Free Survival Events: progression, relapse, or death from any cause as assessed by an Independent Review Committee.</li> <li>3. Percentage of Participants With End of Treatment Response (EOTR) [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ] EOTR was the first response assessment 56 days from the last dose according to the International</li> </ol>
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	<p>Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidelines. CR required: Peripheral blood lymphocytes below <math>4 \times 10^9/L</math>, Absence of significant lymphadenopathy, No hepatomegaly, No splenomegaly, Absence of disease, Blood counts above the following values (Neutrophils <math>&gt;1.5 \times 10^9/L</math>, Platelets <math>&gt;100 \times 10^9/L</math>, Hemoglobin <math>&gt;11g/dL</math>) and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. PR required the following for at least 2 months from end of treatment: <math>\geq 50\%</math> decrease in peripheral blood lymphocyte count from the pre-treatment value AND Either a <math>\geq 50\%</math> reduction in lymphadenopathy OR <math>\geq 50\%</math> reduction of liver enlargement OR <math>\geq 50\%</math> reduction of spleen enlargement PLUS at least one of the following: Neutrophils <math>&gt;1.5 \times 10^9/</math> or <math>\geq 50\%</math> increase, Platelets <math>&gt;100 \times 10^9/L</math> or <math>\geq 50\%</math> increase, Hemoglobin 11 g/dL or <math>\geq 50\%</math> increase.</p> <p>4. Percentage of Participants With Best Overall Response [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ]Best overall response according to IWCLL guidelines was defined as the percentage of patients with CR, CRi,PR or nPR. CR required all of the following: Peripheral blood lymphocytes below <math>4 \times 10^9/L</math>, Absence of significant lymphadenopathy, No hepatomegaly, No splenomegaly, Absence of disease, Blood counts above the following values (Neutrophils <math>&gt;1.5 \times 10^9/L</math>, Platelets <math>&gt;100 \times 10^9/L</math>, Hemoglobin <math>&gt;11g/dL</math>) and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. PR required the following for at least 2 months from end of treatment: <math>\geq 50\%</math> decrease in peripheral blood lymphocyte count from the pre-treatment value AND Either a <math>\geq 50\%</math> reduction in lymphadenopathy OR <math>\geq 50\%</math> reduction of liver enlargement OR <math>\geq 50\%</math> reduction of spleen enlargement PLUS at least one of the following: Neutrophils <math>&gt;1.5 \times 10^9/</math> or <math>\geq 50\%</math> increase, Platelets <math>&gt;100 \times 10^9/L</math> or <math>\geq 50\%</math> increase, Hemoglobin 11 g/dL or <math>\geq 50\%</math> increase.</p> <p>5. Event Free Survival [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ]Event-free survival (EFS) was defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-leukemic therapy. Progressive disease as per IWCLL criteria required at least one of the following: <math>\geq 50\%</math> increase in the absolute number of lymphocytes, appearance of new palpable lymph nodes (<math>&gt;15</math> mm in longest diameter) or any new extra nodal lesion, <math>\geq 50\%</math> increase in the longest diameter of any previous site of clinically significant lymphadenopathy, <math>\geq 50\%</math> increase in the enlargement of the liver and/or spleen, Transformation to a more aggressive histology or After treatment, the progression of any cytopenia (a decrease of hemoglobin levels <math>&gt;20</math> g/L or <math>&lt;10</math> g/dL or a decrease of platelet counts <math>&gt;50\%</math> or <math>&lt;100 \times 10^9/L</math> or by a decrease of neutrophil counts <math>&gt;50\%</math> or <math>&lt;1.0 \times 10^9/L</math>).</p> <p>6. Overall Survival [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ]Overall Survival (OS) was defined as the time between the date of randomization and the date of death due to any cause.</p>
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	<p>7. Duration of Response [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ]Duration of Response was defined as the date the response [either Complete Response (CR) or Partial Response (PR)] was first recorded until the date of Disease Progression or death due to any cause. Response was assessed according IWCLL guidelines.</p> <p>8. Percentage of Participants With Molecular Remission at the End of Treatment [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ]Molecular remission was defined as a minimal residual disease (MRD)-negative result at the end of treatment (assessment that occurred between 56 days and 6 months of last treatment). Molecular remission was assessed for all patients using a blood sample. Additionally, a bone marrow sample was obtained from patients whom the investigator assumed to have a complete response, consistent with the IWCLL guidelines. A combined analysis of blood and bone marrow results was conducted. A patient was considered MRD negative if result was less than 1 chronic lymphocytic leukemia (CLL) cell in 10000 leukocytes (MRD value &lt; 0.0001) based on the method of allele specific polymerase chain reaction (ASO-PCR)</p> <p>9. Time to Re-Treatment/New-antileukemic Therapy [ Time Frame: Randomization to clinical cutoff date of 10 Oct 2017 (median observation 62.5 months from randomization) ] Time to re-treatment/new anti-leukemic therapy was defined as time between the date of randomization and the date of first intake of re-treatment or new anti-leukemic therapy</p> <p>10. Pharmacokinetics of Obinutuzumab (RO5072759) in Combination With Chlorambucil (Clb) [ Time Frame: Pre- and post-dose sampling on day 1 of cycles 1-6 (Up to 26.8 months) Blood samples were collected from all patients allocated to the GClb treatment arm pre- and post-dose Day 1 of Cycles 1 to 6 and were sent to a laboratory. The concentration of obinutuzumab in serum was determined using a validated enzyme-linked immunosorbent assay (ELISA) and was reported in micrograms/milliliter (<math>\mu\text{g}/\text{mL}</math>).</p> <p>11. European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire Score [ Time Frame: Baseline and Cycle 4 Day 1 (Cy4D1) ] The EORTC Quality of Life Questionnaire QLQ-C30 was used to assess patient-reported outcomes (PRO) and symptom burden. The QLQ-C30 contains 30 items including the functional scales of physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items) and symptom scales including fatigue (3 items), nausea and vomiting (2 items), and pain (4 items) and six single item scales on dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact. Final scores are transformed such that they range from 0 - 100, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 - 10 points considered to be of minimally important difference to participants. A positive change from Baseline indicated improvement.</p>
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**Table A2 Main study characteristics CLL11**

	<p>12. European Organization for Research and Treatment of Cancer (EORTC) QLQ-CLL16 Questionnaire Score [ Time Frame: Baseline and Cycle 4 Day 1 (Cy4D1) ] EORTC Quality of Life Questionnaire (QLQ-CLL16) module was used to assess patient-reported outcomes and symptom burden. The QLQ-CLL16 module includes three multi-item scales assessing fatigue (2 items), treatment side effects and disease symptoms (8 items), infection (4 items) and two single item scales on social activities and future health worries. Final scores are transformed such that they range from 0 - 100, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 - 10 points considered to be of minimally important difference to participants. A positive change from Baseline indicated improvement.</p>
<b>Method of analysis</b>	<p>The primary analysis was a two-sided logrank test stratified according to Binet stage. The type 1 error was controlled through the closedtesting procedure (the global test was a three-group log-rank test). The comparison between the Obinutuzumab chlorambucil group and the rituximab-chlorambucil group included two interim looks at the data and an O'Brien-Fleming efficacy boundary with a Lan-DeMets alpha-spending function to adjust for multiple comparisons.</p>
<b>Subgroup analyses</b>	<p>Secondary end points were analyzed with the use of a two sided test at a 5% alpha level without adjustment for multiple comparisons.</p>



Table A2 Main study characteristics Tedeschi [25]

Table A2 Main study characteristics Tedeschi	
<b>Trial name</b>	<p>RESONATE-2 A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 versus Chlorambucil in Patients 65 Years or Older with Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.</p> <p>iLLUMINATE- A Randomized, Multi-center, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Subjects With Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma</p>
<b>NCT number</b>	NCT 01722487 + NCT02264574
<b>Objective</b>	There are no data comparing single-agent ibrutinib with obinutuzumab-containing regimens. Thus the objective was to perform a prespecified cross-trial analysis of the RESONATE-2 and iLLUMINATE studies to compare outcomes with single agent ibrutinib versus chlorambucil-obinutuzumab.
<b>Publications – title, author, journal, year</b>	Tedeschi A, Greil R, Demirkan F, Robak T, Moreno C, Barr PM, et al. A cross-trial comparison of single-agent ibrutinib versus chlorambucil-obinutuzumab in previously untreated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. <i>Haematologica</i> . 2020;105(4):e164-e8
<b>Study type and design</b>	cross-trial analysis of the RESONATE-2 and iLLUMINATE. This cross-trial analysis included all patients in the ibrutinib arm from RESONATE-2 and patients without del(17p) from iLLUMINATE, given the exclusion of patients with del(17p) from RESONATE-2.
<b>Follow-up time</b>	RESONATE-2 48.8 months and iLLUMINATE 31.3 months

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p>all patients in the ibrutinib arm from RESONATE-2 and patients without del(17p) from iLLUMINATE, given the exclusion of patients with del(17p) from RESONATE-2</p> <p><b>RESONATE-2:</b></p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> <li>1. Males or females of 65 years of age or greater. Patients between the ages of 65 and 70 years of age must have 1 or more of the following comorbidities that may preclude the use of frontline chemo-immunotherapy with fludarabine, cyclophosphamide, or rituximab:             <ul style="list-style-type: none"> <li>○ creatinine clearance &lt; 70 mL/min using the Cockcroft-Gault equation</li> <li>○ platelet count &lt; 100,000/<math>\mu</math>L or hemoglobin &lt; 10 g/dL</li> <li>○ clinically apparent autoimmune cytopenia (autoimmune hemolytic anemia or immune thrombocytopenia)</li> <li>○ ECOG performance score = 1 or 2</li> </ul> </li> <li>2. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008)</li> <li>3. Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment:             <ul style="list-style-type: none"> <li>○ Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia Massive, progressive, or symptomatic splenomegaly</li> <li>○ Massive nodes or progressive or symptomatic lymphadenopathy</li> <li>○ Progressive lymphocytosis</li> <li>○ Autoimmune hemolytic anemia and/or immune thrombocytopenia that is poorly responsive to corticosteroids or standard therapy</li> <li>○ Constitutional symptoms</li> </ul> </li> <li>4. Measurable nodal disease by computed tomography (CT)</li> <li>5. ECOG performance status of 0-2</li> <li>6. Life expectancy &gt; 4 months from randomization</li> <li>7. Adequate hematologic function, defined as absolute neutrophil count (ANC) <math>\geq</math> 1,000/<math>\mu</math>L (independent of growth factor support for at least 7 days prior to screening) and platelet count <math>\geq</math> 50,000/<math>\mu</math>L (independent of transfusion and growth factor support for at least 7 days prior to screening)</li> </ol>
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8. Adequate hepatic function, defined as serum aspartate transaminase (AST) and alanine transaminase (ALT) < 2.5 x upper limit of normal (ULN), and total bilirubin  $\leq$  1.5 x ULN
9. Adequate renal function, defined as estimated creatinine clearance  $\geq$  30 mL/min using the Cockcroft-Gault equation
10. Willingness to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers study drug for the entire study
11. Willingness of male patients, if sexually active with a female of childbearing potential, to use an effective barrier method of contraception during the study and for 3 months following the last dose of study drug
12. Ability to provide written informed consent and to understand and comply with the requirements of the study

Exclusion Criteria:

1. Known involvement of the central nervous system by lymphoma or leukemia
2. History or current evidence of Richter's transformation or prolymphocytic leukemia
3. Documentation of deletion of the short arm of chromosome 17: del(17p13.1) in more than 20% of cells examined on any pretreatment fluorescence in situ hybridization (FISH) or cytogenetic evaluation
4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura
5. Any previous treatment (chemotherapy, radiotherapy, and/or monoclonal antibodies) intended specifically to treat CLL/SLL
6. Received any immunotherapy, vaccine, or investigational drug within 4 weeks prior to randomization
7. Corticosteroid use within 1 week prior to first dose of study drug, with the exception of inhaled, topical, or other local administrations. Patients requiring systemic steroids at daily doses > 20 mg prednisone (or corticosteroid equivalent, see Appendix N), or those who are administered steroids for leukemia control or white blood cell (WBC)-count-lowering are excluded.
8. Major surgery within 4 weeks prior to randomization
9. History of prior malignancy, with the exception of the following:
  - o malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to screening and felt to be at low risk for recurrence by treating physician

	<ul style="list-style-type: none"> <li>○ adequately treated nonmelanomatous skin cancer or lentigo maligna melanoma without current evidence of disease</li> <li>○ adequately treated cervical carcinoma in situ without current evidence of disease</li> </ul> <ol style="list-style-type: none"> <li>10. Currently active, clinically significant cardiovascular disease or a history of myocardial infarction within 6 months prior to randomization</li> <li>11. Inability to swallow capsules or tablets, or disease significantly affecting gastrointestinal function</li> <li>12. Uncontrolled active systemic fungal, bacterial, viral, or other infection or requirement for intravenous (IV) antibiotics</li> <li>13. Known history of infection with human immunodeficiency virus (HIV)</li> <li>14. Serologic status reflecting active hepatitis B or C infection</li> <li>15. History of stroke or intracranial hemorrhage within 6 months prior to enrollment</li> <li>16. Current life-threatening illness, medical condition, or organ-system dysfunction that could compromise patient safety or put the study at risk</li> <li>17. Requirement for anticoagulation with warfarin</li> <li>18. Requirement for treatment with a strong CYP3A4/5 and/or CYP2D6 inhibitor</li> </ol> <p><b>ILLUMINATE:</b> Inclusion Criteria:</p> <p>Disease Related:</p> <ol style="list-style-type: none"> <li>1. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria.</li> <li>2. Age 65 yrs and older OR if less than 65 years, must have at least one of the following criteria: <ul style="list-style-type: none"> <li>○ Cumulative Illness Rating Score (CIRS) &gt;6</li> <li>○ Creatinine clearance estimated &lt;70 mL/min using Cockcroft-Gault equation.</li> <li>○ Del 17p by fluorescence in situ hybridization (FISH) or TP53 mutation by polymerase chain reaction (PCR) or Next Generation Sequencing</li> </ul> </li> <li>3. Active disease meeting at least 1 of the following IWCLL criteria for requiring treatment: <ul style="list-style-type: none"> <li>○ Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and thrombocytopenia</li> <li>○ Massive, progressive, or symptomatic splenomegaly</li> <li>○ Massive nodes (at least 10 cm longest diameter), or progressive or symptomatic lymphadenopathy.</li> </ul> </li> </ol>
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	<ul style="list-style-type: none"> <li>○ Progressive lymphocytosis with an increase of more than 50 percent over a 2-month period or a lymphocyte doubling time (LDT) of &lt;6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of &lt;30,000/<math>\mu</math>L, LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded.</li> <li>○ Autoimmune hemolytic anemia and/or immune thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.</li> <li>○ Autoimmune hemolytic anemia is defined by at least one marker of hemolysis (indirect bilirubin above the upper limit of normal (ULN) not due to liver disease, increased lactate dehydrogenase (above ULN) without alternative etiology, or increased absolute reticulocytosis (above ULN) or bone marrow erythropoiesis in the absence of bleeding AND at least one marker direct or indirect autoimmune mechanism (positive direct antiglobulin for immunoglobulin G [IgG] or C3d, cold agglutinins).</li> <li>○ Immune thrombocytopenia is defined by platelets <math>\leq</math>100,000/<math>\mu</math>L and increased megakaryocytes on the bone marrow exam.</li> <li>○ Constitutional symptoms, defined as one or more of the following disease-related symptoms or signs, documented in the patient's record prior to randomization: <ul style="list-style-type: none"> <li>○ unintentional weight loss &gt;10 percent within 6 months prior to screening.</li> <li>○ significant fatigue (inability to work or perform usual activities).</li> <li>○ fevers &gt;100.5°F or 38.0°C for 2 or more weeks prior to screening without evidence of infection.</li> <li>○ night sweats for more than 1 month prior to screening without evidence of infection.</li> </ul> </li> <li>4. Measurable nodal disease by computed tomography (CT), defined as at least 1 lymph node &gt;1.5 cm in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended. <p style="margin-left: 20px;">Laboratory</p> <ul style="list-style-type: none"> <li>5. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening and randomization.</li> <li>6. Adequate hepatic and renal function</li> <li>7. Men and women <math>\geq</math> 18 years of age.</li> </ul> </li> </ul>
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8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Exclusion Criteria:

1. Any prior treatment of CLL or SLL
2. Evidence of central nervous system (CNS) involvement with primary disease of CLL/SLL
3. History of other malignancies, except:
  - o Malignancy treated with curative intent and with no known active disease present for  $\geq 3$  years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura
5. Known or suspected history of Richter's transformation.
6. Concurrent administration of  $>20\text{mg/day}$  of prednisone within 7 days of randomization unless indicated for prophylaxis or management of allergic reactions (eg, contrast)
7. Known hypersensitivity to one or more study drugs
8. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
9. Any uncontrolled active systemic infection or an infection requiring systemic treatment that was completed  $\leq 7$  days before randomization.
10. Known bleeding disorders or hemophilia.
11. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
12. Known history of human immunodeficiency virus (HIV) or active with hepatitis B virus (HBV) or hepatitis C virus (HCV).
13. Major surgery within 4 weeks of randomization.
14. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
15. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
16. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
17. Concomitant use of warfarin or other vitamin K antagonists.

**Table A2 Main study characteristics Tedeschi**

	<ul style="list-style-type: none"> <li>18. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor.</li> <li>19. Lactating or pregnant</li> <li>20. Unwilling or unable to participate in all required study evaluations and procedures.</li> <li>21. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).</li> </ul>
<b>Intervention</b>	<p>RESONATE-2: Arm: Ibrutinib</p> <p>Ibrutinib will be supplied as hard gelatin 140-mg capsules for oral (PO) administration. Ibrutinib 420 mg (3 x 140-mg capsules) is administered orally once daily. The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to patients in bottles at each visit.</p> <p>iLLUMINATE: Arm: CLB + OB Chlorambucil (CLB) given orally at a dose of 0.5 mg/kg body weight up to a total of 6 cycles on Days 1 and 15 of each cycle or until disease progression or unacceptable toxicity.</p> <p>Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until disease progression or unacceptable toxicity.</p>

**Table A2 Main study characteristics Tedeschi**

Baseline characteristics	Ibrutinib n=136	Chlorambucil-obinutuzumab n=62
	Age, years	
Median (range)	71 (45-88)	73 (48-86)
≥70, n (%)	86 (71)	63 (64)
Time since initial diagnosis, months, median (range)	30.5 (1-204)	42.9 (3-489)
Rai stage II/IV at screening, n (%)	68 (50)	49 (50)
ECOG performance status, n (%)		
0	41 (45)	44 (45)
1-2	75 (55)	54 (55)
Bulky disease (lymph node ≥5 cm), n (%)	34 (40)	36 (37)
High-risk features (unmutated IGHV, del(11q), and/or TP53 mutation), n (%)	74/35 (57)	57 (58)
Unmutated IGHV, n/N (%)	58/98 (51)	45/90 (50)
del(11q), n/N (%)	29/30 (22)	22/90 (24)
TP53 mutation, n/N (%)	12/24 (19)	5/92 (5)
Any cytopenia, n (%)	72 (53)	51 (52)
Anemia (hemoglobin <11 g/dL)	31 (38)	40 (41)
Thrombocytopenia (platelets <100×10 <sup>9</sup> /L)	35 (26)	21 (21)
Neutropenia (absolute neutrophil count <1.5×10 <sup>9</sup> /L)	10 (7)	1 (1)

\*% patients with available data. ECOG Eastern Cooperative Oncology Group.

**Primary and secondary endpoints**

Primary analysis was investigator-assessed PFS of patients treated with single-agent ibrutinib in RESONATE-2 versus PFS of patients treated with chlorambucil-obinutuzumab in iLLUMINATE.

Secondary analyses included investigator-assessed PFS in genomic high-risk patients [those with TP53 mutation, del(11q), and/or unmutated IGHV], and medical resource utilization during the first 6 months on study treatment

analysis comprised investigator assessed overall response rate, including complete response; development of lymphocytosis [absolute lymphocyte count (ALC) increased 50% from baseline to  $\geq 5 \times 10^9/L$ ], duration and resolution of lymphocytosis  $=$ (ALC decreased to baseline level or lower or  $< 5 \times 10^9/L$ ); and time to normalization of ALC ( $< 4 \times 10^9/L$ ).

**Method of analysis**

The analysis of PFS will be performed in the ITT population to compare PFS (as assessed by the IRC) for the 2 treatment arms using a stratified log-rank test based on the 2 randomization stratification factors: Rai stage and ECOG performance score. Distribution of PFS will be summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% confidence interval (CI). The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. A sensitivity analysis of PFS will be conducted based on the investigator assessment.

Survival rate at landmark points will be summarized for each treatment group using Kaplan-Meier point estimates in the primary analysis



**Table A2 Main study characteristics Tedeschi**

<b>Subgroup analyses</b>	The hazard ratio (ibrutinib/chlorambucil) with its 95% CI will be calculated based on an unstratified Cox regression model for each subgroup and be presented by a forest
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**Table A2 Main study characteristics CLL-10**

<b>Table A2 Main study characteristics CLL-10</b>	
<b>Trial name</b>	<b>CLL-10</b> Phase III Trial of Combined Immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Bendamustine and Rituximab (BR) in Patients With Previously Untreated Chronic Lymphocytic Leukaemia
<b>NCT number</b>	NCT00769522
<b>Objective</b>	<ul style="list-style-type: none"> <li>• To compare the therapeutic efficacy of fludarabine phosphate, cyclophosphamide, and rituximab vs bendamustine hydrochloride and rituximab in patients with previously untreated B-cell chronic lymphocytic leukemia.</li> <li>• To compare the incidence of major side effects (e.g., myelosuppression) associated with these regimens in these patients.</li> <li>• To compare the rate of infections and secondary neoplasias in patients treated with these regimens.</li> </ul>
<b>Publications – title, author, journal, year</b>	Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. <i>The Lancet Oncology</i> . 2016;17(7):928-42 [26]
<b>Study type and design</b>	<p>Randomized open label Phase III non-inferiority Trial of Combined Immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Bendamustine and Rituximab (BR) in Patients With Previously Untreated Chronic Lymphocytic Leukaemia</p> <p><b>Arm I:</b> Patients receive fludarabine phosphate IV and cyclophosphamide IV on days 1-3. Patients also receive rituximab IV on day 0 of course 1 and on day 1 of courses 2-6. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.</p>

**Table A2 Main study characteristics CLL-10**

**Arm II:** Patients receive bendamustine hydrochloride IV on days 1 and 2. Patients also receive rituximab as in arm I. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.

Patients completed quality of life questionnaires (EORTC-C30 and EURO-QOL) at baseline and then at 12, 24, 36, 48, and 60 months.

After completion of study therapy, patients are followed every 3 months for 2 years, every 6 months for 3 years, and then once a year thereafter

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**Follow-up time**

 37,1months
 

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**Population (inclusion and exclusion criteria)**
**DISEASE CHARACTERISTICS:**

- Confirmed diagnosis of B-cell chronic lymphocytic leukemia (CLL) meeting 1 of the following criteria:
- Binet stage C disease or stage B or A disease requiring treatment
- Binet stage B or A disease meeting  $\geq 1$  of the following:
  - B-symptoms (e.g., night sweats, weight loss  $\geq 10\%$  within the past 6 months, fevers  $> 38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$  for  $\geq 2$  weeks without evidence of infection) or constitutional symptoms (e.g., fatigue)
  - Progressive lymphocytosis, defined as peripheral lymphocyte count  $> 5 \times 10^9/\text{L}$  (i.e.,  $> 50\%$  increase over a 2-month period or doubling of peripheral blood lymphocyte count  $< 6$  months)
  - Evidence of progressive marrow failure as manifested by the development/worsening of anemia and/or thrombocytopenia
  - Massive, progressive, or painful splenomegaly or hypersplenism
  - Massive lymph nodes or lymph node clusters ( $> 10$  cm in longest diameter) or progressive or symptomatic lymphadenopathy
- No 17p deletion by FISH
- No aggressive B-cell cancer, such as Richter syndrome

**PATIENT CHARACTERISTICS:**

- WHO performance status 0-2
  - Life expectancy  $\geq 6$  months
  - Total bilirubin  $\leq 2$  times upper limit of normal (ULN) (unless directly attributable to CLL)
  - AST and ALT  $\leq 2$  times ULN (unless directly attributable to CLL)
-

**Table A2 Main study characteristics CLL-10**

- Creatinine clearance  $\geq 70$  mL/min (creatinine clearance is to be calculated only in patients with serum creatinine  $\geq 1.1$  mg/dL)
  - Not pregnant or nursing
  - Negative pregnancy test
  - Fertile patients must use effective contraception during and for  $\geq 6$  months after completion of study therapy
  - Hepatitis B and C negative
  - HIV negative
  - CIRS score  $> 6$  or a single score of 4 for one organ category
  - No active secondary malignancy requiring treatment, except basal cell carcinoma or malignant tumor curatively treated by surgery, or successfully treated secondary malignancies in complete remission  $> 5$  years prior to enrollment
  - No history of anaphylaxis following exposure to monoclonal antibodies
  - No active bacterial, viral, or fungal infection
  - No medical condition requiring prolonged use of oral corticosteroids (i.e.,  $> 1$  month)
  - No cerebral dysfunction or legal incapacity
  - No circumstance that would preclude completion of the study or the required follow-up
- PRIOR CONCURRENT THERAPY:**
- No prior CLL specific-chemotherapy, radiotherapy, and/or immunotherapy
  - Prednisolone administered immediately prior to initiation of study therapy allowed for very high lymphocyte counts
  - No concurrent participation in another clinical trial

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**Intervention**
**Arm A**

*Biological: Rituximab*

cycle 1: 375 mg/m<sup>2</sup> i.v., day 0, q28d

cycle 2-6: 500 mg/m<sup>2</sup> i.v., day 1, q28d

*Drug: Cyclophosphamide*

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**Table A2 Main study characteristics CLL-10**

cycle 1-6: 250 mg/m<sup>2</sup> i.v., days 1-3, q28d

*Drug: Fludarabine*

cycle 1-6: 25 mg/m<sup>2</sup> i.v., days 1-3, q28d

**Arm B**

*Biological: Rituximab*

cycle 1: 375 mg/m<sup>2</sup> i.v., day 0, q28d

cycle 2-6: 500 mg/m<sup>2</sup> i.v., day 1, q28d

*Drug: Bendamustine*

cycle 1-6: 90mg/m<sup>2</sup> i.v., day 1-2, q28d

**Baseline characteristics**

	Fludarabine, cyclophosphamide and rituximab (n=272)	Bendamustine and rituximab (n=270)
Age (years)	62.7 (52.0-67.0)	63.0 (54.0-68.0)
-Males	86 (31%)	108 (40%)
-Females	186 (69%)	162 (60%)
Sex		
Males	211 (78%)	202 (75%)
Females	81 (29%)	72 (27%)
Median time from diagnosis to study entry (months)	33.0 (4.0-53.0)	24.0 (0.0-50.1)
WHO stage		
A	53 (19%)	52 (19%)
B	205 (75%)	207 (76%)
C	14 (5%)	11 (4%)
Rai stage		
I	752 (1%)	102 (4%)
II	302 (11%)	330 (12%)
III	867 (31%)	842 (31%)
IV	447 (16%)	345 (13%)
V	552 (20%)	650 (24%)
CLL-I performance status		
0	1802 (64%)	1777 (64%)
I	912 (33%)	882 (32%)
≥ 2	405 (15%)	421 (15%)
Disruptions present	136 (5%)	132 (5%)
Median CRP	2.0 (0.0-10)	2.0 (0.0-10)
Total CRP (g/l)	240 (80%)	254 (94%)
Presence of treated CLL (category: n)	51 (19%)	149 (55%)
Median hemoglobin (g/dL)	11.7 (7.7-16.6)	11.6 (7.6-16.1)
Median creatinine (μmol/L)	100 (27.7-174)	100 (27.0-174)
Bilirubin (μmol/L)	8.0 (2.1-13)	8.0 (2.1-13)
Alkaline phosphatase (U/L)	68 (3.0)	63 (2.3)
LDH (U/L)	183 (5.0)	182 (5.0)
Urea (mmol/L)	5.5 (2.7-7.9)	5.5 (2.7-7.9)

Median hemoglobin (g/L) or (g/dL), but at least 1 (30) were not assessed at all (n=101). Median creatinine (μmol/L) or (mg/dL) and bilirubin (μmol/L) or (mg/dL) were not assessed in 10 patients because they were not measurable due to laboratory error. Many observations were missing due to missing data points. CLL-I performance status: CLL-I=0, CLL-II=1, CLL-III=2, CLL-IV=3, CLL-V=4. CLL-I=0, CLL-II=1, CLL-III=2, CLL-IV=3, CLL-V=4.

**Table 3 Baseline characteristics of the eligible patients**

**Primary and secondary endpoints**

**Table A2 Main study characteristics CLL-10**
**Primary Outcome Measures :**

- Progression-free survival rate after 24 months (Time Frame: 2008-2015)
- estimated time point when 198 needed events for the final analysis(PD or deaths) have occurred

**Secondary Outcome Measures:**

- Minimal residual disease, complete response rates, and partial response rates [ Time Frame: 2008-2015 ] done within the final analysis
- Duration of remission [ Time Frame: 2008-2015 ]done within the final analysis
- Event-free survival [ Time Frame: 2008-2015 ]done within the final analysis
- Overall survival [ Time Frame: 2008-2015 ]done within the final analysis
- Overall response rate [ Time Frame: 2008-2015 ]done within the final analysis
- Response rates in and survival times in biological subgroups [ Time Frame: 2008-2015 ] done within the final analysis
- Toxicity rates [ Time Frame: 2008-2015 ] done within the final analysis
- Quality of life [ Time Frame: 2008-2015 ] done within the final analysis

Standard safety analysis [ Time Frame: 2008-2015 ] done within the final analysis

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**Method of analysis**

The primary endpoint of progression-free survival was used to calculate the sample size of the study. The noninferiority hypothesis of bendamustine and rituximab compared with fl udarabine, cyclophosphamide, and rituximab was tested by assessing whether the 90,4% CI of the hazard ratio (HR) excluded a predefined non-inferiority margin including the adjustment for one interim analysis using the O'Brien and Fleming method. it was assumed that treatment with fl udarabine, cyclophosphamide, and rituximab would lead to a 75% progression-free survival at 2 years. We aimed to show that the 2-year progression free survival with bendamustine and rituximab was not 67,5% or less with a corresponding non-inferiority margin of 1,388 for the HR. 198 progression-free survival events were required to have 80% power (alpha was 0,048, one sided). 511 patients needed to be enrolled with these assumptions. Time-to-event endpoints including 95% CIs were estimated according to the Kaplan-Meier method and survival curves were compared using two-sided nonstratified log-rank tests. For comparison of the treatment groups, Fisher's exact test or Pearson's  $\chi^2$  test (categorical variables) or Wilcoxon rank-sum test (continuous variables) were used. All analyses were done in the intention-to-treat population.

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**Subgroup analyses**

Exploratory post hoc subgroup analyses for progression-free survival and response were done considering the factors age, Binet stage, cytogenetic categories, IGHV mutation status, and sex. Methods included two-sided non-stratified log-

**Acalabrutinib\_endeligansøgning\_16112021**

**Table A2 Main study characteristics CLL-10**

rank tests and the calculation of HRs including 95% CIs. Additionally, the interaction with study treatment was explored for each factor; a term for the interaction between the factor and the study treatment was included in a Cox regression

**Table A2 Main study characteristics MABLE**
**Table A2 Main study characteristics MABLE**

<b>Trial name</b>	<b>MABLE-A Randomized Study to Assess the Effect on Response Rate of MabThera (Rituximab) Added to a Standard Chemotherapy, Bendamustine or Chlorambucil, in Patients With Chronic Lymphocytic Leukemia</b>
<b>NCT number</b>	NCT01056510
<b>Objective</b>	This randomized, open-label, parallel group study will assess the effect on response rate and the safety of MabThera added to either bendamustine or chlorambucil in patients with chronic lymphocytic leukemia.
<b>Publications – title, author, journal, year</b>	Michallet AS, Aktan M, Hiddemann W, Ilhan O, Johansson P, Laribi K, et al. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. <i>Haematologica</i> . 2018;103(4):698-706 [28]
<b>Study type and design</b>	Randomized, open-label Phase IV
<b>Follow-up time</b>	23,5 months
<b>Population (inclusion and exclusion criteria)</b>	<p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• adult patients, <math>\geq 18</math> years of age</li> <li>• chronic lymphocytic leukemia</li> <li>• active CLL with progressive Binet stage B or C</li> <li>• ineligible for treatment with fludarabine</li> <li>• for second line patients, only pretreatment with rituximab and/or chlorambucil is allowed</li> </ul>

**Table A2 Main study characteristics MABLE**

- EOCG performance status  $\geq 2$

**Exclusion Criteria:**

- patients who have relapsed within <12 months of first dose of prior rituximab or chlorambucil first-line therapy
- previous or planned stem cell transplantation
- radioimmunotherapy within 6 months prior to starting study treatment
- transformation to aggressive B-cell malignancy
- any other concurrent anti-cancer therapy, or glucocorticoid  $\geq 20$ mg daily prednisolone or equivalent

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**Intervention**

Arm A: rug: bendamustine

90mg/m<sup>2</sup> (first-line) or 70mg/m<sup>2</sup> (second-line) iv, days 1 and 2 every 4 weeks, cycles 1-6

Drug: rituximab [MabThera/Rituxan]

375mg/m<sup>2</sup> iv day 1 of cycle 1, followed by 500mg/m<sup>2</sup> iv every 4 weeks cycles 2-6

Arm B: Drug: chlorambucil

10mg/m<sup>2</sup> po days 1-7 every 4 weeks, for up to 12 cycles

Drug: rituximab [MabThera/Rituxan]

375mg/m<sup>2</sup> iv day 1 of cycle 1, followed by 500mg/m<sup>2</sup> iv every 4 weeks cycles 2-6

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**Table A2 Main study characteristics MABLE**
**Baseline characteristics**

**Table 1. Characteristics corresponding to baseline analysis (N=200)**

	N (%)	n (%)
<b>Age (years)</b>		
Median (range)	72 (50-90)	72 (50-90)
< 70 years of age	95 (47.5)	95 (47.5)
≥ 70 years of age	105 (52.5)	105 (52.5)
<b>Sex</b>		
Male	115 (57.5)	115 (57.5)
Female	85 (42.5)	85 (42.5)
<b>International Prognostic Index</b>		
Median (range)	1 (0-3)	1 (0-3)
<b>WHO stage (N=200)</b>		
I	145 (72.5)	145 (72.5)
II	25 (12.5)	25 (12.5)
III	30 (15.0)	30 (15.0)
IV	0 (0.0)	0 (0.0)
V	0 (0.0)	0 (0.0)
VI	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
<b>Median hemoglobin (g/dL)</b>	12.0 (8.0-16.0)	12.0 (8.0-16.0)
<b>Median platelets (x10<sup>9</sup>/L)</b>	150 (30-400)	150 (30-400)
<b>Median total lymphocyte count (x10<sup>9</sup>/L)</b>	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Median	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Range	0.5-12.0	0.5-12.0
Unknown	0 (0.0)	0 (0.0)
<b>Median total lymphocyte count (x10<sup>9</sup>/L)</b>	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Median	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Range	0.5-12.0	0.5-12.0
Unknown	0 (0.0)	0 (0.0)
<b>Median total lymphocyte count (x10<sup>9</sup>/L)</b>	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Median	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Range	0.5-12.0	0.5-12.0
Unknown	0 (0.0)	0 (0.0)
<b>Median total lymphocyte count (x10<sup>9</sup>/L)</b>	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Median	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Range	0.5-12.0	0.5-12.0
Unknown	0 (0.0)	0 (0.0)
<b>Median total lymphocyte count (x10<sup>9</sup>/L)</b>	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Median	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Range	0.5-12.0	0.5-12.0
Unknown	0 (0.0)	0 (0.0)
<b>Median total lymphocyte count (x10<sup>9</sup>/L)</b>	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Median	4.0 (0.5-12.0)	4.0 (0.5-12.0)
Range	0.5-12.0	0.5-12.0
Unknown	0 (0.0)	0 (0.0)

**Primary and secondary endpoints**
**Primary Outcome Measures :**

1. Percentage of Participants Achieving Confirmed Complete Response (CR) According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Guidelines in the First-Line Subpopulation After 6 Cycles of Therapy [ Time Frame: At least 2 months after completion of therapy (up to 32 weeks) ]

The definition of confirmed CR required all of the following criteria as assessed at least 2 months after completion of therapy: peripheral blood lymphocytes less than (<) 4 times 10<sup>9</sup> cells per liter (cells/L); absence of significant lymphadenopathy, hepatomegaly, or splenomegaly due to chronic lymphocytic leukemia (CLL) involvement; absence of constitutional symptoms; normal complete blood count (CBC) without need for transfusion or exogenous growth factors, as exhibited by neutrophils at least (>/=) 1.5 times 10<sup>9</sup> cells/L, platelets greater than (>) 100 times 10<sup>9</sup> cells/L, and hemoglobin > 11.0 grams per deciliter (g/dL); normocellular bone marrow (BM) aspirate with < 30 percent (%) lymphocytes; absence of lymphoid nodules; and BM biopsy without CLL activity. The percentage of participants achieving confirmed CR was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed, multiplied by 100.



**Table A2 Main study characteristics MABLE**
**Secondary Outcome Measures :**

1. Percentage of Participants Achieving Confirmed CR According to IWCLL 2008 Guidelines in the Pooled Population After 6 Cycles of Therapy [ Time Frame: At least 2 months after completion of therapy (up to 32 weeks) ]

The definition of confirmed CR required all of the following criteria as assessed at least 2 months after completion of therapy: peripheral blood lymphocytes  $< 4 \times 10^9$  cells/L; absence of significant lymphadenopathy, hepatomegaly, or splenomegaly due to CLL involvement; absence of constitutional symptoms; normal CBC without need for transfusion or exogenous growth factors, as exhibited by neutrophils  $\geq 1.5 \times 10^9$  cells/L, platelets  $> 100 \times 10^9$  cells/L, and hemoglobin  $> 11.0$  g/dL; normocellular BM aspirate with  $< 30\%$  lymphocytes; absence of lymphoid nodules; and BM biopsy without CLL activity. The percentage of participants achieving confirmed CR was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed, multiplied by 100.

2. Percentage of Participants Achieving Confirmed CR According to IWCLL 2008 Guidelines in the Second-Line Subpopulation After 6 Cycles of Therapy [ Time Frame: At least 2 months after completion of therapy (up to 32 weeks) ]

The definition of confirmed CR required all of the following criteria as assessed at least 2 months after completion of therapy: peripheral blood lymphocytes  $< 4 \times 10^9$  cells/L; absence of significant lymphadenopathy, hepatomegaly, or splenomegaly due to CLL involvement; absence of constitutional symptoms; normal CBC without need for transfusion or exogenous growth factors, as exhibited by neutrophils  $\geq 1.5 \times 10^9$  cells/L, platelets  $> 100 \times 10^9$  cells/L, and hemoglobin  $> 11.0$  g/dL; normocellular BM aspirate with  $< 30\%$  lymphocytes; absence of lymphoid nodules; and BM biopsy without CLL activity. The percentage of participants achieving confirmed CR was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed, multiplied by 100.

3. Percentage of Participants Achieving a Best Overall Response of CR, CR With Incomplete Marrow Recovery (CRi), Partial Response (PR), or Nodular PR (nPR) in the First-Line Subpopulation [ Time Frame: After 3 and 6 treatment cycles and from Baseline to the end-of-treatment (EOT) visit, completed within 10 days before cutoff for data collection ]

The criteria for CR are identified in previous outcome measure(s). Those fulfilling CR criteria but who have persistent anemia, thrombocytopenia, or neutropenia were considered CRi. The definition of PR required that the following be documented for minimum 2 months:  $\geq 50\%$  decrease in peripheral blood lymphocytes from Baseline; reduction in lymphadenopathy;  $\geq 50\%$  reduction in spleen or liver

**Table A2 Main study characteristics MABLE**

enlargement; and CBC with one of the following without need for transfusion or exogenous growth factors: polymorphonuclear leukocytes  $\geq 1.5$  times  $10^9$  cells/L, platelets  $> 100$  times  $10^9$  cells/L or  $\geq 50\%$  improvement from Baseline, or hemoglobin  $> 11.0$  g/dL or  $\geq 50\%$  improvement from Baseline. Participants with lymphoid nodules who otherwise met CR criteria were considered nPR. The percentage of participants achieving each level of response was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed, multiplied by 100.

4. Percentage of Participants by Disease Response Category in the First-Line Subpopulation [ Time Frame: After 6 treatment cycles and at the confirmation of response assessment at least 12 weeks later (up to 36 weeks) ]

The criteria for CR, CRi, PR, and nPR are identified in previous outcome measure(s). PD was defined by at least one of the following: the presence of lymphadenopathy; an increase in the previously noted enlargement of the liver or spleen by  $\geq 50\%$  or the de novo appearance of hepatomegaly or splenomegaly; an increase in the number of blood lymphocytes by  $\geq 50\%$  with  $\geq 5000$  B-cells per microliter (B-cells/mcL); transformation to a more aggressive histology; or occurrence of cytopenia attributable to CLL. Participants not achieving a CR or PR, and who did not exhibit PD, were considered to have stable disease (SD). The percentage of participants achieving each level of response was calculated as the number of participants meeting the above criteria divided by the number of participants analyzed. The rows below are labeled first by the level of response at the end of 6 cycles (C6), then by level of response at the confirmation assessment.

5. Percentage of Participants Experiencing PD or Death in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for PD are identified in previous outcome measure(s). The percentage of participants experiencing PD or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100.

6. Progression-Free Survival (PFS) in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for PD are identified in previous outcome measure(s). PFS was defined as the time from the first dose of trial treatment to the first documentation of PD or death, whichever occurred first. PFS was calculated in months as [first event date minus first dose date plus 1] divided by 30.44.

**Table A2 Main study characteristics MABLE**

7. Percentage of Participants With Tumor Response of CR or CRi Experiencing PD or Death in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for CR, CRi, and PD are identified in previous outcome measure(s). The percentage of participants experiencing PD or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100.

8. Disease-Free Survival (DFS) in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for CR, CRi, and PD are identified in previous outcome measure(s). DFS was defined as the time from the first assessment of CR or CRi to the first documentation of PD or death, whichever occurred first. DFS was calculated in months as [first event date minus first assessment date of CR/CRi plus 1] divided by 30.44.

9. Percentage of Participants Experiencing PD, Documented Intake of New Leukemia Therapy, or Death in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for PD are identified in previous outcome measure(s). The percentage of participants experiencing PD, intake of new (post-trial) leukemia therapy, or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100.

10. Event-Free Survival (EFS) in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for PD and SD are identified in previous outcome measure(s). EFS was defined as the time from the first dose of trial treatment to the first documentation of PD, the beginning of new treatment for any hematologic malignancy, or death from any cause. Those with SD were considered event-free. EFS was calculated in months as [first event date minus first dose date plus 1] divided by 30.44.

11. Percentage of Participants With Documented Intake of New Leukemia Therapy in the First-Line Subpopulation [ Time Frame: During Cycles 1 to 6 (both treatment arms), Cycles 7 to 12 (Rituximab + Chlorambucil arm), after

**Table A2 Main study characteristics MABLE**

an additional 8 weeks, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The percentage of participants with documented intake of new (post-trial) leukemia therapy was calculated as the number of participants with new therapy divided by the number of participants analyzed, multiplied by 100.

12. Time to Next Leukemia Treatment (TNLT) in the First-Line Subpopulation [ Time Frame: During Cycles 1 to 6 (both treatment arms), Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

TNLT was defined as the time from the first dose of trial treatment to the first documentation of any new leukemia treatment. TNLT was calculated in months as [first new treatment date minus first dose date plus 1] divided by 30.44.

13. Percentage of Participants With Tumor Response of CR, CRi, PR, or nPR Experiencing PD or Death in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for CR, CRi, PR, nPR, and PD are identified in previous outcome measure(s). The percentage of participants experiencing PD or death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100.

14. Duration of Response in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

The criteria for CR, CRi, PR, nPR, and PD are identified in previous outcome measure(s). Duration of response was defined as the time from the first assessment of CR, CRi, PR, or nPR to the first documentation of PD or death, whichever occurred first. Duration of response was calculated in months as [first event date minus first assessment date of CR/CRi/PR/nPR plus 1] divided by 30.44.

15. Percentage of Participants Experiencing Death in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

**Table A2 Main study characteristics MABLE**

The percentage of participants experiencing death was calculated as the number of participants with event divided by the number of participants analyzed, multiplied by 100.

16. Overall Survival (OS) in the First-Line Subpopulation [ Time Frame: End of Cycles 3 and 6 (both treatment arms), end of Cycles 7 to 12 (Rituximab + Chlorambucil arm), after an additional 8 weeks as confirmation of response, then every 3 months for 1 year, then every 6 months until study cutoff (up to 4.5 years) ]

OS was defined as the time from recorded diagnosis to death from any cause. OS was calculated in months as [death date or last-known alive date minus diagnosis date plus 1] divided by 30.44.

17. Percentage of Participants Achieving Molecular Response in the First-Line Subpopulation [ Time Frame: Up to 4 months after the last treatment cycle (up to 40 weeks) ]

Molecular response was defined as negative minimal residual disease (MRD) during study treatment or within 4 months after the end of treatment. Negative MRD was defined as a proportion of malignant B-cells in normal B-cells  $< 0.0001$ . The percentage of participants achieving molecular response was calculated as the number of participants with negative MRD divided by the number of participants analyzed.

18. Number of Participants With Positive and Negative Outcome for MRD in the First-Line Subpopulation [ Time Frame: After 6 treatment cycles (up to 24 weeks) ]

Negative MRD was defined as a proportion of malignant B-cells in normal B-cells  $< 0.0001$ , and positive MRD was defined as a proportion of malignant B-cells in normal B-cells  $\geq 0.0001$ .

19. Proportion of Malignant B-cells in Normal B-cells Among Participants With a Positive Outcome for MRD in the First-Line Subpopulation [ Time Frame: After 6 treatment cycles (up to 24 weeks) ]

The proportion of malignant B-cells in normal B-cells was quantitatively determined, and was calculated as the number of malignant B-cells divided by the number of normal B-cells observed.

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**Method of analysis**

Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). The safety population included all randomized patients who received treatment.

For 1L patients, the between-arm difference in response rates was tested using a one-sided continuity-corrected  $\chi^2$  test. A two sided continuity-corrected  $\chi^2$  test assessed between-arm differences in overall response rates (ORRs) and molecular responses.

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**Table A2 Main study characteristics MABLE**

	PFS and OS were summarized by Kaplan–Meier estimates and compared <i>via</i> the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the Cox proportional hazard model, with and without baseline Binet stage as a covariate.
<b>Subgroup analyses</b>	An exploratory logistic regression analysis assessed the influence of baseline covariates (Binet stage, IgVH mutational status, 17p/11q deletion, and Eastern Cooperative Oncology Group performance status) on treatment outcome. When adjusting for covariates, the odds ratio for treatment was estimated and the <i>P</i> -value of the Wald test was derived. Disease response and safety data were summarized using descriptive statistics.

**Table A2 Main study characteristics iLLUMINATE**

Table A2 Main study characteristics iLLUMINATE	
<b>Trial name</b>	iLLUMINATE- A Randomized, Multi-center, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Subjects With Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
<b>NCT number</b>	NCT02264574
<b>Objective</b>	To investigate the efficacy of the combination of ibrutinib plus obinutuzumab with chlorambucil plus obinutuzumab in first-line chronic lymphocytic leukaemia or small lymphocytic lymphoma.
<b>Publications – title, author, journal, year</b>	Moreno C. et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia: Lancet Oncol 2019;20:43-56. [29]
<b>Study type and design</b>	A multicentre, randomised, open-label, phase 3 trial done at 74 academic and community hospitals. In patients with previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma, either aged 65 years or older or younger than 65 years with coexisting conditions. Patients were randomly assigned (1:1) using a blocked randomisation schedule, stratified by Eastern Cooperative Oncology Group performance status and cytogenetics, to receive ibrutinib plus obinutuzumab (oral ibrutinib [420 mg once daily continuously] combined with intravenous obinutuzumab [100 mg on day 1, 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 of cycle 1 and on day 1 of subsequent 28-day cycles, for a total of six cycles]) or chlorambucil plus obinutuzumab (oral chlorambucil [0.5 mg/kg bodyweight on days 1 and 15 of each 28-day cycle for six cycles] combined with the same obinutuzumab regimen).

Table A2 Main study characteristics iLLUMINATE

<b>Follow-up time</b>	Between Oct 6, 2014, and Oct 12, 2015, 229 patients were enrolled and randomly assigned to receive ibrutinib plus obinutuzumab (n=113) or chlorambucil plus obinutuzumab (n=116). Assuming a median progression-free survival duration of 27 months for patients in the chlorambucil plus obinutuzumab group, 94 events of disease progression or death would provide 80% power to detect a hazard ratio (HR) of 0.55 with a two-sided statistical significance level of 5%. With an estimated accrual rate of 18 patients per month, approximately 212 eligible patients were to be enrolled to observe 94 events of disease progression or death over approximately 36 months. median follow-up of 31.3 months (IQR 29.4–33.2)
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<p><b>Population (inclusion and exclusion criteria)</b></p>	<p><b>Inclusion Criteria:</b></p> <p>Disease related:</p> <ol style="list-style-type: none"> <li>1. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria.</li> <li>2. Age 65 yrs and older OR if less than 65 years, must have at least one of the following criteria: <ul style="list-style-type: none"> <li>✓ Cumulative Illness Rating Score (CIRS) &gt;6</li> <li>✓ Creatinine clearance estimated &lt;70 mL/min using Cockcroft-Gault equation.</li> <li>✓ Del 17p by fluorescence in situ hybridization (FISH) or TP53 mutation by polymerase chain reaction (PCR) or Next Generation Sequencing</li> </ul> </li> <li>3. Active disease meeting at least 1 of the following IWCLL criteria for requiring treatment: <ul style="list-style-type: none"> <li>✓ Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and thrombocytopenia</li> <li>✓ Massive, progressive, or symptomatic splenomegaly</li> <li>✓ Massive nodes (at least 10 cm longest diameter), or progressive or symptomatic lymphadenopathy.</li> <li>✓ Progressive lymphocytosis with an increase of more than 50 percent over a 2-month period or a lymphocyte doubling time (LDT) of &lt;6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of &lt;30,000/<math>\mu</math>L, LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded.</li> <li>✓ Autoimmune hemolytic anemia and/or immune thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.</li> <li>✓ Autoimmune hemolytic anemia is defined by at least one marker of hemolysis (indirect bilirubin above the upper limit of normal (ULN) not due to liver disease, increased lactate dehydrogenase (above ULN) without alternative etiology, or increased absolute reticulocytosis (above ULN) or bone marrow erythropoiesis in the absence of bleeding AND at least one marker direct or indirect autoimmune mechanism (positive direct antiglobulin for immunoglobulin G [IgG] or C3d, cold agglutinins).</li> <li>✓ Immune thrombocytopenia is defined by platelets <math>\leq</math>100,000/<math>\mu</math>L and increased megakaryocytes on the bone marrow exam.</li> <li>✓ Constitutional symptoms, defined as one or more of the following disease-related symptoms or signs, documented in the patient's record prior to randomization: <ul style="list-style-type: none"> <li>✓ unintentional weight loss &gt;10 percent within 6 months prior to screening.</li> <li>✓ significant fatigue (inability to work or perform usual activities).</li> </ul> </li> </ul> </li> </ol>
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	<ul style="list-style-type: none"> <li>✓ fevers &gt;100.5°F or 38.0°C for 2 or more weeks prior to screening without evidence of infection.</li> <li>✓ night sweats for more than 1 month prior to screening without evidence of infection.</li> </ul> <p>4. Measurable nodal disease by computed tomography (CT), defined as at least 1 lymph node &gt;1.5 cm in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended.</p> <p>Laboratory</p> <ul style="list-style-type: none"> <li>5. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening and randomization.</li> <li>6. Adequate hepatic and renal function</li> <li>7. Men and women ≥ 18 years of age.</li> <li>8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>1. Any prior treatment of CLL or SLL</li> <li>2. Evidence of central nervous system (CNS) involvement with primary disease of CLL/SLL</li> <li>3. History of other malignancies, except:             <ul style="list-style-type: none"> <li>○ Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.</li> </ul> </li> <li>4. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura</li> <li>5. Known or suspected history of Richter's transformation.</li> <li>6. Concurrent administration of &gt;20mg/day of prednisone within 7 days of randomization unless indicated for prophylaxis or management of allergic reactions (eg, contrast)</li> <li>7. Known hypersensitivity to one or more study drugs</li> <li>8. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.</li> <li>9. Any uncontrolled active systemic infection or an infection requiring systemic treatment that was completed ≤ 7 days before randomization.</li> <li>10. Known bleeding disorders or hemophilia.</li> <li>11. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.</li> <li>12. Known history of human immunodeficiency virus (HIV) or active with hepatitis B virus (HBV) or hepatitis C virus (HCV).</li> </ul>
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**Table A2 Main study characteristics iLLUMINATE**

	<ol style="list-style-type: none"> <li>13. Major surgery within 4 weeks of randomization.</li> <li>14. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.</li> <li>15. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.</li> <li>16. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.</li> <li>17. Concomitant use of warfarin or other vitamin K antagonists.</li> <li>18. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor.</li> <li>19. Lactating or pregnant</li> <li>20. Unwilling or unable to participate in all required study evaluations and procedures.</li> </ol> <p>Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).</p>
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Table A2 Main study characteristics iLLUMINATE

**Intervention**

## ▶ Arm A: IBR + OB

Ibrutinib (IBR) given orally at a dose of 420 mg/day until progressive disease or unacceptable toxicity. Intravenous obinutuzumab (OB) given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until progressive disease or unacceptable toxicity.

Interventions:

- ✓ Drug: Ibrutinib
- ✓ Drug: Obinutuzumab

## ▶ Arm B: CLB + OB

Chlorambucil (CLB) given orally at a dose of 0.5 mg/kg body weight up to a total of 6 cycles on Days 1 and 15 of each cycle or until disease progression or unacceptable toxicity.

Intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles or until disease progression or unacceptable toxicity.

**Baseline characteristics**

[https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(18\)30788-5/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30788-5/fulltext)

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<p><b>Primary and secondary endpoints</b></p>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Primary Analysis: Progression Free Survival (PFS) Based on Independent Review Committee (IRC) Assessment - Kaplan Meier Landmark Estimates at Month 30 [ Time Frame: Month 30 (Median follow-up time was 31.3 months at the time of the primary analysis [data cutoff date: 26 March 2018]). ]</li> <li>2. Final Analysis: PFS Based on Investigator Assessment - Kaplan Meier Landmark Estimates at Month 48 [ Time Frame: Month 48 (Median follow-up time was 44.6 months at the time of the final analysis [data cutoff date: 17 October 2019]).</li> </ol> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Primary Analysis: PFS in High-Risk Sub-Population (del17p/TP53 Mutation/Del 11q) Based on IRC Assessment - Kaplan Meier Landmark Estimates at Month 30 [ Time Frame: Month 30 (Median follow-up time was 31.3 months at the time of the primary analysis [data cutoff date: 26 March 2018]). ]</li> <li>2. Primary Analysis: Rate of Sustained Hemoglobin Improvement [ Time Frame: Median follow-up time was 31.3 months at the time of the primary analysis (data cutoff date: 26 March 2018). ]</li> <li>3. Primary Analysis: Rate of Minimal Residual Disease (MRD)-Negative Response [ Time Frame: Median follow-up time was 31.3 months at the time of the primary analysis (data cutoff date: 26 March 2018). ]</li> <li>4. Primary Analysis: Overall Response Rate (ORR) Based on IRC Assessment [ Time Frame: Median follow-up time was 31.3 months at the time of the primary analysis (data cutoff date: 26 March 2018). ]</li> <li>5. Primary Analysis: Overall Survival (OS) - Kaplan Meier Landmark Estimates at Month 30 [ Time Frame: Month 30 (Median follow-up time was 31.3 months at the time of the primary analysis [data cutoff date: 26 March 2018]). ]</li> <li>6. Primary Analysis: Rate of Grade <math>\geq</math> 3 or Serious Infusion-Related Reaction (IRR) Adverse Events [ Time Frame: Median follow-up time was 31.3 months at the time of the primary analysis (data cutoff date: 26 March 2018). ]</li> <li>7. Primary Analysis: Rate of Sustained Platelet Improvement [ Time Frame: Median follow-up time was 31.3 months at the time of the primary analysis (data cutoff date: 26 March 2018). ]</li> <li>8. Primary Analysis: Rate of Clinically Meaningful Improvement in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EuroQol Five-Dimension (EQ-5D-5L) [ Time Frame: Median follow-up time was 31.3 months at the time of the primary analysis (data cutoff date: 26 March 2018). ]</li> <li>9. Final Analysis: PFS in High-Risk Population (del17p/TP53 Mutation/Del 11q/Unmutated Immunoglobulin Heavy Chain Variable Region [IGHV]) Based on Investigator Assessment - Kaplan Meier Landmark Estimates at Month 48 [ Time Frame: Month 48 (Median follow-up time was 44.6 months at the time of the final analysis [data cutoff date: 17 October 2019]). ]</li> <li>10. Final Analysis: Rate of Sustained Hemoglobin Improvement [ Time Frame: Median follow-up time was 44.6 months at the time of the final analysis (data cutoff date: 17 October 2019). ]</li> </ol>
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**Table A2 Main study characteristics iLLUMINATE**

	<p>11. Final Analysis: Rate of Minimal Residual Disease (MRD)-Negative Response [ Time Frame: Median follow-up time was 44.6 months at the time of the final analysis (data cutoff date: 17 October 2019). ]</p> <p>12. Final Analysis: ORR Based on Investigator Assessment [ Time Frame: Median follow-up time was 44.6 months at the time of the final analysis (data cutoff date: 17 October 2019). ]</p> <p>13. Final Analysis: Overall Survival (OS) - Kaplan Meier Landmark Estimates at Month 48 [ Time Frame: Month 48 (Median follow-up time was 44.6 months at the time of the final analysis [data cutoff date: 17 October 2019]). ]</p> <p>Final Analysis: Rate of Sustained Platelet Improvement [ Time Frame: Median follow-up time was 44.6 months at the time of the final analysis (data cutoff date: 17 October 2019). ]</p>
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**Method of analysis**

To preserve the studywise type I error rate, tests of primary and secondary endpoints were performed at the two-sided significance level of 0.05 based on a serial gatekeeping testing procedure prespecified in the statistical analysis plan in the following sequential hierarchy: (1) progression-free survival by IRC, (2) progression-free survival by IRC in the high-risk population, (3) sustained haemoglobin improvement, (4) undetectable MRD, (5) overall response by IRC, (6) overall survival, (7) infusion-related reactions, and (8) sustained platelet improvement. For IRC-assessed endpoints (progression-free survival and overall response), sensitivity analyses were done using investigator assessments. Time-to-event endpoints were estimated using the Kaplan-Meier method; HRs were calculated using Cox proportional hazards modelling, and treatment groups were compared using the log-rank test. Sustained haemoglobin improvement, sustained platelet improvement, undetectable MRD, overall response, and infusion-related reactions were compared between treatment groups using the  $\chi^2$  test.

**Subgroup analyses**

Prespecified subgroup analyses of efficacy outcomes by baseline characteristics, including by high-risk features, were also done. Analyses were performed using SAS (version 9.4). Efficacy was analysed in the intention-to-treat population according to randomly assigned treatment group. Safety was analysed according to actual treatment received in all patients who received at least one dose of any study medication.

**Table A2 Main study characteristics HELIOS**

**Table A2 Main study characteristics HELIOS**

<b>Trial name</b>	Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination With Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
<b>NCT number</b>	NCT01611090
<b>Objective</b>	The purpose of this study is to examine the safety and efficacy of Ibrutinib administered in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
<b>Publications – title, author, journal, year</b>	Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. <i>The Lancet Oncology</i> . 2016;17(2):200-11. [30]
<b>Study type and design</b>	Randomized, Double-blind, Placebo-controlled Phase 3 Study  The HELIOS trial was an international, double-blind, placebo controlled, phase 3 study in adult patients (≥18 years of age) who had active chronic lymphocytic leukaemia or small lymphocytic lymphoma with measurable lymph node disease (>1 · 5 cm) by CT scan, and had relapsed or refractory disease following one or more previous lines of systemic therapy consisting of at least two cycles of a chemotherapy-containing regimen, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate bone marrow, liver, and kidney function. Patients with del(17p) were excluded because of known poor response to bendamustine plus rituximab. Patients who had received previous treatment with ibrutinib or other BTK inhibitors, refractory disease or relapse within 24 months with a previous bendamustine-containing regimen, or haemopoietic stem-cell transplant were also excluded. Patients were randomly assigned (1:1) by a web-based system to receive bendamustine plus rituximab given in cycles of 4 weeks' duration (bendamustine: 70 mg/m <sup>2</sup> intravenously on days 2–3 in cycle 1, and days 1–2 in cycles 2–6; rituximab: 375 mg/m <sup>2</sup> on day 1 of cycle 1, and 500 mg/m <sup>2</sup> on day 1 of cycles 2–6 for a maximum of six cycles) with either ibrutinib (420 mg daily orally) or placebo until disease progression or unacceptable toxicity.
<b>Follow-up time</b>	Between Sept 19, 2012, and Jan 21, 2014, 578 eligible patients were randomly assigned to ibrutinib or placebo in combination with bendamustine plus rituximab (289 in each group). The primary endpoint was met at the preplanned interim analysis (March 10, 2015). median follow-up of 17 months

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) that meets protocol-defined criteria</li> <li>• Active disease meeting at least 1 of the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria for requiring treatment</li> <li>• Measurable nodal disease by computed tomography</li> <li>• Relapsed or refractory CLL or SLL following at least 1 prior line of systemic therapy consisting of at least 2 cycles of a chemotherapy-containing regimen</li> <li>• Eastern Cooperative Oncology Group Performance Status score of 0 or 1</li> <li>• Hematology and biochemical values within protocol-defined limits</li> <li>• Agrees to protocol-defined use of effective contraception</li> <li>• Women of childbearing potential must have negative blood or urine pregnancy test at screening</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Recent therapeutic interventions within 3 (chemotherapy/radiotherapy) to 10 weeks (immunotherapy)</li> <li>• Prior treatment with ibrutinib or other Bruton's tyrosine kinase inhibitors or prior randomization in any other clinical study evaluating ibrutinib</li> <li>• The presence of deletion of the short arm of chromosome 17</li> <li>• Patients previously treated with a bendamustine-containing regimen who did not achieve a response or who relapsed and required treatment within 24 months of treatment with that regimen</li> <li>• Patients for whom the goal of therapy is tumor debulking prior to stem cell transplant</li> <li>• Received a hematopoietic stem cell transplant</li> <li>• Known central nervous system leukemia/lymphoma or Richter's transformation</li> <li>• Patients with uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia</li> <li>• Chronic use of corticosteroids</li> <li>• History of prior malignancy, except: malignancy treated with curative intent and with no known active disease present for <math>\geq 3</math> years before randomization; adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; adequately treated cervical carcinoma in situ without evidence of disease</li> <li>• History of stroke or intracranial hemorrhage within 6 months prior to randomization; or clinically significant cardiovascular disease</li> </ul>
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**Table A2 Main study characteristics HELIOS**

	<ul style="list-style-type: none"> <li>• Requires anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with strong CYP3A4/5 inhibitors</li> <li>• Known history of human immunodeficiency virus or hepatitis C, or active infection with hepatitis B or C</li> <li>• Any uncontrolled active systemic infection or any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk</li> <li>• A woman who is pregnant or breast feeding, or a man who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug</li> </ul>
<b>Intervention</b>	<p>Experimental: Ibrutinib + BR</p> <p>Ibrutinib 420 mg will be administered orally once daily on a continuous schedule. All subjects will receive background therapy with bendamustine and rituximab (BR) for a maximum of 6 cycles (a cycle is defined as 28 days, with the exception of Cycle 1, which will be 29 days to allow for rituximab dosing prior to bendamustine and study medication).</p> <p>Placebo Comparator: Placebo + BR</p> <p>Matching placebo will be administered orally once daily on a continuous schedule. All subjects will receive background therapy with BR for a maximum of 6 cycles (a cycle is defined as 28 days, with the exception of Cycle 1, which will be 29 days to allow for rituximab dosing prior to bendamustine and study medication).</p>



## Baseline characteristics

	ibrutinib, bendamustine, and rituximab (n=289)	Placebo, bendamustine, and rituximab (n=289)
Age (years)	64 (31-86)	63 (36-83)
Sex		
Male	193 (67%)	189 (65%)
Female	96 (33%)	100 (35%)
Diagnosis		
Chronic lymphocytic leukaemia	257 (89%)	257 (89%)
Small lymphocytic lymphoma	32 (11%)	32 (11%)
ECOG performance status		
0	125 (43%)	126 (44%)
1	164 (57%)	163 (56%)
Rai stage*	256	258
0-II	157 (61%)	139 (54%)
III-IV	99 (39%)	119 (46%)
Binet stage*	256	258
A	26 (10%)	23 (9%)
B	132 (52%)	119 (46%)
C	98 (38%)	116 (45%)
Bulky disease > 5 cm	168 (58%)	156 (54%)
Del(11q)	87 (30%)	65 (22%)
IGHV status*	259	260
Mutated	49 (19%)	52 (20%)
Unmutated	210 (81%)	208 (80%)
ZAP70 expression*	271	276
Raised	204 (75%)	190 (69%)
Not raised	67 (25%)	86 (31%)
Purine analogue refractory	75 (26%)	74 (26%)
Previous lines of therapies	289	288
Mean (range)	2 (1-11)	2 (1-9)
1 previous line	140 (48%)	138 (48%)
2 previous lines	72 (25%)	78 (27%)
≥ 3 previous lines	77 (27%)	72 (25%)
Previous therapy		
Purine analogue	206 (71%)	209 (72%)
Alkylating agent	275 (95%)	275 (95%)
Anti-CD20	203 (70%)	200 (69%)
Common regimens used		
FCR	120 (42%)	109 (38%)
Other flutardabine-based combinations	92 (32%)	102 (35%)
Bendamustine plus rituximab	10 (3%)	9 (3%)
Chlorambucil plus anti-CD20 mAb	16 (6%)	15 (5%)
Time from progression or relapse since last line of treatment to randomisation (months)	2.9 (0-48)	2.6 (0-73)
Time from last treatment to randomisation (months)	24.0 (0.7-154.8)	20.9 (0.2-160.8)

Data are median (range), n (%), or n, unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. FCR=flutardabine, cyclophosphamide, and rituximab. mAb=monoclonal antibody. \*Staging criteria for patients with chronic lymphocytic leukaemia only using diagnosis at study entry; not all samples were available for biomarker data.

Table 1. Baseline characteristics

**Primary and secondary endpoints**
**Primary Outcome Measures :**

1. Progression-free Survival (PFS) [ Time Frame: Up to 5 years ] PFS was defined as the interval between the date of randomization and the date of disease progression or death, whichever was first reported. IWCLL 2008 criteria for PD: New enlarged nodes >1.5 cm, new hepatomegaly or splenomegaly, or other new organ infiltrates, bone lesion, ascites, or pleural effusion confirmed due to chronic lymphocytic leukemia (CLL); >=50% increase in existing lymph nodes; >=50% increase in enlargement of liver or spleen; >=50% increase from baseline in lymphocyte count (and to >=5\*10<sup>9</sup>/L) or >=50% increase from nadir count confirmed on >=2 serial assessments if absolute lymphocyte count (ALC) >=30,000 per microliter and lymphocyte doubling time is rapid, unless considered treatment-related lymphocytosis; new cytopenia (Hemoglobin b [Hgb] or platelets) attributable to CLL; and transformation to a more aggressive histology.

**Secondary Outcome Measures :**

1. Overall Response Rate (ORR) [ Time Frame: Up to 5 years ] ORR defined as number of participants achieving a complete response (CR), complete response with incomplete marrow recovery (CRi), nodular partial response (nPR) or partial response (PR). IWCLL 2008 criteria: CR- No lymphadenopathy and hepatosplenomegaly, no constitutional symptoms, neutrophils >1.5\*10<sup>9</sup>/liter (L), platelets >100\*10<sup>9</sup>/L, Hgb >11 gram per deciliter (g/dL) and absolute lymphocyte count <4000/microliter (mCL); CRi- CR with incomplete recovery of bone marrow; nPR- participants meet criteria for CR, but the bone marrow biopsy shows B-lymphoid nodules, may represent a clonal infiltrate; PR- 2 of the following when abnormal at baseline: >=50% decrease in ALC, >=50% decrease in sum products of up to 6 lymph nodes, >=50% decrease in enlargement of spleen or liver; and 1 of the following: neutrophils >1.5\*10<sup>9</sup>/L, Platelets >100\*10<sup>9</sup>/L and Hgb>11 g/dL or >=50% improvement over baseline in any of these; no new enlarged nodes or new hepatosplenomegaly
2. Overall Survival (OS) [ Time Frame: Up to 5 years ] OS was defined as the interval between the date of randomization and the date of death from any cause
3. Percentage of Participants With Minimal Residual Disease (MRD)-Negative Response [ Time Frame: Up to 5 years ] MRD-negative response was defined as the percentage of participants who reach MRD negative disease status (less than 1 chronic lymphocytic leukemia [CLL] cell per 10,000 leukocytes) in either bone marrow or peripheral blood. All randomized participants were included in this analysis. Participants with missing MRD data were considered non-responders.
4. Percentage of Participants With Sustained Hematologic Improvement [ Time Frame: Up to 5 years ] Sustained hematologic improvement was defined as hematologic improvement that was

	<p>sustained continuously for greater than or equal to (<math>\geq</math>) 56 days without blood transfusion or growth factors: 1) Platelet counts greater than (<math>&gt;</math>)<math>100 \times 10^9</math>/liter (L) if baseline less than or equal to (<math>\leq</math>) <math>100 \times 10^9</math>/L or increase <math>\geq</math> 50 percent (%) over baseline; 2) Hemoglobin <math>&gt;11</math> gram per deciliters (g/dL) if baseline <math>\leq</math> 11 g/dL or increase <math>\geq</math> 2 g/dL over baseline.</p> <ol style="list-style-type: none"> <li>5. Median Time to Clinically Meaningful Improvement in FACIT-Fatigue Scale [ Time Frame: Up to 2 years ]Time to improvement is defined as the time interval (months) from randomization to the first observation of improvement. FACIT-Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases. Responses to the 13-item FACIT Fatigue Scale are reported on a 5-point categorical response scale ranging from 0 (not at all) to 4 (very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worst score) to 52 (best score)</li> <li>6. Number of Participants With Clinically Relevant Shifts in Disease-Related Symptoms [ Time Frame: From the date of randomization to disease progression (Up to 2 years) ]The disease-related symptoms included fatigue, weight loss, fevers, night sweats, abdominal discomfort/splenomegaly and anorexia.</li> <li>7. Number of Participants Who Received Subsequent Antineoplastic Therapy [ Time Frame: Up to 5 years ]Number of participants who received subsequent antineoplastic therapy was reported.</li> <li>8. Change From Baseline in Beta2 Microglobulin at End of Treatment (EOT) [ Time Frame: Baseline to EOT (Up to 2 years) ]Change from baseline in beta2 microglobulin at end of treatment at time of primary analysis was reported.</li> <li>9. Change From Baseline in FACIT-Fatigue Scale at End of Treatment [ Time Frame: Baseline to EOT (up to 2 years) ]FACIT-Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases. Responses to the 13-item FACIT Fatigue Scale are reported on a 5-point categorical response scale ranging from 0 (not at all) to 4 (very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worst score) to 52 (best score).</li> <li>10. Change From Baseline in EORTC QLQ-C30 Physical Functioning Score at End of Treatment [ Time Frame: Baseline to EOT (up to 2 years) ]EORTC QLQ-C30 Physical Functioning Score is a</li> </ol>
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**Table A2 Main study characteristics HELIOS**

	<p>questionnaire to assess quality of life of cancer patients. It is composed of 30 items, multi-item measure (28 items) and 2 single-item measures. For the multiple item measure, 4-point scale is used and the score for each item range from "1 = not at all" to "4 = very much". Higher scores indicate worsening. The 2 single-item measure involves question about the overall health and overall quality of life which was rated on a 7-point scale ranging from "1 = very poor" to "7 = excellent". Lower scores indicate worsening. All scale and item scores were linearly transformed to be in range from 0-100. A higher score represents a higher (better) level of functioning, or a higher (worse) level of symptoms.</p> <ol style="list-style-type: none"> <li>11. Change From Baseline in EORTC QLQ-CLL 16 Domain Scores at End of Treatment [ Time Frame: Baseline to EOT (up to 2 years) ]The EORTC QLQ-CLL 16 is a 16-item disease specific module that comprises 5 domains of patient-reported health status important in CLL. There are three multi-item scales that include fatigue (2 items), treatment side effects and disease symptoms (8 items), and infection (4 items), and 2 single-item scales on social activities and future health worries. Responses are measured on a 4 point scale ranging from 1 (not at all) to 4 (very much).</li> <li>12. Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Visual Analog Scale at End of Treatment [ Time Frame: Baseline to EOT (up to 2 years) ] The EQ-5D questionnaire is a brief, generic health-related quality of life assessment (HRQOL) that can also be used to incorporate participant preferences into health economic evaluations. The EQ-5D questionnaire assesses HRQOL in terms of degree of limitation on 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and as overall health using a visual analog scale with response options ranging from 0 (worst imaginable health) to 100 (best imaginable health)</li> <li>13. Change From Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Utility Score Scale at End of Treatment [ Time Frame: Baseline to EOT (up to 2 years) ]The EuroQol-5 is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1=no problems, 2=some problems, 3=extreme problems). The responses to the five EQ-5D dimensions were scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1. High score indicating a high level of utility.</li> </ol>
<b>Method of analysis</b>	<p>The distribution of time-to-event endpoints, including progression-free survival and overall survival, was estimated by the Kaplan-Meier method. All statistical tests were based on a two-sided alpha level of 0 · 05. Negative response for minimal residual disease was analysed by use of Fisher's exact test</p>

**Table A2 Main study characteristics HELIOS**

<b>Subgroup analyses</b>	A preplanned subgroup analysis of progression-free survival outcomes based on baseline patient and disease characteristics was also undertaken. See method of analysis.
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**Table A2 Main study characteristics CLL14**

<b>Table A2 Main study characteristics CLL14</b>	
<b>Trial name</b>	CLL14-A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare The Efficacy and Safety of A Combined Regimen of Obinutuzumab and Venetoclax (GDC-0199/ABT-199) Versus Obinutuzumab and Chlorambucil in Previously Untreated Patients With CLL and Coexisting Medical Conditions
<b>NCT number</b>	NCT02242942
<b>Objective</b>	The aim was to investigate fixed-duration treatment with venetoclax and obinutuzumab in patients with previously untreated CLL and coexisting conditions.
<b>Publications – title, author, journal, year</b>	Fischer K. et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med 2019;380:2225-2236. [31]
<b>Study type and design</b>	Open-label, multicenter, randomized Phase III study. Patients were randomly assigned in a 1:1 ratio to receive either venetoclax–obinutuzumab or chlorambucil–obinutuzumab with the use of a Web and voice mail system based on a computer-generated randomization schedule. A block size of six was used to balance the randomization. Patients were stratified according to Binet stage and geographic region. The treatment duration in both groups consisted of 12 cycles lasting 28 days each; no crossover was allowed.
<b>Follow-up time</b>	median follow-up of 28.1 months

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Documented previously untreated CLL according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria</li> <li>• CLL requiring treatment according to IWCLL criteria</li> <li>• Total Cumulative Illness Rating Scale (CIRS score) greater than (&gt;) 6</li> <li>• Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as per protocol, unless cytopenia is due to marrow involvement of CLL</li> <li>• Adequate liver function</li> <li>• Life expectancy &gt; 6 months</li> <li>• Agreement to use highly effective contraceptive methods per protocol</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Transformation of CLL to aggressive Non-Hodgkin's lymphoma (Richter's transformation or pro-lymphocytic leukemia)</li> <li>• Known central nervous system involvement</li> <li>• Participants with a history of confirmed progressive multifocal leukoencephalopathy (PML)</li> <li>• An individual organ/ system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive the treatment regimen of this trial with the exception of eyes, ears, nose, throat organ system</li> <li>• Participants with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia</li> <li>• Inadequate renal function</li> <li>• History of prior malignancy, except for conditions as listed in the protocol if participants have recovered from the acute side effects incurred as a result of previous therapy</li> <li>• Use of investigational agents or concurrent anti-cancer treatment within the last 4 weeks of registration</li> <li>• Participants with active bacterial, viral, or fungal infection requiring systemic treatment within the last two months prior to registration</li> <li>• History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products</li> <li>• Hypersensitivity to chlorambucil, obinutuzumab, or venetoclax or to any of the excipients</li> </ul>
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Table A2 Main study characteristics CLL14

	<ul style="list-style-type: none"><li>• Pregnant women and nursing mothers</li><li>• Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology) or positive test result for hepatitis C (hepatitis C virus [HCV] antibody serology testing)</li><li>• Participants with known infection with human immunodeficiency virus (HIV) or human T-cell leukemia virus-1 (HTLV-1)</li><li>• Requires the use of warfarin, marcumar, or phenprocoumon</li><li>• Received agents known to be strong and moderate Cytochrome P450 3A inhibitors or inducers within 7 days prior to the first dose of study drug</li></ul>
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<b>Intervention</b>	<p>Patients were randomly assigned in a 1:1 ratio to receive either venetoclax–obinutuzumab or chlorambucil–obinutuzumab. A block size of six was used to balance the randomization. Patients were stratified according to Binet stage and geographic region. The treatment duration in both groups consisted of 12 cycles lasting 28 days each; no crossover was allowed. Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6. Chlorambucil was administered orally at 0.5 mg per kilogram of body weight on days 1 and 15 of each cycle until completion of 12 cycles. The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of cycle 12. The risk of tumor lysis syndrome was assessed on the basis of the absolute lymphocyte count and lymph-node size to guide prophylactic measures.</p> <ul style="list-style-type: none"> <li>• Arm A: Obinutuzumab + Chlorambucil Participants will receive obinutuzumab for 6 cycles and chlorambucil for 12 cycles. Cycles will comprise 28 days.</li> <li>• Arm B: Obinutuzumab + Venetoclax Participants will receive obinutuzumab for 6 cycles and venetoclax for 12 cycles. Cycles will comprise 28 days.</li> </ul> <p>Drug: Venetoclax Venetoclax, oral tablet: 20 mg daily during Cycle 1, Day 22-28; 50 mg daily during Cycle 2, Day 1-7; 100 mg daily during Cycle 2, Day 8-14; 200 mg daily during Cycle 2, Day 15-21; 400 mg daily during Cycle 2, Day 22-28 and on Day 1-28 for all subsequent cycles until the end of Cycle 12. Other Name: ABT-0199, GDC-0199</p> <p>Drug: Obinutuzumab Obinutuzumab, IV infusion: 100 mg or 1000 mg, depending on splitting rules, at Cycle 1, Day 1 (if 100 mg was received on Day 1, 900 mg will be administered on Cycle 1, Day 2); 1000 mg at Cycle 1, Day 8 and Day 15; 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6 Other Name: GA-101; Gazyva</p> <p>Drug: Chlorambucil</p>
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Table A2 Main study characteristics CLL14

	<p>Chlorambucil 0.5 milligrams per kilogram (mg/kg) orally at Day 1 and Day 15 at of each 28 day cycle for 12 cycles.</p> <p>Drug: Obinutuzumab</p> <p>Obinutuzumab, IV infusion: 100 mg or 1000 mg, depending on splitting rules, at Cycle 1, Day 1 (if 100 mg was received on Day 1, 900 mg will be administered on Cycle 1, Day 2); 1000 mg at Cycle 1, Day 8 and Day 15; 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6</p> <p>Other Name: GA-101; Gazyva</p>
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**Baseline characteristics**
**Table 2. Grade 3 or 4 Adverse Events (Safety Population).<sup>\*</sup>**

Adverse Event	Venetoclax–Obinutuzumab (N = 212) <sup>†</sup>			Chlorambucil–Obinutuzumab (N = 214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	<i>number of patients (percent)</i>					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in $\geq 3\%$ of the patients in either treatment group <sup>‡</sup> :						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders <sup>§</sup>	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders <sup>¶</sup>	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea <sup>  </sup>	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders <sup>**</sup>	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions <sup>††</sup>	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)
Nervous system disorders	9 (4.2)	1 (0.5)	10 (4.7)	7 (3.3)	0	7 (3.3)
Respiratory, thoracic, and mediastinal disorders	10 (4.7)	0	10 (4.7)	5 (2.3)	1 (0.5)	6 (2.8)
Musculoskeletal and connective-tissue disorders	6 (2.8)	0	6 (2.8)	7 (3.3)	0	7 (3.3)
Skin and subcutaneous tissue disorder <sup>‡‡</sup>	2 (0.9)	0	2 (0.9)	8 (3.7)	0	8 (3.7)

\* Summaries of all adverse events of any grade and all serious adverse events are provided in Tables S6 and S7, respectively, in the Supplementary Appendix. Toxic effects in the two treatment groups were similar in severity, with significant differences detected only in the percentage of patients with metabolism and nutrition disorders and gastrointestinal disorders, including diarrhea.

<sup>†</sup> Nine patients received obinutuzumab only.

<sup>‡</sup> Adverse events are reported according to *Medical Dictionary for Regulatory Activities* superclass and preferred terms and National Cancer Institute Common Terminology Criteria for Adverse Events grade.

<sup>§</sup> Category includes tumor lysis syndrome and changes in electrolyte levels, each occurring in less than 3% of patients in each group. The two-sided P value was 0.02 for the between-group difference.

<sup>¶</sup> The two-sided P value was 0.03 for the between-group difference.

<sup>||</sup> The two-sided P value was 0.01 for the between-group difference.

<sup>\*\*</sup> Category includes hypertension and hypotension, each occurring in less than 3% of patients in each group.

<sup>††</sup> Category includes asthenia, pyrexia, fatigue, and chest pain, each occurring in less than 3% of patients in each group.

<sup>‡‡</sup> Category includes different types of rash, each occurring in less than 3% of patients in each group.

<p><b>Primary and secondary endpoints</b></p>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression Free Survival (PFS) Based on Investigator Assessment According to IWCLL Criteria [ Time Frame: Baseline until disease progression or death up to approximately 3.75 years ]</li> </ol> <p>PFS was determined according to IWCLL 2008 criteria and defined as the time from randomization to the first occurrence of PD or death from any cause. Disease progression was characterized by at least one of the following: 1) <math>\geq 50\%</math> increase in the absolute number of circulating lymphocytes to at least <math>5 \times 10^9/L</math>, 2) Appearance of new palpable lymph nodes (<math>&gt; 15</math> mm in longest diameter) or any new extra-nodal lesion; 3) <math>\geq 50\%</math> increase in the longest diameter of any previous site of lymphadenopathy; 4) <math>\geq 50\%</math> increase in the enlargement of the liver and/or spleen; 5) Transformation to a more aggressive histology</p> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression Free Survival (PFS) Based on Institutional Review Committee (IRC)-Assessments According to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Criteria [ Time Frame: Baseline until disease progression or death up to approximately 3.75 years ]</li> </ol> <p>PFS was determined according to IWCLL 2008 criteria and defined as the time from randomization to the first occurrence of progressive disease (PD) or death from any cause. Disease progression was characterized by at least one of the following: 1) <math>\geq 50\%</math> increase in the absolute number of circulating lymphocytes to at least <math>5 \times 10^9/L</math>, 2) Appearance of new palpable lymph nodes (<math>&gt; 15</math> mm in longest diameter) or any new extra-nodal lesion; 3) <math>\geq 50\%</math> increase in the longest diameter of any previous site of lymphadenopathy; 4) <math>\geq 50\%</math> increase in the enlargement of the liver and/or spleen; 5) Transformation to a more aggressive histology.</p> <ol style="list-style-type: none"> <li>2. Percentage of Participants With an Overall Response (OR) at Completion of Treatment, as Determined by the Investigator According to IWCLL Criteria [ Time Frame: At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months) ]</li> </ol> <p>OR was defined as complete response (CR), CR with incomplete bone marrow recovery (CRi), or partial response (PR) according to IWCLL 2008 criteria. CR requires all of the following: peripheral blood lymphocytes below <math>4 \times 10^9/L</math>, absence of lymphadenopathy by physical examination and computed tomography (CT) scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils <math>&gt; 1.5 \times 10^9/L</math>, platelets <math>&gt; 100 \times 10^9/L</math> and hemoglobin <math>&gt; 110</math> g/L, bone marrow at least normocellular for age without clonal infiltrate (except for Cri). PR: two of the following features for at least 2 months: <math>\geq 50\%</math> decrease in</p>
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	<p>peripheral blood lymphocyte count from the pretreatment value, <math>\geq 50\%</math> reduction in lymphadenopathy, <math>\geq 50\%</math> reduction of liver and/or spleen enlargement, and at least one of the following blood counts: neutrophils <math>&gt;1.5 \times 10^9/L</math>, platelets <math>&gt;100 \times 10^9/L</math> and hemoglobin <math>&gt;110</math> g/L.</p> <p>3. Percentage of Participants With a Complete Response Rate (CRR) at the Completion of Treatment Assessment as Determined by the Investigator According to IWCLL Criteria [ Time Frame: At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months) ]</p> <p>CRR was defined as the rate of a clinical response of CR or CRi according to IWCLL 2008 criteria. CR requires all of the following: peripheral blood lymphocytes below <math>4 \times 10^9/L</math>, absence of lymphadenopathy by physical examination and CT scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils <math>&gt;1.5 \times 10^9/L</math>, platelets <math>&gt;100 \times 10^9/L</math> and hemoglobin <math>&gt;110</math> g/L, bone marrow at least normocellular for age without clonal infiltrate (except for Cri).</p> <p>4. Percentage of Participants With Minimal Residual Disease (MRD) Negativity in Peripheral Blood as Measured by Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR) at Completion of Treatment [ Time Frame: At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months) ]</p> <p>MRD negativity was defined as having <math>&lt; 1</math> CLL cell per 10,000 leucocytes in peripheral blood.</p> <p>5. Percentage of Participants With MRD Negativity in Bone Marrow as Measured by ASO-PCR at Completion of Treatment [ Time Frame: At the completion of treatment assessment 3 months after treatment completion (at approximately 15 months) ]</p> <p>MRD negativity was defined as having <math>&lt; 1</math> CLL cell per 10,000 leucocytes in bone marrow.</p> <p>6. Overall Survival (OS) [ Time Frame: Baseline until death, up to approximately 5.75 years ]</p> <p>OS was defined as the time between the date of randomization and the date of death due to any cause.</p>
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7. Percentage of Participants With MRD Negativity in Peripheral Blood as Measured by ASO-PCR at Completion of Combination Treatment Assessment [ Time Frame: Day 1 Cycle 9 or 3 months after last IV infusion, approximately 9 months ]

MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in peripheral blood.

8. Percentage of Participants With MRD Negativity in Bone Marrow as Measured by ASO-PCR at Completion of Combination Treatment Assessment [ Time Frame: Day 1 Cycle 9 or 3 months after last IV infusion at approximately 9 months ] MRD negativity was defined as having < 1 CLL cell per 10,000 leucocytes in bone marrow.

9. Percentage of Participants With OR at Completion of Combination Treatment Response Assessment [ Time Frame: Day 1 Cycle 7 or 28 days after last IV infusion, approximately 6 months ] OR was defined as CR, CRi or PR according to IWCLL 2008 criteria. CR required all of the following: peripheral blood lymphocytes below  $4 \times 10^9/L$ , absence of lymphadenopathy by physical examination, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils  $>1.5 \times 10^9/L$ , platelets  $>100 \times 10^9/L$  and hemoglobin  $>110 \text{ g/L}$ . PR: two of the following features for at least 2 months:  $\geq 50\%$  decrease in peripheral blood lymphocyte count from the pretreatment value,  $\geq 50\%$  reduction in lymphadenopathy,  $\geq 50\%$  reduction of liver and/or spleen enlargement, and at least one of the following blood counts: neutrophils  $>1.5 \times 10^9/L$ , platelets  $>100 \times 10^9/L$  and hemoglobin  $>110 \text{ g/L}$ .

10. Duration of Objective Response (DOR) [ Time Frame: Time from the first occurrence of a documented objective response to the time of PD as determined by the investigator or death from any cause, up to approximately 5.75 years ] PD was defined as lymphadenopathy,  $\geq 50\%$  increase in liver or spleen size,  $\geq 50\%$  increase in lymphocyte count, transformation to a more aggressive histology or occurrence of cytopenia.

11. Percentage of Participants By Best Response Achieved (CR, CRi, PR, Stable Disease (SD), or PD) [ Time Frame: Baseline up to the completion of treatment assessment 3 months after treatment completion (up to approximately 15 months) ] CR: peripheral blood lymphocytes below  $4 \times 10^9/L$ , absence of lymphadenopathy by physical examination and CT scan, no hepatomegaly or splenomegaly, absence of disease or constitutional symptoms, blood counts of neutrophils  $>1.5 \times 10^9/L$ , platelets  $>100 \times 10^9/L$  and hemoglobin  $>110 \text{ g/L}$ , bone marrow at least normocellular for age without clonal infiltrate (except for Cri). PR: any two for at least 2 months:  $\geq 50\%$  decrease in peripheral blood lymphocyte count from the pretreatment value,  $\geq 50\%$  reduction in lymphadenopathy,  $\geq 50\%$  reduction of liver and/or spleen enlargement, and at least one of the

	<p>following blood counts: neutrophils <math>&gt;1.5 \times 10^9/L</math>, platelets <math>&gt;100 \times 10^9/L</math> and hemoglobin <math>&gt;110 \text{ g/L}</math>. PD: lymphadenopathy, <math>\geq 50\%</math> increase in liver or spleen size, <math>\geq 50\%</math> increase in lymphocyte count, transformation to a more aggressive histology or occurrence of cytopenia. SD: a non-response and used to characterize participants who did not achieve a CR or a PR, and who have not exhibited PD.</p> <ol style="list-style-type: none"> <li>12. Event-Free Survival [ Time Frame: Time between date of randomization and the date of disease progression/relapse on the basis of investigator-assessment, death, or start of a new anti-leukemic therapy, up to 5.75 years ]</li> <li>13. Time to Next Anti-Leukemic Treatment [ Time Frame: Time between the date of randomization and the date of first intake of new anti-leukemic therapy, up to 5.75 years ]</li> <li>14. Number of Participants With Adverse Events (AEs) [ Time Frame: Up to approximately 5.75 years ] An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs.</li> <li>15. Percentage of Participants With CD19 + /CD5+ B Cells or CD14+ Monocytes [ Time Frame: Baseline up to approximately 5.75 years ]</li> <li>16. Percentage of Participants With Human-Anti-Human Antibodies [ Time Frame: Baseline up to approximately 5.75 years ]</li> <li>17. Percentage of Participants Recorded as Premature Study Withdrawals [ Time Frame: Up to approximately 5.75 years ]</li> <li>18. Plasma Concentrations of Venetoclax [ Time Frame: Pre-venetoclax dose (0 hour) and 4 hours post-venetoclax dose on Day 1 Cycle 4 ]</li> <li>19. Serum Concentrations of Obinutuzumab [ Time Frame: Pre-obinutuzumab infusion (0 hour) and end of obinutuzumab infusion on Day 1 Cycle 4 ]</li> <li>20. Change From Baseline in M.D. Anderson Symptom Inventory-CLL (MDASI-CLL) Score [ Time Frame: Baseline up to approximately 5.75 years ] The MDASI-CLL is a questionnaire of 25 items related to CLL specific symptoms that a participant may have experienced in the past 24 hours. Participants were asked to rate the severity of 13 symptoms called mean core symptom severity (i.e., pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sadness, vomiting, and numbness or tingling), 6 disease-specific symptoms called mean module symptom severity (night sweats, fevers and chills, lymph node swelling, diarrhea, easy bruising or bleeding, and constipation) and 6 mean interference</li> </ol>
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**Table A2 Main study characteristics CLL14**

	<p>on life questions (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) on a scale from 0 to 10 with 0 indicating that the symptom is "not present" or "did not interfere" with the participant's activities and 10 indicating "as bad as you can imagine" or "interfered completely". Scores were averaged (range 0 to 10) for each of three parts.</p> <p>21. Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30) [ Time Frame: Baseline up to approximately 5.75 years ]</p> <p>The EORTC QLQ-C30 is a validated and reliable self-report measure consisting of 30 questions incorporated into five functional scales (physical, role, cognitive, emotional, and social scales), three symptom scales (fatigue, pain, nausea, and vomiting scales), and a global health status/global quality-of-life scale. The remaining single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) assess the additional symptoms experienced by patients with cancer and the perceived financial burden of treatment. The 28 function and symptom items were scored on a 4-point scale that ranged from "not at all" to "very much," and the 2 global health status/global quality-of-life items were scored on a 7-point scale that ranged from "very poor" to "excellent." Raw average scale scores were linearly transformed to range 0-100 with higher scores indicating higher response levels (i.e., higher functioning, higher symptom severity).</p> <p>22. Change From Baseline in EuroQol 5 Dimension Questionnaire (EQ-5D-3L) [ Time Frame: Baseline up to approximately 5.75 years ] The EQ-5D-3L questionnaire is a generic, preference based health utility measure that assesses 5 health states (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is used to build a composite of the patient's health status. The EQ-5D-3L was employed in this study to calculate health utilities for economic modeling, which ranged 0-1. The EQ-5D-3L also contained a visual analog scale (VAS) to assess the participant's overall health, which ranged from 0-100 with a higher score indicating a worse health status.</p>
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**Table A2 Main study characteristics CLL14**

<b>Method of analysis</b>	<p>The sample size for the study is determined given the requirements to perform a hypothesis test for clinically relevant statistical superiority in the primary endpoint of PFS. Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:</p> <ul style="list-style-type: none"> <li>• Log-rank test at the two-sided 0.05 level of significance</li> <li>• Median PFS for obinutuzumab and chlorambucil control arm (27 months)</li> <li>• 80% power to detect HR= 0.65 for the comparison of obinutuzumab +GDC-0199 experimental arm versus GClb, with median PFS for obinutuzumab +GDC-0199 increased to 41.5 months</li> <li>• Exponential distribution of PFS</li> <li>• Annual drop-out rate of 10%</li> <li>• One interim analysis for efficacy after 75% of PFS events, utilizing a stopping boundary according to the <math>\gamma</math> family error spending function with parameter <math>\gamma = -16</math>.</li> </ul> <p>Based on these assumptions, a total of 170 PFS events are required for the final analysis of PFS. With 420 patients, assuming non-linear accrual over 20 months, the cut off at the required number of events for the primary analysis is expected to be reached after 42.5 months. PFS analysis cutoffs will be determined based on the number of investigator PFS events. The minimum detectable difference at the final analysis corresponds approximately to an HR= 0.74. The sample size calculation was performed using EAST version 6.2.</p>
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**Table A2 Main study characteristics CLL14**

<b>Subgroup analyses</b>	<p><b>Subgroup analyses</b></p> <p>Pre-specified subgroup analyses of investigator-assessed PFS and MRD negativity [based on ASO-PCR] in peripheral blood 3 months after treatment completion were performed to assess internal consistency using the ITT population. The odds ratios of MRD response and their 95% confidence intervals, HR of PFS and their 95% confidence intervals (based on similar analyses as described for the primary endpoint), as well as the sample sizes were reported separately for each level of the following subgroups in forest plots:</p> <p>Pre-specified subgroups include:</p> <ul style="list-style-type: none"> <li>- Binet stage at screening (A, B, C)</li> <li>- Age</li> <li>- Gender (male, female)</li> <li>- Cytogenetic factors (deletion 17p, 11q and 13q, and trisomy 12)</li> <li>- <i>TP53</i> status (deletion and/or mutation, none)</li> <li>- IGVH mutational status (unmutated, mutated)</li> </ul> <p>Since the study was powered for the ITT population, all subgroup analyses were exploratory only without reporting any P-values from statistical testing procedures.</p>
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**Table A2 Main study characteristics Furman**

<b>Trial name</b>	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia
<b>NCT number</b>	NCT01539512
<b>Objective</b>	This Phase 3, randomized, double-blind, placebo-controlled study is to evaluate the effect of idelalisib in combination with rituximab on the onset, magnitude, and duration of tumor control in participants previously treated for chronic lymphocytic leukemia (CLL). Eligible patients will be randomized with a 1:1 ratio into 1 of the 2 treatment arms to receive either idelalisib plus rituximab or placebo plus rituximab. Participants who are tolerating primary study therapy but experience definitive CLL progression are eligible to receive active idelalisib therapy in the extension study, GS-US-312-0117.
<b>Publications – title, author, journal, year</b>	Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. <i>The New England journal of medicine</i> . 2014;370(11):997-1007. [34]
<b>Study type and design</b>	A multicenter, randomized, double-blind, placebo-controlled, phase 3 study, assessed the efficacy and safety of idelalisib, an oral inhibitor of the delta isoform of phosphatidylinositol 3-kinase, in combination with rituximab versus rituximab plus placebo. The study randomly assigned 220 patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses to receive rituximab and either idelalisib (at a dose of 150 mg) or placebo twice daily. The primary end point was progression-free survival.
<b>Follow-up time</b>	At the first prespecified interim analysis, the study was stopped early on the recommendation of the data and safety monitoring board owing to overwhelming efficacy.

**Table A2 Main study characteristics Furman**

<b>Population (inclusion and exclusion criteria)</b>	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>• Adult subjects with previously treated recurrent CLL who have measurable lymphadenopathy</li> <li>• Require therapy for CLL</li> <li>• Have experienced CLL progression &lt; 24 months since the completion of the last prior therapy</li> <li>• Currently not sufficiently fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or comorbidities.</li> </ul>
<b>Intervention</b>	<p>Active Comparator: Idelalisib + rituximab  Participants will receive idelalisib plus rituximab</p> <p>Placebo Comparator: Placebo + rituximab  Participants will receive placebo to match idelalisib plus rituximab</p>

**Table A2 Main study characteristics Furman**
**Baseline characteristics**

**Table 1. Characteristics of the Patients at Baseline and Study Status.<sup>a</sup>**

Characteristic	Icôtilob plus Rituximab (N=110)	Placebo plus Rituximab (N=110)
Median age (range) — yr	71 (48–90)	71 (47–92)
Ris stage — % of patients <sup>b</sup>		
0	0	1
1 or 2	31	26
3 or 4	64	65
Missing data	5	7
Extent of CLL — % of patients		
Anemia		
Any grade	75	72
Grade ≥3	0	11
Neutropenia		
Any grade	34	33
Grade ≥3	17	16
Thrombocytopenia		
Any grade	62	61
Grade ≥3	16	29
Median absolute lymphocyte count (range) — per mm <sup>3</sup>	31,300 (200–262,700)	30,880 (240–393,740)
Median estimated maximum clearance (range) — mL/min	62 (1–164)	61 (23–190)
Genetic stratification factors — % of patients		
Unmutated IGHV	83	85
17p Deletion or TP53 mutation	47	45
Median CRF score (range) <sup>c</sup>	8 (3–18)	8 (1–19)
Previous CLL treatment		
Median no. of drugs (range)	3 (1–12)	3 (1–9)
Drugs — % of patients		
Flutamide	91	88
Cyclophosphamide	64	70
Fludauridine	20	64
Fluorouracil	58	54
Chlorambucil	33	22
Study status — %		
Underwent randomization	100	100
Continued participation in the study	81	52
Discontinued participation in the study	19	48
Disease progression	7	31
Death <sup>d</sup>	3	8
Adverse events	5	5
Physician's decision	1	1
Patient's decision	5	5
Other	1	0

<sup>a</sup> There were no significant differences between the two groups at baseline. Percentages may not total the overall number in the category because of rounding. CLL denotes chronic lymphocytic leukemia.

<sup>b</sup> In the Rai staging system, stage 0 denotes low risk disease, stage 1 or 2 intermediate risk, and stage 3 or 4 high risk.

<sup>c</sup> Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 54, with higher scores indicating an increased number or severity of coexisting illnesses.

<sup>d</sup> The listed deaths do not include one in the ibrutinib group and four in the placebo group that occurred after the patients withdrew from the study because of an adverse event or disease progression.

<p><b>Primary and secondary endpoints</b></p>	<p><b>Primary Outcome Measures :</b></p> <ol style="list-style-type: none"> <li>1. Progression-Free Survival [ Time Frame: Up to 17 months ]</li> </ol> <p>Progression-free survival was defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression was CLL progression based on standard criteria (other than lymphocytosis alone) as defined by the 2008 update of the International Workshop on CLL guidelines, ie, appearance of any new lesion; increase by <math>\geq 50\%</math> in the sum of the products of the perpendicular diameters of measured lymph nodes (SPD); new or <math>\geq 50\%</math> enlargement of liver or spleen; transformation to a more aggressive histology (eg, Richter's or prolymphocytic transformation); reduction in the number of blood cells (cytopenia) attributable to CLL.</p> <p><b>Secondary Outcome Measures :</b></p> <ol style="list-style-type: none"> <li>1. Overall Response Rate [ Time Frame: Up to 17 months ]</li> </ol> <p>Overall response rate was defined as the percentage of participants who achieved a best overall response of complete response or partial response.</p> <p>Complete response was defined as no lymphadenopathy, hepatomegaly, splenomegaly; normal complete blood count; confirmed by bone marrow aspirate &amp; biopsy.</p> <p>Partial response was defined as <math>&gt;1</math> of the following criteria: a 50% decrease in peripheral blood lymphocytes, lymphadenopathy, liver size, spleen size; plus <math>\geq 1</math> of the following: <math>\geq 1500/\mu\text{L}</math> absolute neutrophil count, <math>&gt; 100000/\mu\text{L}</math> platelets, <math>&gt; 11.0</math> g/dL hemoglobin or 50% improvement for either of these parameters without transfusions or growth factors.</p> <ol style="list-style-type: none"> <li>2. Lymph Node Response Rate [ Time Frame: Up to 17 months ]</li> </ol> <p>Lymph node response rate was defined as the percentage of participants who achieved a <math>\geq 50\%</math> decrease from baseline in the SPD of index lymph nodes</p>
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**Table A2 Main study characteristics Furman**

	<p>3. Overall Survival [ Time Frame: Up to 17 months ] Overall survival was defined as the interval from randomization to death from any cause</p> <p>4. Complete Response Rate [ Time Frame: Up to 17 months ] Complete response rate was defined as the percentage of participants who achieved a complete response</p>
Method of analysis	calculated progression-free survival, which was defined as the interval from randomization to disease progression or death from any cause (whichever came first), using the Kaplan–Meier method and compared rates using a stratified log-rank test. We used a Cox model with adjustment for stratification to calculate hazard ratios.
Subgroup analyses	For binary-response end points, we used the Cochran–Mantel–Haenszel chi-square test, adjusted for stratification, to assess between-group differences. A sequential testing procedure was applied to adjust for the overall type I error rate. Two interim analyses were prespecified after approximately 50% and 75% of the anticipated 119 events had occurred, at alpha levels of 0.001 and 0.005, respectively

**Table A2 Main study characteristics Jones**

<b>Table A2 Main study characteristics Jones</b>	
Trial name	A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia
NCT number	NCT01659021
Objective	The primary objective of this study is to evaluate the effect of the addition of idelalisib to ofatumumab on progression-free survival (PFS) in participants with previously treated chronic lymphocytic leukemia (CLL).

**Table A2 Main study characteristics Jones**

Publications – title, author, journal, year	Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. <i>The Lancet Haematology</i> . 2017;4(3):e114-e26. [35]
Study type and design	Open-label, randomised, controlled phase 3 trial, that enrolled patients with relapsed CLL progressing less than 24 months from last therapy. Patients refractory to ofatumumab were excluded. Patients were stratified by relapsed versus refractory disease, presence or absence of del(17p) or <i>TP53</i> mutation, or both, and <i>IGHV</i> mutated versus unmutated. We randomised patients in a 2:1 ratio using a web-based interactive system that generated a unique treatment code, and assigned patients to receive either idelalisib plus ofatumumab (oral idelalisib 150 mg twice daily continuously plus ofatumumab 300 mg intravenously in week 1, then 1000 mg intravenously weekly for 7 weeks, and every 4 weeks for 16 weeks) or ofatumumab alone (ofatumumab dosing as per the combination group, except 2000 mg was substituted for the 1000 mg dose).
Follow-up time	Between Dec 17, 2012, and March 31, 2014, 261 patients were enrolled, primary analysis (data cutoff Jan 15, 2015) and an updated analysis (data cutoff Sept 1, 2015) were performed. At data cutoff Sept 1, 2015 median follow up time was 16.1 months. Long term follow up 5 years



**Table A2 Main study characteristics Jones**

<b>Population (inclusion and exclusion criteria)</b>	<p>Eligible patients were aged 18 years or older, had a confirmed diagnosis of CLL, and required treatment according to criteria from the 2008 International Workshop on Chronic Lymphocytic Leukaemia (IWCLL). Patients were required to have had previous therapy with two or more cycles of a purine analogue or bendamustine and must have had disease progression in less than 24 months from completion of last therapy. Inclusion criteria further specified a Karnofsky performance score of 60 or higher and adequate organ function (transaminases <math>\leq 2 \cdot 5 \times</math> upper limit of normal, total bilirubin <math>\leq 1 \cdot 5 \times</math> upper limit of 24 months from completion of last therapy).</p> <p><b>Inclusion criteria further specified a Karnofsky performance score of 60 or higher and adequate organ function (transaminases <math>\leq 2 \cdot 5 \times</math> upper limit of normal, total bilirubin <math>\leq 1 \cdot 5 \times</math> upper limit of normal, and Cockcroft-Gault estimated creatinine clearance <math>&gt;0 \cdot 5</math> mL/s); however, patients were eligible irrespective of baseline blood cell counts. The presence of at least one lymph node of long dimension 2 cm or greater must have been confirmed by central imaging review. Exclusion criteria included a history of Richter or other histological transformation of CLL, previous allogeneic stem-cell or solid-organ transplantation, and chronic active hepatitis or other chronic liver impairment. Patients who had received previous therapy with an inhibitor of AKT, Bruton's tyrosine kinase, Janus kinase, mTOR, PI3K, or spleen tyrosine kinase were excluded, and patients with previous ofatumumab exposure were excluded if their disease had progressed within 6 months of completing monotherapy or combination therapies with these agents</b></p>
<b>Intervention</b>	<p>Experimental: Idelalisib+ofatumumab</p> <p>Randomized Initial Therapy (24 weeks): Idelalisib + ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 1000 mg weekly for 7 weeks, and then 1000 mg every 4 weeks for 4 doses)</p> <p>Continuing Therapy/Observation: Idelalisib 150 mg tablets twice daily until the earliest of participant withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.</p> <p>Randomized Initial Therapy (24 weeks): Ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 2000 mg weekly for 7 weeks, and then 2000 mg every 4 weeks for 4 doses)</p> <p>Continuing Therapy/Observation: Observation until the earliest of participant withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.</p>

**Table A2 Main study characteristics Jones**
**Baseline characteristics**

	Idelalisib plus ofatumumab (n=174)	Ofatumumab (n=87)
<b>Sex</b>		
Men	124 (71%)	62 (71%)
Women	50 (29%)	25 (29%)
<b>Age, years</b>	68 (61-74)	67 (62-74)
<b>Time since diagnosis, years</b>	7.8 (5-11)	7.6 (5-11)
<b>Rai stage at screening</b>		
II	26 (15%)	21 (24%)
III	24 (14%)	10 (12%)
IV	93 (53%)	39 (45%)
<b>Binet stage at screening</b>		
B	51 (29%)	29 (33%)
C	107 (62%)	45 (52%)
<b>CRS score</b>	4 (2-7)	4 (2-7)
<b>Karnofsky score</b>	80 (80-90)	80 (80-90)
<b>Creatinine clearance*, mL/s</b>	1.19 (0.92-1.46)	1.22 (0.91-1.54)
<b>β2 microglobulin†, mg/L</b>	6.0 (3.9-8.1)	5.2 (4.1-7.2)
<b>Bulky disease</b>		
≥5 cm lymph node	87 (50%)	48 (55%)
≥10 cm lymph node	19 (11%)	10 (12%)
<b>Refractory disease</b>	82 (47%)	47 (54%)
<b>Hepatomegaly or splenomegaly ‡</b>	89 (51%)/132 (76%)	49 (56%)/61 (70%)
<b>Del(17p) or TP53 mutation</b>	70 (40%)	33 (38%)
<b>IGHV unmutated</b>	137 (79%)	68 (78%)
<b>Time since last therapy, months</b>	9.3 (5.1-20.3)	9.3 (3.6-17.9)
<b>Number of previous regimens</b>	3 (2-4)	3 (2-5)
<b>Most common last regimen at study entry¶</b>		
Bendamustine plus rituximab	54 (31%)	21 (24%)
Fludarabine plus cyclophosphamide plus rituximab	38 (22%)	18 (21%)
Fludarabine plus rituximab	9 (5%)	5 (6%)
Rituximab	8 (5%)	5 (6%)
<b>Previous exposure at any time</b>		
Rituximab	161 (93%)	82 (94%)
Fludarabine	146 (84%)	75 (86%)
Cyclophosphamide	133 (76%)	67 (77%)
Bendamustine	90 (52%)	39 (45%)
Chlorambucil	57 (33%)	24 (28%)
Ofatumumab	3 (2%)	8 (9%)

Data are n (%) or median (IQR). Data cutoff was Sept 1, 2015. CRS=Cumulative Illness Rating Scale. \* Cockcroft-Gault calculated. †71 patients for idelalisib plus ofatumumab and 85 patients for ofatumumab alone. ‡Hepatomegaly was defined by physical exam. §Time since completion of last regimen calculated as date of randomisation (in months) minus date of completion of last regimen (in months) divided by 30/33/35. ¶Regimens received by a 5% of patients in either treatment group.

**Table 2. Demographic and baseline characteristics for the intention-to-treat analysis set**

<p>Primary and secondary endpoints</p>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression-Free Survival [ Time Frame: Randomization to End of Study (up to 60 months) ] <p>Progression-free survival (PFS) was defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression was CLL progression based on standard criteria (other than lymphocytosis alone) as defined by the 2008 update of the International Workshop on CLL guidelines, ie, appearance of any new lesion; increase by <math>\geq 50\%</math> in the sum of the products of the perpendicular diameters of measured lymph nodes (SPD); new or <math>\geq 50\%</math> enlargement of liver or spleen; transformation to a more aggressive histology (eg, Richter's or prolymphocytic transformation); reduction in the number of blood cells (cytopenia) attributable to CLL. PFS was analyzed using Kaplan-Meier (KM) estimates.</p> </li> </ol> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Overall Response Rate [ Time Frame: Randomization to End of Study (up to 60 months) ] <p>Overall response rate was defined as the percentage of participants who achieved a best overall response of complete response or partial response.</p> <ul style="list-style-type: none"> <li>o Complete response was defined as no lymphadenopathy, hepatomegaly, splenomegaly; normal complete blood count; confirmed by bone marrow aspirate &amp; biopsy.</li> <li>o Partial response was defined as <math>&gt;1</math> of the following criteria: a 50% decrease in peripheral blood lymphocytes, lymphadenopathy, liver size, spleen size; plus <math>\geq 1</math> of the following: <math>\geq 1500/\mu\text{L}</math> absolute neutrophil count, <math>&gt; 100000/\mu\text{L}</math> platelets, <math>&gt; 11.0</math> g/dL hemoglobin or 50% improvement for either of these parameters without transfusions or growth factors. Overall response rate was analyzed using KM estimates.</li> </ul> </li> <li>2. Lymph Node Response Rate [ Time Frame: Randomization to End of Study (up to 60 months) ] <p>Lymph node response rate was defined as the proportion of participants who achieved a <math>\geq 50\%</math> decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes.</p> </li> </ol>
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**Table A2 Main study characteristics Jones**

	<ol style="list-style-type: none"> <li>3. Overall Survival [ Time Frame: Randomization to Last Long-Term Follow-Up Visit (up to maximum of 5 years) ] Overall survival was defined as the interval from randomization to death from any cause. Overall survival was analyzed using KM estimates.</li> <li>4. Progression-Free Survival in Subgroup of Participants With Chromosome 17p Deletion and/or TP53 Mutation [ Time Frame: Randomization to End of Study (up to 60 months) ] Progression-free survival in subgroup of participants with chromosome 17p deletion and/or TP53 mutation was analyzed using KM estimates</li> <li>5. Complete Response Rate [ Time Frame: Randomization to End of Study (up to 60 months) ] Complete response rate was defined as the percentage of participants who achieve a complete response and maintain their response for at least 8 weeks (with a 1-week window)</li> </ol>
Method of analysis	<p>progression-free survival was calculated using the Kaplan-Meier method, and compared estimates using a stratified log-rank test. A Cox model with adjustment for stratification was used to calculate hazard ratios.</p>
Subgroup analyses	<p>For binary-response endpoints (ie, overall response and lymph node response), Cochran-Mantel-Haenszel <math>\chi^2</math> test—adjusted for stratification was used—to assess between-group differences. sequential testing procedure was applied to adjust for the overall type I error rate in the primary analysis. If the primary endpoint was significant, the secondary endpoints of overall response, lymph node response, overall survival, progression-free survival in del(17p) or TP53-mutated disease, and complete response would be tested sequentially.</p>

Table A2 Main study characteristics Huang

**Table A2 Main study characteristics Huang**

<b>Trial name</b>	A Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 (Ibrutinib) Versus Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
<b>NCT number</b>	NCT01973187
<b>Objective</b>	This is a randomized (individuals assigned to study treatment by chance), open-label (identity of assigned study drug will be known) study designed to evaluate the efficacy and safety of ibrutinib versus rituximab in adult Asia Pacific region patients with relapsed/refractory CLL or SLL with active disease requiring treatment who have failed at least 1 prior line of therapy and are not considered appropriate candidates for treatment or retreatment with purine analog-based therapy.
<b>Publications – title, author, journal, year</b>	Huang X, Qiu L, Jin J, Zhou D, Chen X, Hou M, et al. Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study. Cancer medicine. 2018;(no pagination) [36]
<b>Study type and design</b>	Randomized, Multicenter, Open-Label, Phase 3 Study. Approximately 150 patients will be randomly assigned in a 1:2 ratio into 2 treatment arms to receive either intravenous rituximab (Treatment Arm A) for 6 cycles or oral ibrutinib (Treatment Arm B) until disease progression or unacceptable toxicity, whichever occurs first. The study will include screening, treatment, and follow-up phases. Treatment will extend from randomization until study drug discontinuation. Follow-up will consist of 2 phases: post-treatment (from the discontinuation of treatment for reasons other than disease progression until the patient has progressive disease) and post-disease progression (subsequent anticancer therapy and survival status will be recorded until death, lost to follow-up, consent withdrawal, or study closure). Patients in the rituximab arm with disease progression or who meet the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for requiring subsequent anti-CLL therapy may be considered for cross over to receive ibrutinib 420 mg orally, daily until disease progression, unacceptable toxicity, withdrawal from study, or until study end whichever occurs earliest. Efficacy evaluations will assess for disease response and progression in accordance with International Workshop on Chronic Lymphocytic Leukemia 2008 criteria. Serial pharmacokinetic (study of what a drug does to the body) blood samples will be collected in the ibrutinib treatment group. Safety will be assessed throughout the study.
<b>Follow-up time</b>	Median follow-up of 17.5 months

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Eastern Cooperative Oncology Group performance status of 0-1</li> <li>• Diagnosis of chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) that meets protocol-defined criteria</li> <li>• Laboratory values within protocol-defined parameters</li> <li>• Active disease meeting International Workshop on Chronic Lymphocytic Leukemia 2008 criteria</li> <li>• Received at least 1 prior therapy for CLL/SLL and not appropriate for treatment or retreatment with purine analog-based therapy</li> <li>• Measurable nodal disease by computed tomography</li> <li>• Female subjects of childbearing potential must have a negative serum or urine pregnancy test at Screening and agree to use highly effective methods of contraception during the study and for 90 days following the last dose with ibrutinib or 12 months following the last dose of rituximab</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Central nervous system lymphoma or leukemia</li> <li>• Prolymphocytic leukemia or history of or currently suspected Richter's transformation</li> <li>• Refractory to prior rituximab-based therapy</li> <li>• Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days prior to first dose of study drug</li> <li>• Corticosteroid use &gt;20 mg within 1 week prior to first dose of study drug</li> <li>• Radio- or toxin-conjugated antibody therapy within 10 weeks prior to first dose of study drug</li> <li>• Prior autologous transplant within 6 months prior to first dose of study drug</li> <li>• Prior allogeneic stem cell transplant</li> <li>• Major surgery within 4 weeks prior to first dose of study drug</li> <li>• History of prior malignancy according to protocol-defined criteria</li> <li>• Currently active clinically significant cardiovascular disease within 6 months prior to first dose with study drug</li> <li>• Uncontrolled active systemic fungal, bacterial, viral, or other ongoing anti-infective treatment administered intravenously</li> <li>• History of human immunodeficiency virus or active infection with hepatitis B or C</li> <li>• History of stroke or intracranial hemorrhage within 6 months prior to random assignment</li> <li>• Pregnant or lactating women</li> <li>• Current life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, or put the study at risk</li> <li>• Requires or receiving anticoagulation with warfarin or equivalent Vitamin K antagonists</li> <li>• Requires treatment with a strong CYP3A4/5 inhibitor</li> <li>• Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), defined as declining hemoglobin or platelet count secondary to autoimmune</li> </ul>
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**Table A2 Main study characteristics Huang**

	<p>destruction within the screening period or requirement for high doses of steroids (greater than [<math>&gt;</math>]20 milligram [mg] daily of prednisone daily or equivalent)</p>
<p><b>Intervention</b></p>	<p><b>Arm A</b> Up to 6 cycles (total of 8 doses administered by intravenous infusion): 375 mg/m<sup>2</sup> on Day 1 of Cycle 1, 500 mg/m<sup>2</sup> on Day 15 of Cycle 1 (Weeks 1-4); 500 mg/m<sup>2</sup> on Day 1 and Day 15 of Cycle 2 (Weeks 5-8); and 500 mg/m<sup>2</sup> on Day 1 of Cycles 3-6 (Weeks 9-24).</p> <p><b>Arm B</b> 420 mg capsules administered by mouth daily until disease progression or unacceptable toxicity, whichever occurs first.</p>

## Baseline characteristics

**Table 1.** Demographics and baseline disease characteristics (ITT population).

	Ibrutinib (n = 106)	Rituximab (n = 54)	Total (N = 160)
<b>Age</b>			
Category, n (%)			
<65	52 (49.1)	23 (42.6)	75 (46.9)
≥65 to 69	22 (20.8)	12 (22.2)	34 (21.3)
≥70	32 (30.2)	19 (35.2)	51 (31.9)
Mean (SD)	63.6 (10.4)	63.6 (13.0)	63.6 (11.3)
Median	65	67	66
Range	(39, 87)	(21, 86)	(21, 87)
<b>Sex, n (%)</b>			
Female	29 (27.4)	18 (33.3)	47 (29.4)
Male	77 (72.6)	36 (66.7)	113 (70.6)
<b>Race, n (%)</b>			
Chinese	91 (85.8)	45 (83.3)	136 (85.0)
White	14 (13.2)	8 (14.8)	22 (13.8)
Asian, not Chinese	1 (0.9)	0	1 (0.6)
Other	0	1 (1.9)	1 (0.6)
<b>Initial diagnosis to randomization (months)</b>			
Mean (SD)	54.7 (57.8)	64.9 (58.7)	58.1 (58.1)
Median	40.1	45.9	41.1
Range	(0.0, 405.4)	(3.8, 283.5)	(0.0, 405.4)
<b>Initial diagnosis, n (%)</b>			
CLL	100 (94.3)	51 (94.4)	151 (94.4)
SLL	6 (5.7)	3 (5.6)	9 (5.6)
<b>Baseline Rai stage (CLL only), n (%)</b>			
N	99	51	150
0	0	0	0
I	9 (9.1)	11 (21.6)	20 (13.3)
II	11 (11.1)	3 (5.9)	14 (9.3)
III	18 (18.2)	9 (17.6)	27 (18.0)
IV	61 (61.6)	28 (54.9)	89 (59.3)
<b>Baseline Binet stage (CLL only), n (%)</b>			
N	100	51	151
A	2 (2.0)	4 (7.8)	6 (4.0)
B	25 (25.0)	10 (19.6)	35 (23.2)
C	73 (73.0)	37 (72.5)	110 (72.8)
<b>Prior purine analog therapy, n (%)</b>			
Yes	69 (65.1)	42 (77.8)	111 (69.4)
Failed to respond	28 (26.4)	12 (22.2)	40 (25.0)
Relapse <6 months	9 (8.5)	7 (13.0)	16 (10.0)
Relapse ≥6 to	5 (4.7)	6 (11.1)	11 (6.9)
<12 months			
Relapse ≥12 to	13 (12.3)	6 (11.1)	19 (11.9)
<24 months			
Relapse ≥24 months	10 (9.4)	9 (16.7)	19 (11.9)
Not evaluable/	4 (3.8)	2 (3.7)	6 (3.8)



<p>Primary and secondary endpoints</p>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression-free Survival (PFS) [ Time Frame: From the date of randomization to the date of disease progression or death, whichever was first reported (Up to 3.7 years) ] Progression-free survival was defined as the interval between the date of randomization and the date of disease progression or death, whichever was first reported. International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria for progressive disease (PD): New enlarged nodes greater than (&gt;)1.5 centimeter (cm), new hepatomegaly or splenomegaly, or other organ infiltrates; greater than or equal to (<math>\geq</math>)50 percent (%) increase from nadir in existing lymph node or <math>\geq</math>50% increase from nadir in sum of product of diameters of multiple nodes; <math>\geq</math>50% increase from nadir in enlargement of liver or spleen; <math>\geq</math>50% increase from baseline in lymphocyte count (and to <math>\geq 5 \times 10^9/L</math>) unless considered treatment-related lymphocytosis; New cytopenia (Hemoglobin b [Hgb] or platelets) attributable to chronic lymphocytic leukemia (CLL) and transformation to a more aggressive histology.</li> </ol> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Overall Response Rate (ORR) [ Time Frame: From the date of randomization to disease progression (Up to 3.7 years) ] ORR defined as number of participants achieving a complete response (CR), complete response with incomplete marrow recovery (CRi), nodular partial response (nPR) or partial response (PR). IWCLL 2008 criteria: CR- No lymphadenopathy and hepatosplenomegaly, no constitutional symptoms, neutrophils <math>&gt;1.5 \times 10^9/liter</math> (L), platelets <math>&gt;100 \times 10^9/L</math>, Hgb <math>&gt;11</math> gram per deciliter (g/dL) and absolute lymphocyte count <math>&lt;4000/microliter</math> (mCL); CRi- CR with incomplete recovery of bone marrow; nPR- participants meet criteria for CR, but the bone marrow biopsy shows B-lymphoid nodules, may represent a clonal infiltrate; PR- <math>\geq 50\%</math> drop in lymphocyte count from baseline or <math>\leq 4.0 \times 10^9/L</math> with following: <math>\geq 50\%</math> decrease in sum products of up to 6 lymph nodes, no new enlarged lymph nodes, When abnormal, <math>\geq 50\%</math> decrease in enlargement of spleen from baseline or normalization and a response in 1 of following: Neutrophils <math>&gt;1.5 \times 10^9/L</math>, Platelets <math>&gt;100000/mCL</math> and Hgb <math>&gt;11</math> g/dL or <math>\geq 50\%</math> improvement over baseline in all.</li> </ol>
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**Table A2 Main study characteristics Huang**

	<ol style="list-style-type: none"> <li>2. Overall Survival (OS) [ Time Frame: From the date of randomization to the date of death (Up to 3.7 years) ] Overall survival was defined as the interval between the date of randomization and the date of death from any cause.</li> <li>3. Number of Participants With Sustained Hematologic Improvement [ Time Frame: From the date of randomization to disease progression (Up to 3.7 years) ] Sustained hematologic improvement was defined as hematological improvement that was sustained continuously for greater than or equal to (<math>\geq</math>) 56 days without blood transfusion or growth factors: 1) Platelet counts greater than (<math>&gt;</math>)<math>100 \times 10^9</math>/liter (L) if baseline less than or equal to (<math>\leq</math>) <math>100 \times 10^9</math>/L or increase <math>\geq 50</math> percent (%) over baseline; 2) Hemoglobin <math>&gt;11</math> gram per deciliters (g/dL) if baseline <math>\leq 11</math> g/dL or increase <math>\geq 2</math> g/dL over baseline.</li> <li>4. Number of Participants With Clinically Relevant Shifts in Disease-Related Symptoms [ Time Frame: From the date of randomization to disease progression (Up to 3.7 years) ] The most common disease-related symptoms associated with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (fatigue, weight loss, fevers, night sweats, and abdominal discomfort/splenomegaly) were reported by grade.</li> </ol>
<b>Method of analysis</b>	<p>The study was designed to detect a hazard ratio (HR) of 0.54 for the ibrutinib arm relative to the rituximab arm with 80% power at a 1-sided significance level of 0.025. An interim analysis using O'Brien-Fleming boundary for superiority was planned after approximately 45 PFS events. The stopping boundary was implemented by Lan-DeMets alpha-spending function resembling the O'Brien-Fleming boundary. Overall survival was estimated with deaths due to any cause in the study considered as events. Distribution of OS was summarized for each treatment arm using median and its corresponding 95% CI based on Kaplan–Meier estimates. The HR estimate and its corresponding 95% CI were calculated using a Cox proportional hazards model stratified by the stratification factors.</p>

**Table A2 Main study characteristics Huang**

<b>Subgroup analyses</b>	<p>The primary efficacy analysis of PFS in the ITT population was compared using a stratified log-rank test based on the stratification factors. The estimate of the HR and its corresponding 95% CI were calculated using a Cox proportional hazards model stratified by stratification factors. A preplanned subgroup analysis of PFS based on prognostic variables was conducted.</p> <p>An ad hoc analysis of PFS was conducted using a multivariate Cox regression model with all key prognostic factors as covariates: treatment, age, sex, Rai stage at screening, baseline Eastern Cooperative Oncology Group score, prior lines of therapy, chromosome 11q deletion (del11q), bulky disease, refractory to purine analog therapy, and del17p</p>
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**Table A2 Main study characteristics Zelenits**
**Table A2 Main study characteristics Zelenits**

<b>Trial name</b>	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia
<b>NCT number</b>	NCT01569295
<b>Objective</b>	The primary objective of this study is to evaluate the effect of the addition of idelalisib (formerly GS-1101) to bendamustine + rituximab (BR) on progression-free survival (PFS) in participants with previously treated chronic lymphocytic leukemia (CLL)
<b>Publications – title, author, journal, year</b>	Zelenetz AD, Barrientos JC, Brown JR, Coiffier B, Delgado J, Egyed M, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. <i>The Lancet Oncology</i> . 2017;18(3):297-311. [37]
<b>Study type and design</b>	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study
<b>Follow-up time</b>	Median follow-up of 14 months

**Table A2 Main study characteristics Zelenits**

<b>Population (inclusion and exclusion criteria)</b>	<b>Key Inclusion Criteria:</b> <ul style="list-style-type: none"> <li>• Previously treated recurrent CLL</li> <li>• Measurable lymphadenopathy</li> <li>• Requires therapy for CLL</li> <li>• Has experienced CLL progression &lt; 36 months since the completion of the last prior therapy</li> </ul> <b>Key Exclusion Criteria:</b> <ul style="list-style-type: none"> <li>• Recent history of a major non-CLL malignancy</li> <li>• Evidence of an ongoing infection</li> <li>• CLL refractory to bendamustine</li> <li>• Concurrent participation in another therapeutic clinical trial</li> </ul>
<b>Intervention</b>	<p>Arm A: Idelalisib+bendamustine+rituximab</p> <p>Arm B: Placebo to match idelalisib+bendamustine+rituximab</p> <p>Idelalisib 150 mg administered orally twice daily</p> <p>Rituximab 375 mg/m<sup>2</sup> on Day 1, then 500 mg/m<sup>2</sup> every 28 days administered intravenously for a maximum of 6 infusions</p> <p>Bendamustine 70 mg/mg<sup>2</sup>/day on 2 consecutive days every 28 days administered intravenously for a maximum of 12 infusions</p>

**Table A2 Main study characteristics Zelenits**

Baseline characteristics	(n=207)		(n=209)		Idelalisib, bendamustine, and rituximab (n=207)		Placebo, bendamustine, and rituximab (n=209)	
	Age (years)	62 (56-69)		64 (56-70)				
Sex								
Men	160 (77%)		156 (75%)					
Women	47 (23%)		53 (25%)					
Ethnic origin								
White	187 (90%)		190 (91%)					
Non-white	20 (10%)		19 (9%)					
Time since diagnosis (months)	74 (46-120)		75 (50-111)					
Rai stage at screening								
0	1 (1%)		5 (2%)					
I	40 (19%)		41 (20%)					
II	61 (29%)		71 (34%)					
III	20 (10%)		16 (8%)					
IV	82 (40%)		69 (33%)					
Unknown	3 (1%)		7 (3%)					
Number of previous treatment regimens	2 (1-4)		2 (1-4)					
Patients refractory to fludarabine	34 (16%)		37 (18%)					
Did not receive anti-CD20 antibody	2 (<1%)		1 (<1%)					
Previous treatment regimens								
Fludarabine-containing regimen	192 (93%)		189 (90%)					
Fludarabine, cyclophosphamide, and rituximab	140 (68%)		138 (66%)					
Fludarabine and cyclophosphamide	50 (24%)		43 (21%)					
Chlorambucil	38 (18%)		37 (18%)					
Bendamustine-containing regimen	37 (18%)		22 (11%)					
(Table 1 continues in next column)								
					(Continued from previous column)			
					Bendamustine and rituximab		Bendamustine alone	
					30 (14%)		17 (8%)	
					1 (<1%)		2 (<1%)	
					Disease status			
					Relapsed		137 (66%)	
					137 (66%)		141 (68%)	
					Refractory		70 (34%)	
					70 (34%)		68 (33%)	
					Chronic lymphocytic leukaemia genetics			
					Del(17p)		38 (18%)	
					38 (18%)		40 (19%)	
					No del(17p)		169 (82%)	
					169 (82%)		169 (81%)	
					Del(17p) and/or TP53 mutation		69 (33%)	
					69 (33%)		68 (33%)	
					Unmutated IGHV		173 (84%)	
					173 (84%)		173 (83%)	
					Duration of exposure (months)		14.8 (5.9-18.0)	
					14.8 (5.9-18.0)		11.4 (5.8-15.3)	
					Patient disposition*			
					Met primary endpoint†		34 (16%)	
					34 (16%)		100 (48%)	
					Discontinued study		83 (40%)	
					83 (40%)		64 (31%)	
					Continuing study treatment		90 (43%)	
					90 (43%)		45 (22%)	
					Reason for early discontinuation from study treatment			
					Adverse event		56 (27%)	
					56 (27%)		28 (13%)	
					Physician decision		7 (3%)	
					7 (3%)		24 (11%)	
					Withdrawal by patient		12 (6%)	
					12 (6%)		8 (4%)	
					Other		4 (2%)	
					4 (2%)		3 (1%)	
					Other therapy initiated		1 (<1%)	
					1 (<1%)		1 (<1%)	
					Lost to follow-up		1 (<1%)	
					1 (<1%)		0	
					Non-compliance		2 (<1%)	
					2 (<1%)		0	
					Data are median (IQR) or n (%). *Per investigator assessment; †disposition from study treatment; ‡Disease progression or death.			
					Table 1: Baseline characteristics			

**Table A2 Main study characteristics Zelenits**

<b>Primary and secondary endpoints</b>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression-Free Survival (PFS) [ Time Frame: Up to 84 months ] <ul style="list-style-type: none"> <li>PFS was defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. <math>PFS (months) = (\text{minimum} (\text{date of disease progression, date of death}) - \text{date of randomization} + 1) / 30.4375</math></li> </ul> </li> </ol> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Overall Response Rate (ORR) [ Time Frame: Up to 84 months ] ORR was the percentage of participants who achieved a complete response (CR), CR with incomplete marrow recovery (CRi,) or partial response (PR) and maintained the response for at least 12 weeks. CR was defined as no lymphadenopathy, hepatomegaly, splenomegaly; normal complete blood count; confirmed by bone marrow aspirate &amp; biopsy. PR was defined as &gt;1 of the following criteria: a 50% decrease in peripheral blood lymphocytes, lymphadenopathy, liver size, spleen size; plus <math>\geq 1</math> of the following: <math>\geq 1500/\mu\text{L}</math> absolute neutrophil count, <math>&gt; 100000/\mu\text{L}</math> platelets, <math>&gt; 11.0 \text{ g/dL}</math> hemoglobin or 50% improvement for either of these parameters without transfusions or growth factors. CRi was defined as all criteria for CR met but with persistent anemia, thrombocytopenia, neutropenia or a hypocellular bone marrow.</li> <li>2. Lymph Node Response Rate [ Time Frame: Up to 84 months ] Lymph node response rate was defined as the percentage of participants who achieved a <math>\geq 50\%</math> decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lesions</li> <li>3. Overall Survival [ Time Frame: Up to 84 months ] <ul style="list-style-type: none"> <li>Overall survival (OS) was defined as the interval from randomization to death from any cause. <math>\text{Overall survival (months)} = (\text{date of death} - \text{date of randomization} + 1) / 30.4375</math></li> </ul> </li> <li>4. Complete Response Rate [ Time Frame: Up to 84 months ] Complete response (CR) rate was defined as the percentage of participants who achieved a CR.</li> </ol>
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**Table A2 Main study characteristics Zelenits**

<b>Method of analysis</b>	With a hazard ratio (HR) equal to 1 under the null hypothesis and an HR of 0.67 under the alternative hypothesis, 260 events of definitive chronic lymphocytic leukaemia progressions were required to achieve a power of 0.90 on the basis of a stratified log-rank test with a two-sided significance level of 0.05. To compensate for a 15% expected rate of loss to follow-up, an estimated sample size of around 195 patients in each group (ie, a total of 390 patients) was needed. To preserve the overall type I error rate across the primary and secondary endpoints, a sequential testing procedure was applied. Secondary endpoints were tested at a two-sided 0.032 significance level.
<b>Subgroup analyses</b>	Categorical variables were compared using the Cochran-Mantel-Haenszel test adjusted for stratification factors.

**Table A2 Main study characteristics ELEVATE RR**
**Table A2 Main study characteristics ELEVATE R/R**

<b>Trial name</b>	ELEVATE-RR
<b>NCT number</b>	
<b>Objective</b>	This phase III trial prospectively compared the efficacy and safety of acalabrutinib with ibrutinib in patients with previously treated CLL to test the hypothesis that acalabrutinib was noninferior to ibrutinib in PFS with improved tolerability.
<b>Publications – title, author, journal, year</b>	<i>Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2021</i>
<b>Study type and design</b>	Randomised, multicentre, open-label Phase III non-inferiority trial. Patients were randomised (1:1) into two arms.
<b>Follow-up time</b>	Median follow-up of 41 months

<p><b>Population (inclusion and exclusion criteria)</b></p>	<p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Men and women <math>\geq 18</math> years of age.</li> <li>• ECOG performance status of 0 to 2.</li> <li>• Diagnosis of CLL.</li> <li>• Must have <math>\geq 1</math> of the following high-risk prognostic factors:             <ul style="list-style-type: none"> <li>○ Presence of 17p del by central laboratory.</li> <li>○ Presence of 11q del by central laboratory.</li> </ul> </li> <li>• Active disease meeting <math>\geq 1</math> of the following IWCLL 2008 criteria for requiring treatment</li> <li>• Must have received <math>\geq 1</math> prior therapies for CLL.</li> <li>• Meet the following laboratory parameters:             <ul style="list-style-type: none"> <li>○ ANC <math>\geq 750</math> cells/<math>\mu</math>L or <math>\geq 500</math> cells/<math>\mu</math>L in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.</li> <li>○ Platelet count <math>\geq 30,000</math> cells/<math>\mu</math>L without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded.</li> <li>○ Serum AST/SGOT and ALT/SGPT <math>\leq 3.0 \times</math> ULN.</li> <li>○ Total bilirubin <math>\leq 1.5 \times</math> ULN.</li> <li>○ Estimated creatinine clearance <math>\geq 30</math> mL/min.</li> </ul> </li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Known CNS lymphoma or leukemia.</li> <li>• Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.</li> <li>• Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.</li> <li>• Prior exposure to ibrutinib or to a BCR inhibitor or a BCL-2 inhibitor.</li> <li>• Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.</li> <li>• Prior radio- or toxin-conjugated antibody therapy.</li> <li>• Prior allogeneic stem cell or autologous transplant.</li> </ul>
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**Table A2 Main study characteristics ELEVATE R/R**

	<ul style="list-style-type: none"> <li>• Major surgery within 4 weeks before first dose of study drug.</li> <li>• Prior malignancy, except for adequately treated lentigo maligna melanoma, non-melanomatous skin cancer, in situ cervical carcinoma or other malignancy treated with no evidence of active disease &gt; 3 years before Screening and at low risk for recurrence.</li> <li>• Significant cardiovascular disease within 6 months of screening.</li> <li>• Known history of infection with HIV.</li> <li>• History of stroke or intracranial hemorrhage within 6 months before randomization.</li> <li>• History of bleeding diathesis.</li> <li>• Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days of first dose of study drug.</li> <li>• Requires treatment with a strong CYP3A inhibitor/inducer.</li> </ul>
<b>Intervention</b>	<p>Calquence (100mg orally twice daily) until disease progression          Ibrutinib (420mg orally once daily) until disease progression or unacceptable toxicity</p>

**Table A2 Main study characteristics ELEVATE R/R**

Baseline characteristics	ITT Population	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
	Median age, years (range)		66 (41-89)
≥75 years, n (%)		44 (16%)	43 (16%)
≥65 years, n (%)		144 (54%)	143 (54%)
Male sex, n (%)		185 (69%)	194 (73%)
Median time from diagnosis to randomization, months (range)		84.8 (1.6-434)	73.0 (1.4-278)
Mean (SD)		95.43 (63.38)	83.36 (52.47)
Median time from last treatment to randomisation, months (range)		19 (0-175)	19 (0-183)
Rai Stage, n (%)			
III		40 (15%)	46 (17%)
IV		91 (34%)	88 (33%)
Bulky Disease, (%)			
≥ 5 cm		128 (48%)	136 (51%)
≥10 cm		33 (12%)	34 (13%)
β2-microglobulin >3.5 mg/L, n (%)		207 (77%)	214 (81%)
Cytopenia at Baseline, Any		148 (55%)	137 (52%)
Neutropenia: ANC <= 1.5x10 <sup>9</sup> /L		25 ( 9.3%)	18 ( 6.8%)
Anaemia: HGB <= 11g/dL		100 ( 37.3%)	96 ( 36.2%)
Thrombocytopenia: PLT <= 100x10 <sup>9</sup> /L		96 ( 35.8%)	92 ( 34.7%)

**Table A2 Main study characteristics ELEVATE R/R**

<b>Primary and secondary endpoints</b>	<p>Primary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Progression-free survival in Arm A compared to Arm B</li> </ol> <p>Secondary Outcome Measures :</p> <ol style="list-style-type: none"> <li>1. Incidence of treatment-emergent Grade <math>\geq 3</math> infections in Arm A versus Arm B</li> <li>2. Incidence of Richter's transformation in Arm A versus Arm B</li> <li>3. Incidence of Atrial fibrillation in Arm A versus Arm B</li> <li>4. Overall survival in Arm A versus Arm B</li> </ol>
<b>Method of analysis</b>	
<b>Subgroup analyses</b>	<ul style="list-style-type: none"> <li>• Age</li> <li>• race</li> <li>• sex</li> <li>• ECOG status</li> <li>• geographic region</li> <li>• presence of chromosomal abnormalities (17p deletion)</li> <li>• number of prior therapies</li> <li>• tumor load and disease stage (Rai)</li> <li>• investigator-assessed PFS</li> </ul>

<b>Trial name:</b>	<b>ELEVATE-TN- A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination With Chlorambucil, Acalabrutinib (ACP-196) in Combination With Obinutuzumab, and Acalabrutinib Monotherapy in Subjects With Previously Untreated CLL [6]</b>									
<b>NCT number:</b>	NCT02475681									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>Median PFS</b>	Acalabrutinib+Obinutuzumab	179	Not reached	NA	NA	NA	90% relative risk reduction in death or progression  HR=0.1	0.06–0.17	p<0.0001	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Acalabrutinib	179	Not reached	NA	NA	NA	[HR] 0.20	0.13–0.3	p<0.0001	
	Chlorambucil + obinutuzumab	177	22.6 months (CI:20.2-27.6)	NA	NA	NA	NA	NA	NA	

<b>Estimated PFS at 24 months</b>	Acalabrutinib+Obinutuzumab	179	93%	NA	87–96%	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Acalabrutinib	179	87%	NA	81–92%	NA	NA	NA	NA	
	Chlorambucil + obinutuzumab	177	47%	NA	39–55	NA	NA	NA	NA	
<b>Median time to event (Progression or death)</b>	Acalabrutinib+Obinutuzumab	14(179)	12.7 months	NA	IQR 8.3–20.2	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Acalabrutinib	26(179)	13.9 months	NA	IQR 5.7–23.4	NA	NA	NA	NA	
	Chlorambucil + obinutuzumab	93(177)	16.4 months	NA	IQR 11.8–21.0	NA	NA	NA	NA	
<b>Estimated PFS at 24 months Unmutated IGHV</b>	Acalabrutinib+Obinutuzumab	103(177)	91%	NA	83–95%	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Chlorambucil + obinutuzumab	106(177)	31%	NA	22–40%	NA	NA	NA	NA	
<b>Estimated PFS at 24 months mutated IGHV</b>	Acalabrutinib+Obinutuzumab	74(179)	96%	NA	87–99%	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional

										modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Chlorambucil + obinutuzumab	59(177)	76%	NA	61–86%	NA	NA	NA	NA	
<b>Estimated PFS at 24 months del(17)(p13. 1)</b>	Acalabrutinib+Obinutuzumab	17(179)	88%	NA	61–97%	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Chlorambucil + obinutuzumab	16(177)	22%	NA	5–45%	NA	NA	NA	NA	
<b>Estimated PFS at 24 months mutated TP53</b>	Acalabrutinib+Obinutuzumab	21(179)	95%	NA	70–99%	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Chlorambucil + obinutuzumab	21(177)	19%	NA	5–41%	NA	NA	NA	NA	
<b>Best overall response</b>	Acalabrutinib+Obinutuzumab	179	94%	NA	89–97	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Chlorambucil + obinutuzumab	177	79%		72–84%	p<0.0001	NA	NA	NA	
<b>Median overall survival</b>	Acalabrutinib+Obinutuzumab	179	NR	NA	NA		HR 0.47 (vs Chlorambucil + obinutuzumab)	0.21-1.06	p=0.06	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional

										modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Acalabrutinib	179	NR				HR 0.60 (vs Chlorambucil + obinutuzumab)	0.28-1.27	p=0.16	
	Chlorambucil + obinutuzumab	177	NR							
<b>Estimated overall survival at 24 months</b>	Acalabrutinib+Obinutuzumab	179	95%	NA	91-97%	NA	NA	NA	NA	Time-to-event endpoints were estimated by use of the Kaplan–Meier method. HRs were calculated by use of Cox proportional modelling, stratified by randomisation stratification factors, and compared by use of a log-rank test.
	Acalabrutinib	179	95%	NA	90-97%	NA	NA	NA	NA	
	Chlorambucil + obinutuzumab	177	92%	NA	86-95%	NA	NA	NA	NA	
<b>Grade 3 or above AEs</b>	Acalabrutinib+Obinutuzumab	178	70.2%	NA	NA	NA	RR=1.01	(0.87-1.15)	NA	AEs and SAEs as coded using the MedDRA reporting system (version 21.1) and graded according to the NCI CTCAE (version 4.03). Safety was analysed in all patients who received at least one dose of any study Calculated by AstraZeneca
	Acalabrutinib	179	49.7%	NA	NA	NA	RR=0.71	(0.60-0.85)	NA	Calculated by AstraZeneca
	Chlorambucil + obinutuzumab	169	69.8%	NA	NA	NA	NA	NA	NA	
<b>SAEs (any grade)</b>	Acalabrutinib+Obinutuzumab	178	38.8%	NA	NA	NA	RR=1.67	(1.15-2.42)	NA	AEs and SAEs as coded using the MedDRA reporting system (version 21.1) and graded according to the NCI CTCAE (version 4.03). Safety was analysed in all patients who received at least one dose of any study Calculated by AstraZeneca

	Acalabrutinib	179	31.8%	NA	NA	NA	RR=1.52	(1.04-2.22)	NA	Calculated by AstraZeneca
	Chlorambucil + obinutuzumab	169	21.9%	NA	NA	NA	NA	NA	NA	Calculated by AstraZeneca
<b>AEs leading to discontinuation</b>	Acalabrutinib+Obinutuzumab	178	11.2%	NA	NA	NA	RR=0.75	(0.43-1.32)	NA	Safety was analysed in all patients who received at least one dose of any study. Calculated by AstraZeneca
	Acalabrutinib	179	8.9%	NA	NA	NA	RR=0.67	(0.37-1.20)	NA	Calculated by AstraZeneca
	Chlorambucil + obinutuzumab	169	14.1%	NA	NA	NA	NA	NA	NA	



Table A3b ASCEND

<b>Trial name:</b>	<b>ASCEND-A</b> Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects With R/R Chronic Lymphocytic Leukemia [9, 10]									
<b>NCT number:</b>	NCT02970318									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>Median PFS</b>	Acalabrutinib	155	NR	NA	NA	NA	NA	NA	NA	A stratified log-rank test was used for the primary comparison of IRC-assessed PFS. A stratified Cox regression model was used to provide estimated PFS HRs and the two-sided 95% CIs. For the primary analysis of IRC-assessed PFS, for patients who were alive and had not had disease progression, the data were censored on the date of the last disease assessment prior to subsequent anticancer therapy (including acalabrutinib monotherapy for patients who crossed over).
	Idelalisib+ Rituximab/BR	155 (119/36)	16.5 months		14.0 to 17.1 months		HR:0.31	0.20 to 0.49	P < .0001	
<b>Median PFS (mFU of 22 monts)</b>	Acalabrutinib	155	NR							

	Idelalisib+ Rituximab/BR	155 (119/36)	16.8months				HR:0.27		P < .0001	
<b>Estimated 12-month PFS</b>	Acalabrutinib	155	88%	NA	81-92%	NA	NA	NA	NA	A stratified log-rank test was used for the primary comparison of IRC-assessed PFS. A stratified Cox regression model was used to provide estimated PFS HRs and the two-sided 95% CIs. For the primary analysis of IRC-assessed PFS, for patients who were alive and had not had disease progression, the data were censored on the date of the last disease assessment prior to subsequent anticancer therapy (including acalabrutinib monotherapy for patients who crossed over).
	Idelalisib+ Rituximab/BR	155 (119/36)	68% / 69%	NA	58%-76% / 50%-82%	NA	NA	NA	NA	
<b>18-m PFS rates at 22month FU (Inv)</b>	Acalabrutinib	155	82%	NA	NA	NA	NA	NA	NA	Distributions of time-to-event endpoints, including PFS, OS, duration of response, and time to next treatment were estimated using the Kaplan–Meier method.
	Idelalisib+ Rituximab/BR	155 (119/36)	48%	NA	NA	NA	NA	NA	NA	
<b>IRC-assessed ORR</b>	Acalabrutinib	155	81%	NA	NA	NA	NA	NA	NA	To adjust for multiple testing, the prespecified hierarchical testing of two key secondary efficacy endpoints was performed in the following order: IRC-assessed ORR and OS.

										Because the study met its primary endpoint, a formal statistical test of IRC-assessed ORR between the two arms was performed at the two-sided significance level of 0.05 using a stratified Cochran–Mantel– Haenszel test. As this endpoint was not statistically significant, P values for the subsequent hierarchically tested endpoints could be considered only descriptive.
	Idelalisib+ Rituximab/BR	155 (119/36)	75%	NA	NA	NA	NA	NA	NA	
<b>ORR (Inv) 22m FU</b>	Acalabrutinib	155	80%	NA	NA	NA	NA	NA	NA	To adjust for multiple testing, the prespecified hierarchical testing of two key secondary efficacy endpoints was performed in the following order: IRC-assessed ORR and OS. Because the study met its primary endpoint, a formal statistical test of IRC-assessed ORR between the two arms was performed at the two-sided significance level of 0.05 using a stratified Cochran–Mantel– Haenszel test. As this endpoint was not statistically significant, P values for the subsequent hierarchically tested endpoints could be considered only descriptive.

	Idelalisib+ Rituximab/BR	155 (119/36)	84%	NA	NA	NA	NA	NA	NA	
<b>Median OS</b>	Acalabrutinib	155	NR	NA	NA	NA	HR:0.84	0.421.66	NA	Distributions of time-to-event endpoints, including PFS, OS, duration of response, and time to next treatment were estimated using the Kaplan–Meier method.
	Idelalisib+ Rituximab/BR	155 (119/36)	NA	NA	NA	NA	NA	NA	NA	
<b>OS at 12 months</b>	Acalabrutinib	155	94%	NA	89%-97%	NA	NA	NA	NA	Distributions of time-to-event endpoints, including PFS, OS, duration of response, and time to next treatment were estimated using the Kaplan–Meier method.
	Idelalisib+ Rituximab/BR	155 (119/36)	91%	NA	85%-94%	NA	NA	NA	NA	
<b>OS at 18 months 22m FU</b>	Acalabrutinib	155	88%	NA		NA	NA	NA	NA	Distributions of time-to-event endpoints, including PFS, OS, duration of response, and time to next treatment were estimated using the Kaplan–Meier method.
	Idelalisib+ Rituximab/BR	155 (119/36)	88%	NA	NA	NA	NA	NA	NA	
<b>Serious AEs</b>	Acalabrutinib	154	29%	NA	NA	NA	NA	NA	NA	All efficacy analyses were conducted in the intention-to-treat population. Safety was analyzed according to actual treatment received in all randomized patients who received ≥1 dose of any study medication were included in the safety analyses.

	Idelalisib+ Rituximab/BR	155 (119/36)	56% / 26%	NA	NA	NA	NA	NA	NA	
<b>Grade 3/4 AEs</b>	Acalabrutinib	154	45%	NA	NA	NA	RR=0.53(vs IR) RR=1.05(vs. BR)	(0.43-0.64) (0.69-1.60)	NA NA	AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. RR Calculated by AZ
	Idelalisib+ Rituximab/BR	118/35	86%/43%	NA	NA	NA	NA	NA	NA	
<b>AEs led to discontinuation</b>	Acalabrutinib	155	11%	NA	NA	NA	RR=0.22(vs IR) RR=0.96(vs. BR)	(0.14-0.36) (0.34-2.68)	NA	AEs were graded using the National Cancer Institute
	Idelalisib+ Rituximab/BR	118/35	49% / 11%	NA	NA	NA	NA	NA	NA	
<b>AEs led to discontinuation mFU 22months</b>	Acalabrutinib	155	16%	NA	NA	NA	NA	NA	NA	AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
	Idelalisib+ Rituximab/BR	118/35	56% / 17%	NA	NA	NA	NA	NA	NA	NA

Table A3b RESONATE-2

<b>Trial name:</b>	<b>RESONATE-2</b> Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma [14]									
<b>NCT number:</b>	NCT01722487									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>5 year Estimated PFS</b>	Ibrutinib	136	70%	NA	NA	NA	HR=0.146	0.098–0.22		PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	12%	NA	NA	NA	NA	NA	NA	
<b>5 year Estimated OS</b>	Ibrutinib	136	83%	NA	NA	NA	HR=0.450	0.266–0.76		PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	68%	NA	NA	NA	NA	NA	NA	

<b>5 year Estimated PFS - TP53 mutation, 11q deletion, and/or unmutated IGHV)</b>	ibrutinib	136	NA	NA	NA	NA	HR=0.083	0.05–0.15	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	NA	NA	NA	NA	NA	NA	NA	
<b>5 year Estimated OS - TP53 mutation, 11q deletion, and/or unmutated IGHV)</b>	ibrutinib	136	NA	NA	NA	NA	HR=0.37	0.18–0.74	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	NA	NA	NA	NA	NA	NA	NA	
<b>5 year Estimated PFS unmutated IGHV)</b>	ibrutinib	136	NA	90%	NA	NA	NA	NA	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	NA	NA	NA	NA	NA	NA	NA	
<b>5 year Estimated PFS mutated IGHV)</b>	ibrutinib	136		85%	NA	NA	NA	NA	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of

										crossover on OS, sensitivity analyses were performed
	chlorambucil	133		NA	NA	NA	NA	NA	NA	
<b>Median PFS at 5 years</b>	ibrutinib	136	NR	NA	10.2–19.4		NA	NA	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	15 m	NA	NA	NA	NA	NA	NA	
<b>5 year PFS -TP53 mutation or TP53 wild type</b>	ibrutinib	136	NA	NA	NA	NA	0.866	0.26–2.85	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	NA	NA	NA	NA	NA	NA	NA	
<b>5-year estimates PFS -TP53 mutation or TP53 wild type</b>	ibrutinib	136	56% and 73%, respectively	NA	NA	NA	NA	NA	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	NA	NA	NA	NA	NA	NA	NA	



<b>5 year Median OS</b>	ibrutinib	136	NR	NA	NA	NA	NA	NA	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	NR	NA	NA	NA	0.450	0.27–0.76		
<b>5 year Estimated OS</b>	ibrutinib	136	83%	NA	NA	NA	NA	NA	NA	PFS and OS were analyzed according to the Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	68%	NA	NA	NA	NA	NA	NA	
<b>5 year OS- TP53 mutation, del[11q], and/or unmutated IGHV),</b>	ibrutinib	136	84%	NA	NA	NA	NA	NA	NA	Kaplan–Meier method. To adjust for the impact of crossover on OS, sensitivity analyses were performed
	chlorambucil	133	62%	NA	NA	NA	0.376	0.180–0.786	NA	
<b>ORR</b>	ibrutinib	136	92%	NA	NA	NA	NA	NA	NA	
	chlorambucil	133	37%	NA	NA	NA	NA	NA	NA	
<b>Grade &gt;3 AEs</b>	ibrutinib	136	83%	NA	NA	NA	NA	NA	NA	Nonhematologic adverse events (AEs) were graded

										using Common Terminology Criteria for Adverse Events, v4.03 [13]. Hematologic AEs were graded using iwCLL criteria
	chlorambucil	133	-	NA	NA	NA	NA	NA	NA	

Table A3b Alliance

<b>Trial name:</b>	ALLIANCE-Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients (≥65 Years of Age) With Chronic Lymphocytic Leukemia (CLL) [15]									
<b>NCT number:</b>	NCT01886872									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
2-year Estimated PFS	BR	183	74%				0.39 (ibrutinib vs BR)	0.26 - 0.58	<0.001	estimated that a sample of 332 patients, with an expected 159 events, would provide the trial with 90% power to detect a hazard ratio for disease progression or death of 0.586 at a one-sided significance level of 0.025 by a log-rank test. The same assumptions, sample, and power calculation applied for the comparison of ibrutinib plus rituximab with bendamustine plus rituximab. If ibrutinib and ibrutinib plus rituximab were each superior to bendamustine plus rituximab, then ibrutinib

										plus rituximab was to be compared with ibrutinib. For the comparison of ibrutinib plus rituximab with ibrutinib, we estimated that a sample of 332 patients, with an expected 119 events, would provide the trial with 90% power to detect a hazard ratio of 0.57 (corresponding to an estimated percentage of patients with progressionfree survival at 2 years of 75% with ibrutinib and 85% with ibrutinib plus rituximab), at a onesided significance level of 0.05 by a log-rank test.
	ibrutinib	182	87%				1.00 (Ibrutinib vs Ibrutinib+R)	0.62 to 1.62	0.49	
	ibrutinib +R	182	88%				0.38 (ibrutinib+R vs BR)	0.25- 0.59	<0.001	
<b>2 year Estimated OS</b>	BR	183	95	91%-98%	NA	NA	NA	NA	P≥0.65 for all pairwise comparisons	
	ibrutinib	182	90%	85% - 94%	NA	NA	NA	NA	P≥0.65 for all pairwise comparisons	
	ibrutinib +R	182	94%	89%-97%	NA	NA	NA	NA	P≥0.65 for all pairwise comparisons	
<b>ORR</b>	BR	183	81%	75%-87%	NA	NA	NA	NA		

	Ibrutinib	182	93%	88%-96%	NA	NA	NA	NA	NA	NA
	Ibrutinib +R	182	94%	89%-97%	NA	NA	NA	NA	NA	NA
<b>grade 3, 4, or 5 hematologic AEs</b>	BR	183	61%	NA	NA	NA	NA	NA	NA	NA
	Ibrutinib	182	41%	NA	NA	NA	NA	NA	NA	NA
	Ibrutinib +R	182	39%	NA	NA	NA	NA	NA	NA	NA
<b>grade 3, 4, or 5 non hematologic AEs</b>	BR	183	63%	NA	NA	NA	NA	NA	NA	NA
	Ibrutinib	182	74%	NA	NA	NA	NA	NA	NA	NA
	Ibrutinib +R	182	74%	NA	NA	NA	NA	NA	NA	NA

Table A3b Ahn

<b>Trial name:</b>	Ahn-A Phase II Study of PCI-32765 for Patients With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Need Therapy and Are Older Than 65 or Have a 17p Deletion [16]									
<b>NCT number:</b>	NCT01500733									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>TP53 cohort- Estimated 5-year PFS</b>	Ibrutinib (TN)	34	74.4%	NA	NA	NA	NA	NA	NA	OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test.
	Ibrutinib (R/R)	16	19.4%	NA		0.0002	NA	NA	NA	
<b>TP53 cohort Estimated 5-year PFS</b>	Ibrutinib (TN+R/R)	51	58.2%	NA	44.5%-74.5%	NA	NA	NA	NA	OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test.
<b>Elderly cohort Estimated 5-year PFS</b>	Ibrutinib (TN+R/R)	35	81.2%	NA	67.1%-98.3%	0.026	NA	NA	NA	OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test.
<b>The elderly cohort, the estimated 5-year PFS</b>	Ibrutinib TN	18	100%	NA	NA	NA	NA	NA	NA	OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test.

	Ibrutinib R/R	16	64.8%	NA	43.9%-95.7%	NA	NA	NA	NA	
<b>TP53 cohort- OS</b>	Ibrutinib (TN)	34	85.3%	NA	74.2%-98.1%	0.023	NA	NA	NA	OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test.
	Ibrutinib (R/R)	16	53.7%	NA	33.4%-86.4%	NA	NA	NA	NA	
<b>TP53 cohort-median OS</b>	Ibrutinib (TN+R/R)	51	75.7%	NA	64.7%-88.7%	NA	NA	NA	NA	OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test.
<b>TP53 cohort-median OS was</b>	Ibrutinib	35	83.8%	NA	70%-100%	NA	NA	NA	NA	
<b>The elderly cohort OS</b>		18	100%	NA		NA	NA	NA	NA	
	Ibrutinib R/R	16	71.6%	NA	51.2%-100%	NA	NA	NA	NA	OS and PFS were estimated by the Kaplan-Meier method and compared between subgroups by the log-rank test.
<b>ORR at 6 months</b>	Ibrutinib Tp53 cohort	51	95.8%	NA	85.7%-99.5%	NA	NA	NA	NA	Simon's minimax 2-stage design to test the null hypothesis that the ORR is 15% or less vs the 1-sided alternative. If 3 or more responses were observed among 16 patients of the first stage, an additional 11 would enter the second

										stage. With 8 or more responses, the null hypothesis would be rejected. For each cohort, 27 patients provide 90% power at the 0.05 significance level when the true response rate is 40%.
	Ibrutinib Elderly cohort	35	93.9%		79.8%-99.3%	NA	NA	NA	NA	
<b>ORR-All patients at 6 months</b>	Ibrutinib	86	95.1%		87.8%-98.6%	NA	NA	NA	NA	Simon's minimax 2-stage design to test the null hypothesis that the ORR is 15% or less vs the 1-sided alternative. If 3 or more responses were observed among 16 patients of the first stage, an additional 11 would enter the second stage. With 8 or more responses, the null hypothesis would be rejected. For each cohort, 27 patients provide 90% power at the 0.05 significance level when the true response rate is 40%.



Table A3b RESONATE

<b>Trial name:</b>	<b>RESONATE</b> -A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [19-21]									
<b>NCT number:</b>	NCT01578707									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>PFS at median FU of 9.4 months</b>	Ibrutinib	195	NR	NA	NA	NA	NA	NA	NA	The primary analysis was a two-sided log-rank test stratified according to the presence or absence of the chromosome 17p13.1 deletion and the disease refractory status at randomization. The type I error was controlled through adjustment of the significance level with the use of the O'Brien–Fleming boundary for the interim analysis and with the use of a hierarchical closed-testing procedure for primary and ordered secondary end points.
	Ofatumumab	196	8.1 months	NA	NA	NA	0.22	NA	P<0.001	

<b>6 month PFS rate</b>	Ibrutinib	195	88%	NA	NA	NA	78% risk reduction			
	Ofatumumab	196	65%	NA	NA	NA			NA	
<b>17p13.1 del median PFS</b>	Ibrutinib	63	NR	NA	NA	NA	HR:0.25	0.14-0.45	NA	
	Ofatumumab	64	5.8 months	NA	NA	NA	NA	NA	NA	
<b>17p13.1 del 6 month PFS rate</b>	Ibrutinib	63	83%	NA	NA	NA	NA	NA	NA	
	Ofatumumab	64	49%	NA	NA	NA	NA	NA	NA	
<b>OS</b>	Ibrutinib	195		NA	NA	NA	HR: 0.43		P = 0.005	
	Ofatumumab	196		NA	NA	NA	NA	NA	NA	
<b>12 month OS rate</b>	Ibrutinib	195	90%	NA	NA	NA	NA	NA	NA	
	Ofatumumab	196	81%	NA	NA	NA	NA	NA	NA	
<b>ORR</b>	Ibrutinib	195	42.6%	NA	NA	P<0.001	NA	NA	NA	
	Ofatumumab	196	4.1%	NA	NA	NA	NA	NA	NA	
<b>AE grade 3 or higher</b>	Ibrutinib	195	57%	NA	NA	NA	NA	NA	NA	Patients in the ibrutinib group had a reporting period for adverse events that was more than 3 months longer than that in the ofatumumab group and no exposure-adjusted analysis of adverse events was performed
	Ofatumumab	196	47%	NA	NA	NA	NA	NA	NA	

<b>At least one SAE</b>	Ibrutinib	195	42%	NA	NA	NA	NA	NA	NA	
	Ofatumumab	196	30%	NA	NA	NA	NA	NA	NA	
<b>Discontinuation due to AE</b>	Ibrutinib	195	4%	NA	NA	NA	NA	NA	NA	
	Ofatumumab	196	4%	NA	NA	NA	NA	NA	NA	
<b>Inv. Median PFS</b>	Ibrutinib	195	44.1 months		38.5-56.2		HR: 0.148	0.113-0.196	P.0001	PFS and OS (with and without censoring at crossover for ofatumumab patients) were analyzed using Kaplan-Meier methodology and hazard ratio (HR) was estimated using Cox regression model. In addition, the rank-preserving structural failure time (RPSFT) randomization-based model was employed to estimate the OS HR using counterfactual survival times that would have been observed in the absence of the extensive crossover
	Ofatumumab	196	8.1 months	NA	7.8-8.3	NA	NA	NA	NA	
<b>Inv. 60-month landmark PFS rate</b>	Ibrutinib	195	40%	NA		NA	NA	NA	NA	
	Ofatumumab	196	3%	NA		NA	NA	NA	NA	
<b>Inv. del[17p], TP53 mutation,</b>	Ibrutinib	168	44.1 months	NA	38.5-56.9	NA	NA	NA	NA	

<b>del[11q], and/or unmutated IGHV status PFS</b>										
	Ofatumumab	154	8 months	NA	6.4-8.2	NA	HR: 0.110	0.080-0.152	NA	
<b>Inv. median OS (6 yrs post rand FU)</b>	Ibrutinib	195	67.7 months	NA	61.0-NE	NA			NA	
	Ofatumumab	196	65.1 months	NA	50.6-NE	NA	HR:0.810	0.602-1.091	NA	
<b>OS with censoring at time of crossover</b>	Ibrutinib	195	NA	NA	NA	NA	HR: 0.639	0.418-0.975	NA	
	Ofatumumab	196	NA	NA	NA	NA			NA	
<b>OS based on the RPSFT</b>	Ibrutinib	195	NA	NA	NA	NA	HR:0.240	0.105-0.550	NA	
	Ofatumumab	196	NA	NA	NA	NA	NA	NA	NA	
<b>Discontinuation due to AE at median treatment duration of 41 months</b>	Ibrutinib	195	16%	NA	NA	NA	NA	NA	NA	
	Ofatumumab	196	NA	NA	NA	NA	NA	NA	NA	

Table A3b COMPLEMENT-1

<b>Trial name:</b>	<b>COMPLEMENT-1</b> A Phase III, Open Label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil Versus Chlorambucil Monotherapy in Previously Untreated Patients With Chronic Lymphocytic Leukemia [22]									
<b>NCT number:</b>	NCT00748189									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>Median PFS</b>	Chlorambucil + Obinutuzumab	221	22.4 months	NA	19.0–25.2	NA	NA	NA	NA	Summarized progression-free survival in Kaplan-Meier curves and compared treatment groups with a stratified log-rank test adjusted for randomisation stratification factors. Progression-free survival was censored for patients with two or more missing visits or start of alternative chronic lymphocytic leukaemia treatment before progression or death. did secondary time-

										to-event endpoint analyses with Kaplan-Meier estimates. compared response rates between the treatment groups with use of a Mantel-Haenszel test that was adjusted for stratification factors.
	Chlorambucil	226	13.1 months	NA	10.6–13.8	NA	0.57	0.45–0.72	p<0.0001	
<b>PFS</b> <b>patients aged &lt;65 years</b>	Chlorambucil + Obinutuzumab	42	NA	NA	NA	NA	NA	0.34–0.85	NA	Summarised progression-free survival in Kaplan-Meier curves and compared treatment groups with a stratified log-rank test adjusted for randomisation stratification factors. Progression-free survival was censored for patients with two or more missing visits or start of alternative chronic lymphocytic leukaemia treatment before progression or

										death. did secondary time-to-event endpoint analyses with Kaplan-Meier estimates. compared response rates between the treatment groups with use of a Mantel-Haenszel test that was adjusted for stratification factors.
	Chlorambucil	38	NA	NA	NA	NA	NA	NA	NA	
<b>PFS ≥65 years</b>	Chlorambucil + Obinutuzumab	109					0.57	0.43–0.76		summarised progression-free survival in Kaplan-Meier curves and compared treatment groups with a stratified log-rank test adjusted for randomisation stratification factors. Progression-free survival was censored for patients with two or more missing visits or start of alternative chronic lymphocytic leukaemia

										treatment before progression or death. did secondary time-to-event endpoint analyses with Kaplan-Meier estimates. compared response rates between the treatment groups with use of a Mantel-Haenszel test that was adjusted for stratification factors.
	Chlorambucil	98	NA	NA	NA	NA	NA	NA	NA	
<b>PFS ≥75 years</b>	Chlorambucil + Obinutuzumab	42	NA	NA	NA	NA	0.56	0.35–0.89	NA	Summarized progression-free survival in Kaplan-Meier curves and compared treatment groups with a stratified log-rank test adjusted for randomisation stratification factors. Progression-free survival was censored for patients with two or more missing visits or start of alternative chronic



										lymphocytic leukaemia treatment before progression or death. did secondary time-to-event endpoint analyses with Kaplan-Meier estimates. compared response rates between the treatment groups with use of a Mantel-Haenszel test that was adjusted for stratification factors.
	Chlorambucil	33	NA	NA	NA	NA	NA	NA	NA	
<b>PFS 17p del</b>	Chlorambucil + Obinutuzumab	11	NA	NA	NA	NA	0.46	0.18–1.19	Non significant	summarised progression-free survival in Kaplan-Meier curves and compared treatment groups with a stratified log-rank test adjusted for randomisation stratification factors. Progression-free survival was censored for patients with two or more missing visits or start of

										alternative chronic lymphocytic leukaemia treatment before progression or death. did secondary time-to-event endpoint analyses with Kaplan-Meier estimates. compared response rates between the treatment groups with use of a Mantel-Haenszel test that was adjusted for stratification factors.
	Chlorambucil	6	NA	NA	NA	NA	NA	NA	NA	
<b>OS at median follow-up 28.9 months,</b>	Chlorambucil + Obinutuzumab	221	NR	NA	NA	NA	NA	NA	NA	secondary time-to-event endpoint analyses with Kaplan-Meier estimates. compared response rates between the treatment groups with use of a Mantel-Haenszel test that was

										adjusted for stratification factors.
	Chlorambucil	226	NR	NA	NA	NA	NA	NA	NA	
<b>OS 2 years</b>	Chlorambucil + Obinutuzumab	196	89%	NA	NA	NA	NA	NA	NA	
	Chlorambucil	196	87%	NA	NA	NA	NA	NA	NA	
<b>3 year OS chlorambucil</b>	Chlorambucil + Obinutuzumab	188	85%	NA	NA	NA	NA	NA	NA	
	Chlorambucil	188	83%	NA	NA	NA	NA	NA	NA	
<b>Grade ≥3 AEs</b>	Chlorambucil + Obinutuzumab	221	50%	NA	NA	NA	NA	NA	NA	
	Chlorambucil	226	43%	NA	NA	NA	NA	NA	NA	

Table A3b CAM307

<b>Trial name:</b>	CAM307- A Phase III Study to Evaluate the Efficacy and Safety of Front-Line Therapy With Alemtuzumab (Campath, MabCampath) vs Chlorambucil in Patients With Progressive B-Cell Chronic Lymphocytic Leukemia [23]									
<b>NCT number:</b>	NCT00046683									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>PFS</b>	<b>Alemtuzumab</b>	149	NA	42% risk reduction	0.58	0.0001	NA	NA	NA	All time-to-event distributions were calculated using Kaplan-Meier method, reported in months, and compared using stratified (Rai stage I to II v III to IV) log-rank test. HRs were calculated using Cox model stratified for Rai stage. Response rates were compared using $\chi^2$ test or Fisher's exact test, as appropriate. by PFS (stratified log-rank $P_{.0001}$ ).
	<b>Chlorambucil</b>	148	NA	NA	NA	NA	NA	NA	NA	

median PFS	<b>Alemtuzumab</b>	149	14.6 months	NA	12.3 to 21.7 months	NA	NA	NA	NA	PFS (stratified log-rank $P_{.0001}$ ).
	<b>Chlorambucil</b>	148	11.7 months	NA	9.9 to 13.2 months	NA	NA	NA	NA	
Median OS	<b>Alemtuzumab</b>	149	NR	NA	NA	NA	NA	NA	NA	All time-to-event distributions were calculated using Kaplan-Meier method, reported in months, and compared using stratified (Rai stage I to II v III to IV) log-rank test. HRs were calculated using Cox model stratified for Rai stage. Response rates were compared using $\chi^2$ test or Fisher's exact test, as appropriate.
	<b>Chlorambucil</b>	148	NR	NA	NA	NA	NA	NA	NA	
Serious drug-related AEs	<b>Alemtuzumab</b>	149	26.5%	NA	NA	NA	NA	NA	NA	Safety was analyzed for all patients who received at least one dose of study drug.
	<b>Chlorambucil</b>	148	6.8%	NA	NA	NA	NA	NA	NA	

Table A3b CLL11

<b>Trial name:</b>	CLL11- An Open-label, Multi-center, Three Arm Randomized Study to Investigate the Safety and Efficacy on Progression-free Survival of RO5072759 + Chlorambucil (GClb) Compared to Rituximab + Chlorambucil (RClb) or Chlorambucil (Clb) Alone in Previously Untreated CLL Patients With Comorbidities. [24]									
<b>NCT number:</b>	NCT01010061									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
median PFS	Obinutuzumab+chlorambucil	238	26.7 months	NA	NA	NA	0.18	0.13 to 0.24	P<0.001	The primary analysis was a two-sided log rank test stratified according to Binet stage. The type 1 error was controlled through the closed testing procedure (the global test was a three-group log-rank test). The comparison between the obinutuzumab - chlorambucil group and the rituximab-chlorambucil group included two interim looks at the data and an O'Brien-Fleming efficacy boundary with a Lan-DeMets alpha-spending function to adjust for multiple comparisons.

	chlorambucil	116	11.1 months	NA	NA	NA	NA	NA	NA	
<b>median PFS</b>	rituximab–chlorambucil	233	16.3 months	NA	NA	NA	0.44	0.34 to 0.57	P<0.001	
	chlorambucil	116	11.1 months	NA	NA	NA				
<b>OS</b>	<b>obinutuzumab–chlorambucil</b>	238		NA	NA	NA	<b>0.41</b>	<b>0.23 to 0.74</b>	<b>0.002</b>	Secondary end points were analyzed with the use of a two sided test at a 5% alpha level without adjustment for multiple comparisons
	<b>chlorambucil</b>	116		NA	NA	NA	NA	NA	NA	
<b>PFS</b>	<b>obinutuzumab–chlorambucil</b>	333					<b>0.39</b>	<b>0.31 to 0.49</b>	<b>P&lt;0.001</b>	The primary analysis was a two-sided log rank test stratified according to Binet stage. The type 1 error was controlled through the closed testing procedure (the global test was a three-group log-rank test). The comparison between the obinutuzumab - chlorambucil group and the rituximab–chlorambucil group included two interim looks at the data and an O'Brien–Fleming efficacy boundary with a Lan–DeMets alpha-spending function to adjust for multiple comparisons.

	rituximab–chlorambucil	330		NA	NA	NA	NA	NA	NA	
<b>Grade ≥3 AEs</b>	Obinutuzumab+chlorambucil	238	73%	NA	NA	NA	NA	NA	NA	
	chlorambucil	118	50%	NA	NA	NA	NA	NA	NA	
<b>Grade ≥3 AEs</b>	rituximab–chlorambucil	233	56%	NA	NA	NA	NA	NA	NA	
	chlorambucil	116	50%	NA	NA	NA	NA	NA	NA	
<b>Grade ≥3 AEs</b>	obinutuzumab–chlorambucil	333	70%	NA	NA	NA	NA	NA	NA	
	rituximab–chlorambucil	330	55%	NA	NA	NA	NA	NA	NA	



Table A3b Tedeschi

Trial name:		Tedeschi A, Greil R, Demirkan F <i>et al.</i> A cross-trial comparison of single-agent ibrutinib versus chlorambucil-obinutuzumab in previously untreated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. <i>Haematologica</i> 2019.[25]									
NCT number:		NCT01578707 and NCT01722487 + NCT01724346									
					Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Hazard/Odds/Risk ratio	95% CI	P value		
PFS median	Ibrutinib	136	NR	83% reduction in risk of progression	NA	NA	0.184	0.111-0.306	P<0.0001	Analysis of PFS performed in the ITT population (as assessed by the IRC) for the 2 treatment arms using a stratified log-rank test based on the 2 randomization stratification factors: Rai stage and ECOG performance score. Distribution of PFS summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% confidence interval (CI). The estimate of the	

										hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. A sensitivity analysis of PFS will be conducted based on the investigator assessment.
	Chlorambucil + Obinutuzumab	98	22.2 months	NA	NA	NA	NA	NA	NA	
<b>30-month PFS</b>	Ibrutinib	136	85%	NA	NA	NA	NA	NA	NA	analysis of PFS performed in the ITT population (as assessed by the IRC) for the 2 treatment arms using a stratified log-rank test based on the 2 randomization stratification factors: Rai stage and ECOG performance score. Distribution of PFS summarized for each treatment arm using the Kaplan-Meier estimate of median and its

										corresponding 95% confidence interval (CI). The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. A sensitivity analysis of PFS will be conducted based on the investigator assessment.
	Chlorambucil + Obinutuzumab	98	40%							
<b>PFS high-risk population (patients with TP53 mutation, del(11q), and/or unmutated IGHV status).</b>	Ibrutinib	74	NR	93% reduction in risk of progression or death	NA	NA	0.072	0.034-0.152	P<0.0001	analysis of PFS performed in the ITT population (as assessed by the IRC) for the 2 treatment arms using a stratified log-rank test based on the 2 randomization stratification factors: Rai stage and ECOG performance score. Distribution of PFS summarized for each treatment arm using the Kaplan-

										Meier estimate of median and its corresponding 95% confidence interval (CI). The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. A sensitivity analysis of PFS will be conducted based on the investigator assessment.
	Chlorambucil + Obinutuzumab	57	18.3 months	NA	NA	NA	NA	NA	NA	
<b>30 month PFS high-risk population (patients with TP53 mutation, del(11q), and/or unmutated IGHV status).</b>	Ibrutinib	74	89%	NA	NA	NA	NA	NA	NA	analysis of PFS performed in the ITT population (as assessed by the IRC) for the 2 treatment arms using a stratified log-rank test based on the 2 randomization stratification factors: Rai stage and ECOG performance score. Distribution of PFS summarized for each

										treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% confidence interval (CI). The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. A sensitivity analysis of PFS will be conducted based on the investigator assessment.
	Chlorambucil + Obinutuzumab	57	19%	NA	NA	NA	NA	NA	NA	
<b>PFS unmutated IGHV [excluded patients with del(17p)]</b>	ibrutinib	58	NR				0.074	<b>0.033-0.164;</b>	<b>P&lt;0.0001</b>	analysis of PFS performed in the ITT population (as assessed by the IRC) for the 2 treatment arms using a stratified log-rank test based on the 2 randomization stratification factors: Rai stage and ECOG performance score. Distribution of PFS

										summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% confidence interval (CI). The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. A sensitivity analysis of PFS will be conducted based on the investigator assessment.
	Chlorambucil + Obinutuzumab	48	18 months	NA	NA	NA	NA	NA	NA	
<b>30-month OS</b>	ibrutinib	136	92%	NA	NA	NA	NA	NA	NA	Survival rate at landmark points will be summarized for each treatment group using Kaplan-Meier point estimates in the primary analysis
	Chlorambucil + Obinutuzumab	98	84%	NA	NA	NA	NA	NA	NA	

<b>Grade ≥3 AEs first 6 months</b>	ibrutinib	135	50%	NA	NA	NA	NA	NA	NA	Safety analyses presented in accordance with the treatment actually received by patients
	Chlorambucil + Obinutuzumab	97	71%							
<b>Grade ≥3 AES total adverse event reporting period</b>	ibrutinib	135	81%	NA	NA	NA	NA	NA	NA	Safety analyses presented in accordance with the treatment actually received by patients
	Chlorambucil + Obinutuzumab	97	71%	NA	NA	NA	NA	NA	NA	

Table A3b CLL-10

<b>Trial name:</b>	NCT00769522									
<b>NCT number:</b>	CLL-10-Phase III Trial of Combined Immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Bendamustine and Rituximab (BR) in Patients With Previously Untreated Chronic Lymphocytic Leukaemia [26, 27]									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>58.2months median PFS</b>	BR	282	42.3months	NA	NA	NA	1.593	1.271–1.996	<0.0001	Time-to-event efficacy endpoints were analyzed using both Kaplan–Meier methodology. Hazard ratios (HRs) including 95% confidence intervals (CI) were calculated using proportional hazards Cox regressions and tested using the likelihood ratio test.
	FCR	279	57.6months	NA	NA	NA	NA	NA	NA	
<b>Patients&gt;65years, median PFS (58.2months)</b>	BR	108	48.5months	NA	NA	NA	1.352	0.91–2.00;	0.134	Time-to-event efficacy endpoints were analyzed using both Kaplan–Meier methodology. Hazard ratios (HRs) including 95% confidence intervals (CI) were calculated using proportional hazards Cox regressions and tested using the likelihood ratio test.
	FCR	86	57.9months	NA	NA	NA	NA	NA	NA	



<b>Patients&lt;65years, median PFS (58.2months)</b>	BR	171	38.2	NA	NA	NA	1.771	1.344–2.335	<0.0001	
	FCR	196	57.6 months	NA	NA	NA	NA	NA	NA	
<b>unmutated IGHV PFS (58.2months)</b>	BR	183	33.9 months	NA	NA	NA	1.545	1.181–2.022	0.0015	
	FCR	152	43 months	NA	NA	NA	NA	NA	NA	
<b>mutated IGHV PFS (58.2months)</b>	BR	87	68.9 months	NA	NA	NA	1.356	0.872–2.137	0.173	
	FCR	123	NR	NA	NA	NA	NA	NA	NA	
<b>Median OS (58.2months)</b>	BR	282	NR	NA	NA	NA	NA	NA	NA	Time-to-event efficacy endpoints were analyzed using both Kaplan–Meier methodology. Hazard ratios (HRs) including 95% confidence intervals (CI) were calculated using proportional hazards Cox regressions and tested using the likelihood ratio test.
	FCR	279	NR	NA	NA	NA	NA	NA	NA	
<b>5-year OS</b>	BR	282	80.1%				1.108	0.755–1.627	0.599	Time-to-event efficacy endpoints were analyzed using both Kaplan–Meier methodology. Hazard ratios (HRs) including 95% confidence intervals (CI) were calculated using proportional hazards Cox regressions and tested using the likelihood ratio test.

	FCR	279	80.9%	NA	NA	NA	NA	NA	NA	
<b>5-year OS &lt;65yrs</b>	BR	171	81.1%				1.516	0.894-2.581	0.122	
	FCR	196	85.6%	NA	NA	NA	NA	NA	NA	
<b>5-year OS &gt;65yrs</b>	BR	108	78.8%				0.712	0.403-1.256	0.241	
	FCR	86	70.9%	NA	NA	NA	NA	NA	NA	
<b>5-year OS IGHV unmutated</b>	BR	183	72.9%				1.203	0.767-1.887	0.420	
	FCR	152	75.5%	NA	NA	NA	NA	NA	NA	
<b>5-year OS IGHV unmutated</b>	BR	87	93.3%	NA	NA	NA	NA	NA	NA	
	FCR	123	87.6%				0.573	0.236-1.393	0.219	
<b>Grade&gt;3 AEs Median 37.1 months</b>	BR	278	84%	NA	NA	NA	NA	NA	NA	
	FCR	279	94%	NA	NA	NA	NA	NA	NA	

Table A3b MABLE

<b>Trial name:</b>	MABLE-Randomized Study to Assess the Effect on Response Rate of MabThera (Rituximab) Added to a Standard Chemotherapy, Bendamustine or Chlorambucil, in Patients With Chronic Lymphocytic Leukemia [28]									
<b>NCT number:</b>	NCT01056510									
				Estimated absolute difference in effect			Estimated relative difference in effect			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
median PFS (23.5 months BR/23.3 months Chlb-R)	BR	121	40 months	NA	NA	0.003	NA	NA	NA	Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). PFS and OS were summarized by Kaplan–Meier estimates and compared <i>via</i> the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the Cox proportional hazard model, with and without baseline Binet stage as a covariate.
	Chlb-R	120	30 months	NA	NA	NA	NA	NA	NA	
<b>ORRs (based on the investigator’s assessment) at the end of rituximab treatment</b>	BR	121	91%	NA	NA	NA	NA	NA	NA	
	Chlb-R	120	86%			0.304				A twosided continuity-corrected $\chi^2$ test assessed

										between-arm differences in overall response rates (ORRs)
<b>PFS was observed with R-B versus R-C1b</b>	BR	121	39.6 months		NA	NA	NA	NA	NA	Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). PFS and OS were summarized by Kaplan–Meier estimates and compared <i>via</i> the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the Cox proportional hazard model, with and without baseline Binet stage as acovariate.
	Ch1b-R	120	29.9 months				0.523	0.339-0.806	0.003	
<b>median OS [adjusted for baseline Binet stage]</b>	BR	121	43.8 months	NA	NA	NA	NA	NA	NA	Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). PFS and OS were summarized by Kaplan–Meier estimates and compared <i>via</i> the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on

										the Cox proportional hazard model, with and without baseline Binet stage as a covariate.
	ChIb-R	120	NR				0.975	0.505-1.880	0.939	
<b>Grade &gt;3 AEs</b>	ChIb-R	120	75%	NA	NA	NA	NA	NA	NA	Safety results are presented for the pooled population (1L and 2L patients).
	BR	121	64%	NA	NA	NA	NA	NA	NA	

Table A3b Illuminate

<b>Trial name:</b>	MABLE-Randomized Study to Assess the Effect on Response Rate of MabThera (Rituximab) Added to a Standard Chemotherapy, Bendamustine or Chlorambucil, in Patients With Chronic Lymphocytic Leukemia [28]									
<b>NCT number:</b>	NCT01056510									
				Estimated absolute difference in effect			Estimated relative difference in effect			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
median PFS (23.5 months BR/23.3 months Chlb-R)	BR	121	40 months	NA	NA	0.003	NA	NA	NA	Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). PFS and OS were summarized by Kaplan–Meier estimates and compared <i>via</i> the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the Cox proportional hazard model, with and without baseline Binet stage as a covariate.
	Chlb-R	120	30 months	NA	NA	NA	NA	NA	NA	
<b>ORRs (based on the investigator’s assessment) at the end of rituximab treatment</b>	BR	121	91%	NA	NA	NA	NA	NA	NA	
	Chlb-R	120	86%			0.304				A twosided continuity-corrected $\chi^2$ test assessed

										between-arm differences in overall response rates (ORRs)
<b>PFS was observed with R-B versus R-C1b</b>	BR	121	39.6 months		NA	NA	NA	NA	NA	Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). PFS and OS were summarized by Kaplan–Meier estimates and compared <i>via</i> the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the Cox proportional hazard model, with and without baseline Binet stage as acovariate.
	Ch1b-R	120	29.9 months				0.523	0.339-0.806	0.003	
<b>median OS [adjusted for baseline Binet stage]</b>	BR	121	43.8 months	NA	NA	NA	NA	NA	NA	Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients). PFS and OS were summarized by Kaplan–Meier estimates and compared <i>via</i> the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on

										the Cox proportional hazard model, with and without baseline Binet stage as a covariate.
	ChIb-R	120	NR				0.975	0.505-1.880	0.939	
<b>Grade &gt;3 AEs</b>	ChIb-R	120	75%	NA	NA	NA	NA	NA	NA	Safety results are presented for the pooled population (1L and 2L patients).
	BR	121	64%	NA	NA	NA	NA	NA	NA	



<b>Trial name:</b>	Illuminate									
<b>NCT number:</b>	NCT02264574									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>median PFS (IRC)</b>	ibrutinib plus obinutuzumab	113	NR	NA	33·6–non-estimable	NA	0·23	0·15–0·37	p<0·0001	Time-to-event endpoints were estimated using the Kaplan-Meier method; HRs were calculated using Cox proportional hazards modelling, and treatment groups were compared using the log-rank test.
	chlorambucil plus obinutuzumab	116	19·0 months		15·1–22·1					
<b>30-month PFS</b>	ibrutinib plus obinutuzumab	113	79%	NA	70–85	NA	NA	NA	NA	endpoints were estimated using the Kaplan-Meier method; HRs were calculated using Cox proportional hazards modelling, and treatment groups were compared using the log-rank test.
	chlorambucil plus obinutuzumab	116	36%	NA	23–40	NA	NA	NA	NA	

<b>investigator-assessed PFS</b>	ibrutinib plus obinutuzumab	113	NR	NA	33·6–NE	NA	0·26	0·16-0·42	<b>p&lt;0·0001</b>	endpoints were estimated using the Kaplan-Meier method; HRs were calculated using Cox proportional hazards modelling, and treatment groups were compared using the log-rank test.
	chlorambucil plus obinutuzumab	116	21·9 months	NA	18·4–26·7	NA	NA	NA	NA	
<b>PFS del17p</b>	ibrutinib plus obinutuzumab	14	NR	NA	14·7–NR	NA	NA	NA	NA	Prespecified subgroup analyses of efficacy outcomes by baseline characteristics, including by high-risk features, were also done For IRC Assessed endpoints (progression-free survival and overall response), sensitivity analyses were done using investigator assessments.
	chlorambucil plus obinutuzumab	18	11·3 months	NA	9·5–15·3	NA	NA	NA	NA	
<b>PFS uIGHV</b>	ibrutinib plus obinutuzumab	66/107	NR		NR-NR	NA	NA	NA	NA	Prespecified subgroup analyses of efficacy outcomes by baseline characteristics, including by high-risk features, were also done For IRC Assessed endpoints

										(progression-free survival and overall response), sensitivity analyses were done using investigator assessments.
	chlorambucil plus obinutuzumab	57/107	14.6 months	NA	11.1–15.1	NA	NA	NA	NA	
<b>grade 3 or 4 AEs</b>	ibrutinib plus obinutuzumab	77	68%	NA	NA	NA	NA	NA	NA	Safety was analysed according to actual treatment received in all patients who received at least one dose of any study medication.
	chlorambucil plus obinutuzumab	80	70%	NA	NA	NA	NA	NA	NA	
<b>Median OS</b>	ibrutinib plus obinutuzumab	113	NR	0.92	0.48–1.77	NA	NA	NA	NA	
	chlorambucil plus obinutuzumab	116	NR	NA	NA	NA	NA	NA	NA	
<b>OS 30 months</b>	ibrutinib plus obinutuzumab	113	86%	NA	77-91	NA	NA	NA	NA	endpoints were estimated using the Kaplan-Meier method; HRs were calculated using Cox proportional hazards modelling, and treatment groups were compared using the log-rank test
	chlorambucil plus obinutuzumab	116	85%	NA	77-90	NA	NA	NA	NA	

Table A3b HELIOS

<b>Trial name:</b>	HELIOS- Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination With Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [30]									
<b>NCT number:</b>	NCT01611090									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>PFS</b>	Ibrutinib	289	NR	NA	NA	NA	0.203	0.150–0.276	p<0.0001	The distribution of time-to-event endpoints, including progression-free survival and overall survival, was estimated by the Kaplan-Meier method. All statistical tests were based on a two-sided alpha level of 0.05. To adjust for unequal lengths of study treatment duration among patients, and potentially between treatment groups, exposure-adjusted incidence was also used.
	Placebo	289	13.3 months	NA	11.3–13.9	NA	NA	NA	NA	
<b>IRC-assessed PFS at 18 months</b>	Ibrutinib	289	79%	NA	73–83	NA	NA	NA	NA	The distribution of time-to-event endpoints, including progression-free

										survival and overall survival, was estimated by the Kaplan-Meier method. All statistical tests were based on a two-sided alpha level of 0.05. To adjust for unequal lengths of study treatment duration among patients, and potentially between treatment groups, exposure-adjusted incidence was also used.
	Placebo	289	24%	NA	18–31	NA	0.203	0.150–0.276	p<0.0001	The distribution of time-to-event endpoints, including progression-free survival and overall survival, was estimated by the Kaplan-Meier method. All statistical tests were based on a two-sided alpha level of 0.05. To adjust for unequal lengths of study treatment duration among patients, and potentially between treatment groups, exposure-adjusted incidence was also used.
<b>Median OS</b>	Ibrutinib	289	NR	NA	NA	NA	0.628	0.385–1.024;	p=0.0598	
	Placebo	289	NR	NA	NA	NA	NA	NA	NA	NA

<b>PFS when adjusting for crossover</b>	Ibrutinib	289+90 crossing over	NR	NA	NA	NA	0.577, 95% CI;	0.348–0.957	p=0.033	
	Placebo	90/289 pts crossed over to Ibrutinib	NR	NA	NA	NA	NA	NA	NA	NA
<b>grade 3–4 AEs</b>	Ibrutinib	287	77%	NA	NA	NA	NA	NA	NA	NA
	Placebo	287	74%	NA	NA	NA	NA	NA	NA	NA

Table A3b CLL14

<b>Trial name:</b>	CLL14- A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare The Efficacy and Safety of A Combined Regimen of Obinutuzumab and Venetoclax Versus Obinutuzumab and Chlorambucil in Previously Untreated Patients With CLL and Coexisting Medical Conditions [31]									
<b>NCT number:</b>	NCT02242942									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>PFS 24 months</b>	venetoclax–obinutuzumab	216	88.2%	NA	83.7 to 92.6	NA	NA	NA	NA	Median PFS and 95% confidence limits were estimated using the Brookmeyer–Crowley method, with the Kaplan–Meier survival curve presented to provide a visual description. PFS rates for 1, 2, and 3 years after randomization with 95% CIs using the Brookmeyer–Crowley method were reported. Estimates of the treatment effect were expressed as the HR including 95% CIs estimated through a Cox proportional hazards analysis stratified by Binet stage and geographic region
	chlorambucil–Obinutuzumab	216	64.1%		57.4 to 70.8					

<b>OS</b>	venetoclax–obinutuzumab	216	NA	NA	NA	NA	1.24	0.64 to 2.40	NA	NA
	chlorambucil–Obinutuzumab	216	NA	NA	NA	NA	NA	NA	NA	NA
<b>grade 3 or 4 AEs</b>	venetoclax–obinutuzumab	212	78.8%	NA	NA	NA	NA	NA	NA	NA
	chlorambucil–Obinutuzumab	214	76.5%	NA	NA	NA	NA	NA	NA	NA



Table A3b Furman

<b>Trial name:</b>	Furman-A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia [34]									
<b>NCT number:</b>	NCT01539512									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>Median PFS</b>	Idelalisib plus Rituximab	110	NR	NA	NA	NA	NA	NA	NA	All efficacy analyses were based on the intention- to-treat principle unless otherwise stated. For binary-response end points, the Cochran–Mantel–Haenszel chi-square test, was used and it was adjusted for stratification, to assess between group differences. A sequential testing procedure was applied to adjust for the overall type I error rate
	Placebo plus Rituximab	110	5.5 months	NA	NA	NA	0.15	0.08 to 0.28	P<0.001	

<b>24 weeks, PFS</b>	Idelalisib plus Rituximab	110	93%				0.15; 95% confidence interval [CI], 0.08 to 0.28; unadjusted P<0.001,	NA	NA	
	Placebo plus Rituximab	110	46%	NA	NA	NA				
<b>OS 12 months</b>	Idelalisib plus Rituximab	110	92%	NA	NA	NA	0.28	0.09 to 0.86	0.02	If the primary end point was significant, the secondary end points of rates of overall response, lymph-node response, and overall survival would be tested sequentially
	Placebo plus Rituximab	110	80%	NA	NA	NA	NA	NA	NA	
<b>Grade <math>\geq</math>3 AEs</b>	Idelalisib plus Rituximab	110	56%	NA	NA	NA	NA	NA	NA	
	Placebo plus Rituximab	107	48%	NA	NA	NA	NA	NA	NA	

Table A3b Jones

<b>Trial name:</b>	Jones- A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia [35]									
<b>NCT number:</b>	NCT01659021.									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>Median progression</b>	Idelalisib plus ofatumumab	174	16.3		(13.6–17.8)		0.27	0.19–0.39	<0.0001	Progression-free survival was calculated using the Kaplan-Meier method, and compared estimates using a stratified log-rank test. A Cox model with adjustment for stratification was used to calculate hazard ratios. For binary-response endpoints (ie, overall response and lymph node response), we used the Cochran-Mantel-Haenszel X2 test—adjusted for stratification—to assess between-group differences. A sequential testing procedure was applied to adjust

										for the overall type I error rate in the primary analysis.
	Ofatumumab	87	8.0	NA	5.7–8.2	NA	NA	NA	NA	
Median PFS del(17p) or TP53 mutated subgroup	Idelalisib plus ofatumumab	174	13.7 months	NA	11.0–17.8	NA	NA	NA	NA	survival was calculated using the Kaplan-Meier method, and compared estimates using a stratified log-rank test. A Cox model with adjustment for stratification was used to calculate hazard ratios. For binary-response endpoints (ie, overall response and lymph node response), we used the Cochran-Mantel-Haenszel X2 test—adjusted for stratification—to assess between-group differences. A sequential testing procedure was applied to adjust for the overall type I error rate in the primary analysis.
	Ofatumumab	87	5.8		4.5-8.4		0.32	0.18–0.57	<0.0001	
Median overall survival	Idelalisib plus ofatumumab	174	20.9 months		20.9-NR		0.74	0.44-1.25	0.27	survival was calculated using the Kaplan-Meier method, and compared estimates using a stratified

										log-rank test. A Cox model with adjustment for stratification was used to calculate hazard ratios. For binary-response endpoints (ie, overall response and lymph node response), we used the Cochran-Mantel-Haenszel X2 test—adjusted for stratification—to assess between-group differences. A sequential testing procedure was applied to adjust for the overall type I error rate in the primary analysis.
	Ofatumumab	87	19.4 months	NA	16.9-NR	NA	NA	NA	NA	
<b>Grade ≥ 3 AEs</b>	Idelalisib plus ofatumumab	173	91%	NA		NA	NA	NA	NA	
	Ofatumumab	86	56%	NA		NA	NA	NA	NA	

Table A3b Huang

<b>Trial name:</b>	Huang- A Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 (Ibrutinib) Versus Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [36]									
<b>NCT number:</b>	NCT01973387									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
PFS	ibrutinib	106	NA	NA	NA	NA	0.180	0.105–0.308	P < 0.0001	The primary efficacy analysis of PFS in the ITT population was compared using a stratified log-rank test based on the stratification factors. Distribution of PFS was summarized using median and corresponding 95% confidence interval (CI) based on Kaplan–Meier estimates. The estimate of the HR and its corresponding 95% CI were calculated using a Cox proportional hazards model stratified by stratification factors. A preplanned subgroup analysis of PFS based on

										prognostic variables was conducted. An ad hoc analysis of PFS was conducted using a multivariate Cox regression model with all key prognostic factors as covariates
	rituximab	54	NA	NA	NA	NA	NA	NA	NA	
<b>estimated 24-month OS</b>	ibrutinib	106	79.8%	NA	68.9–87.2%	NA	NA	NA	NA	Distribution of OS was summarized for each treatment arm using median and its corresponding 95% CI based on Kaplan–Meier estimates. The HR estimate and its corresponding 95% CI were calculated using a Coxproportion
	rituximab	54	57.6	NA	36.2–74.1%	NA	NA	NA	NA	
<b>OS</b>	ibrutinib	106	NA	NA	NA	NA	0.446	0.221–0.900	0.0206	Distribution of OS was summarized for each treatment arm using median and its corresponding

										95% CI based on Kaplan–Meier estimates. The HR estimate and its corresponding 95% CI were calculated using a Cox proportion
	rituximab	54		NA	NA	NA	NA	NA	NA	
<b>grade ≥3 AEs</b>	<b>ibrutinib</b>	104	<b>82.7%</b>	NA	NA	NA	NA	NA	NA	
	<b>rituximab</b>	52	<b>59.6%</b>	NA	NA	NA	NA	NA	NA	



Table A3b Zelenits

<b>Trial name:</b>	Zelenits- A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia [37]									
<b>NCT number:</b>	NCT01569295									
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
<b>Median PFS</b>	idelalisib	207	20.8 months	NA	16.6–26.4	NA	0.33	0.25–0.44	p<0.0001	the difference in progression-free survival between treatment groups was assessed by Kaplan-Meier methods and the stratified log-rank test. HRs and corresponding 95% CIs were calculated using a Cox proportional hazards regression model. Categorical variables were compared using the Cochran-Mantel-Haenszel test adjusted for stratification factors. All randomised patients were included in the efficacy analyses (intention-to-treat population).

	placebo	209	11.1 months	NA	8.9–11.1	NA	NA	NA	NA	
<b>Median PFS del(17p) or TP53 mutation (or both mutations)</b>	idelalisib	69	11.3 months		8.8-16.6		0.47	0.31-0.72	p<0.0001	the difference in progression-free survival between treatment groups was assessed by Kaplan-Meier methods and the stratified log-rank test. HRs and corresponding 95% CIs were calculated using a Cox proportional hazards regression model. Categorical variables were compared using the Cochran-Mantel-Haenszel test adjusted for stratification factors. All randomised patients were included in the efficacy analyses (intention-to-treat population).
	placebo	68	8.3 months	NA	5.9-8.5	NA	NA	NA	NA	
<b>unmutated IGHV, median PFS</b>	idelalisib		19.5 months		16.1–24.6	NA	NA	NA	NA	the difference in progression-free survival between treatment groups was assessed by Kaplan-Meier methods and the stratified log-rank test. HRs and corresponding 95% CIs were calculated using a Cox proportional hazards regression model. Categorical variables were

										compared using the Cochran-Mantel-Haenszel test adjusted for stratification factors. All randomised patients were included in the efficacy analyses (intention-to-treat population).
	placebo		10.9 months	NA	8.6–11.1		0.36	0.27–0.48		
<b>median OS unmutated IGHV</b>	idelalisib	207	NR	NA	26.8–NR	NA	NA	NA	NA	To preserve the overall type I error rate across the primary and secondary endpoints, a sequential testing procedure was applied. Secondary endpoints were tested at a two-sided 0.032 significance level
	placebo	209	31.6 months	NA	22.2–NR		0.73	0.47–1.12		
<b>Median OS patients with del(17p) or TP53 mutation (or both mutations)</b>	idelalisib	69	NR	NA	12.2–NR	NA	NA	NA	NA	To preserve the overall type I error rate across the primary and secondary endpoints, a sequential testing procedure was applied. Secondary endpoints were tested at a two-sided 0.032 significance level
	placebo	68	20.3 months	NA	12.1–31.6	NA	NA	NA	NA	
<b>Median OS</b>	idelalisib	207	NR		NR–NR		0.62	0.42–0.92	0.031	To preserve the overall type I

										error rate across the primary and secondary endpoints, a sequential testing procedure was applied. Secondary endpoints were tested at a two-sided 0.032 significance level
	placebo	209	31.6 months	NA	21.3-NR	NA	NA	NA	NA	
<b>Grade ≥3 AEs</b>	idelalisib	207	Not reported	NA	NA	NA	NA	NA	NA	
	placebo	209	Not reported	NA	NA	NA	NA	NA	NA	

<b>Trial name:</b>	ELEVATE RR Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2021 [5]									
<b>NCT number:</b>										
				<b>Estimated absolute difference in effect</b>			<b>Estimated relative difference in effect</b>			<b>Description of methods used for estimation</b>
<b>Outcome</b>	<b>Study arm</b>	<b>N</b>	<b>Result (CI)</b>	<b>Difference</b>	<b>95% CI</b>	<b>P value</b>	<b>Hazard/Odds/Risk ratio</b>	<b>95% CI</b>	<b>P value</b>	
Median PFS(IRC assessed)	acalabrutinib	268	38.4 m	0			HR=1.00;	(0.79; 1.27)	NA	Data cut off September 2020. Median follow up 40.9 mdr
	ibrutinib	265	38.4 m							
investigator-assessed PFS	acalabrutinib	268	46.9(42.4; NR)	1.8 m	NA	NA	HR 0.90	(0.69; 1.16)	NA	Between-group differences were assessed using two-sided Cochran-Mantel Haenszel tests adjusted for del(17)(p13.1) status (yes or no) and number of prior therapies (1-3 v 4 or more) for all secondary end points
	ibrutinib	265	44.1(41.5; NR))							
ORR	acalabrutinib	268	81%(76%; 85%)	4 %	(-2.9% to 10.9%)	0.2503	RR=0.83	(0.59; 1.15)	NA	95% confidence interval based on normal approximation with use of Wilson s score ** Based on Cochran-Mantel-Haenzel test stratified by 17p deletion status and number of prior therapies (1-3 vs. ≥4
	ibrutinib	265	77% (72%; 82%)							
Median OS	acalabrutinib	268	63/23.5%(NA)	4.00	NA	0.2517	HR=0.82	(0.59, 1.15)	NA	RR calculated by AstraZeneca
	ibrutinib	265	7/27.5%(NA)							
TAES leading to Discontinuations	acalabrutinib	266	39/14.7%	6.6%	NA	NA	RR=0.69	(0.49; 1.00)	NA	RR calculated by AstraZeneca
	ibrutinib	263	56/21.3%							

Grade ≥3 TEAEs	acalabrutinib	266	183/68.8%)	6.1%	NA	NA	RR=0.92	(0.83; 1.02)	NA	TEAEs were defined as any event with an onset date on or after the date of the first dose of study drug or any ongoing event that worsened in severity after the first dose of study drug, and before 30 days after the date of the last dose of study drug or the date of first starting new anti-cancer therapy
	ibrutinib	263	197/74.9%							
Grade ≥3 STEAEs	acalabrutinib	266	126 (47.4%)	5.1 %	NA	NA	RR=0.90	(0.76; 1.07)	NA	See above RR calculated by AstraZeneca
	ibrutinib	263	138 (52.5%)							

## 12.3 Results per PICO A4

### Clinical Question 1. Acalabrutinib vs Obinutuzumab + Chlorambucil

Table A4 Results referring to clinical question 1 ACALA vs O + Chl without p17/del53								
Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
Median OS vs. O+CL ITT	ELEVATE [6]	NR	NA	NA	HR=0.60	0.28–1.27	$p = 0.1556$	The time from date of randomization to death due to any cause
Median OS without p17/del53 vs. O+CL	ELEVATE [6], NMA [44], Davids et al [7]; iLLUMINATE [29], CLL11 [24], CLL14 [31], Tedeschi [25]	NR	NA	NA	NA	NA	NA	The time from date of randomization to death due to any cause

**Table A4 Results referring to clinical question 1 ACALA vs O + Chl without p17/del53**

OS rate at 3 years ITT vs. O+CL	ELEVATE [6]	5.4 %	NA	NA	NA	NA	NA	OS rate at 3 years without p17/del53 vs. O+CL is not available
Median PFS vs. O+CL. ITT	ELEVATE [6]	NR	NA	NA	HR=0.20	0.13–0.30	$p < 0.0001$	The time from the date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first
PFS rate at 3 years vs. O+CL. ITT	ELEVATE [6]	32,6 %	NA	NA	NA	NA	NA	The time from the date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first
PFS rate at 3 years without p17/del53 vs. O+CL	ELEVATE [6]	37,9 %	NA	NA	HR= 0.19	(0.11-0.31)	NA	Data are not available for the population without p17/del53. ITT data has been used. PFS:The time from the date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first
Grade AE 3 or more	ELEVATE [6]	20,1%	(9.9 – 31.1)	NA	RR=0.71	(0.6-0.85)	NA	Confidence interval and RR Calculated by AstraZeneca
Grade 3 or more SAEs. vs O+CL. ITT	ELEVATE [6]	<b>10,1 %</b>	(-19.5; -0.3)	NA	RR=1.52	(1.0- 2.22)	NA	AEs and SAEs as coded using the MedDRA reporting system (version 21.1) and graded according to the NCI CTCAE (version 4.03). Grade 3 or more AEs. vs O+CL. is not reported for the populations without p17/del53 vs. O+CL. RR calculated by AstraZeneca



**Table A4 Results referring to clinical question 1 ACALA vs O + Chl without p17/del53**

HQoL. ITT population vs. O+CL	ELEVATE [6]	0.25	NA	p=0.9222	NA	NA	NA	Change from baseline in FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D scores EORTC QLQ-C30 HQoL data are not available for the populations without p17/del53 vs. O+CL
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ACALA = acalabrutinib, O=obinutuzumab, Cl= chlorambucil, B=bendamustine, R=rituximab

### Clinical question 1 Acalabrutinib vs Bendamustine + Rituximab

**Table A4 Results referring to clinical question 1 ACALA vs. B + R without p17/del53**

Results per outcome:								Methods used for quantitative synthesis
	Absolute difference in effect				Relative difference in effect			
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
Median OS vs. B+R ITT	ELEVATE [6], Narrative: Alliance (A041202) [15],MAIC [43]; Alliance (A041202) [15]	NA NA	NA NA	NA NA	HR= 1.18 (MAIC) HR=0.61(NMA)	(0.51–2.71) (0.23; 1.60)	p = 0.70	NMA and MAIC details are described in the application

**Table A4 Results referring to clinical question 1 ACALA vs. B + R. without p17/del53**

Median OS without p17/del53(ITT)	ELEVATE [6]	NR	NA	NA	HR=0.60	(0.28–1.27)	$p = 0.1556$	Median OS(follow-up 28,3 m) is not reached in ELEVATE and is not available for the population without p17/del53. However the ITT data should be representative for the patient group without p17/del53
OS rate at 3 years ITT vs. B+R	ELEVATE [6], Narrative: Alliance [15] CLL-10 [26]	93.5% (ELEVATE) 92%(CLL10)	(88.6–96.3)	NA	NA	NA	NA	OS rate at 3 years without p17/del53 vs. B + R is not available. Lack of mature data makes a narrative comparison in conclusive

**Table A4 Results referring to clinical question 1 ACALA vs. B + R without p17/del53**

PFS vs. B+R . ITT	ELEVATE [6], Narrative: Alliance (A041202) [15],MAIC [43]: Alliance (A041202) [15]	NA NA	NA NA	NA NA	HR = 0.38(MAIC) HR = 0.15(NMA)	(0.20-0.72) (0.08-0.27)	p < 0.001. NA	<ul style="list-style-type: none"> <li>• NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers</li> <li>• MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison</li> <li>• PFS is not available in patients without p17/del53</li> </ul>
PFS rate at 3 years vs. B+R. ITT	ELEVATE [6]	63.9% (29.4–84.9)	NA	NA	NA	NA	NA	The reported PFS rate is from the ITT population but should be representative for the group without p17/del53

**Table A4 Results referring to clinical question 1 ACALA vs. B + R without p17/del53**

PFS rate at 2 years without p17/del53 vs. B+R	ELEVATE [6] Narrative CLL-10 [26] MABLE [28]	87,3%(80.9–91.7) (ELEVATE ITT) 79% (CLL-10) 79%(MABLE)	NA	NA	NA	NA	NA	Narrative/naive comparison.
Grade 3 or more AEs. vs B+R. ITT	ELEVATE [6] . Narrative: CLL-10 [26] MABLE [28]	49,7% (ELEVATE) 84% (CLL-10) 75% (MABLE)	NA	NA	NA	NA	NA	Narrative/naive comparison.  Grade 3 or more AEs is not reported for the populations without p17/del53 vs. O+CL
HQoL. ITT population vs. B+R	ELEVATE [6]	- 1.87  0.51	NA	p=0.2898  P=0.8510	NA	NA	NA	EORTC QLQ-C30 HQoL data are not available for the populations without p17/del53 and we cannot compare HQoL data vs B+R studies due to different tools and lack of data

ACALA = acalabrutinib, O=obinutuzumab, Cl= chlorambucil, B=bendamustine, R=rituximab

**Clinical Question 2. Acalabrutinib + Obinutuzumab vs Obinutuzumab + Chlorambucil**

Table A4 Results referring to clinical question 2 ACALA + O vs O + CL without p17/del53								
Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
Median OS vs. O+CL ITT	ELEVATE [6]	NR	NA	NA	HR: 0.47	0.21–1.06	$p = 0.0577$	Median OS is not reached. Patients who crossed over from chlorambucil plus obinutuzumab to acalabrutinib monotherapy were included in the analysis of OS in the chlorambucil plus obinutuzumab arm; this may have affected the results.
Median OS without p17/del53 vs. O+CL	ELEVATE [6], NMA [44], Davids et al [7]: iLLUMINATE [29], CLL11 [24], CLL14 [31], Tedeschi [25]	NR/NA	NA	NA	NA	NA		OS: The time from date of randomization to death due to any cause Median OS is not reached
OS rate at 3 years ITT vs. O+CL	ELEVATE [6]	6.8%	NA	NA	NA	NA	NA	OS rate at 3 years without p17/del53 vs. O+CL is not available

**Table A4 Results referring to clinical question 2 ACALA + O vs O + CL without p17/del53**

PFS vs. O+CL. ITT	ELEVATE [6], NMA [44]; iLLUMINATE [29], CLL11 [24], CLL14 [31], Tedeschi [25]	NR in ACALA + O 22.6 m (20.2–27.6) in O + CL	NA	NA	HR = 0.10 .	[0.06,0.19]	$p < 0.0001$	PFS:The time from the date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first. This is data from ITT population
PFS rate at 3 years vs. O+CL. ITT	ELEVATE [6]	58,3%	NA	NA	NA	NA	NA	ITT data
PFS rate at 3 years without p17/del53 vs. O+CL	ELEVATE [6]	NA	NA	NA	NA	NA	NA	PFS rate at 3 years without p17/del53 vs. O+CL is not available
Grade 3 or more. ITT	ELEVATE [6]	0.4 %	NA(-9.6; 10.4)	NA	RR=1.01	(0.88-1.15)	NA	Confidence interval and RR calculated by AstraZeneca
SAEs. vs O+CL. ITT	ELEVATE [6]	13,1 %	(-22,8, -3.4)	NA	RR=1.67	(1,15; 2,42)	NA	AEs and SAEs as coded using the MedDRA reporting system (version 21.1) and graded according to the NCI CTCAE (version 4.03)  Grade 3 or more AEs. vs O+CL. is not reported for the populations without p17/del53 vs. O+CL. ITT data has been used  CI and RR calculated by AstraZeneca
HQoL. ITT population vs. O+CL	ELEVATE [6]	- 1.87  0.51	NA	p=0.2898  P=0.8510	NA	NA	NA	EORTC QLQ-C30 HQoL data are not available for the populations without p17/del53 vs. O+CL  Change from baseline in FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D scores

Clinical question 2. Acalabrutinib + Obinutuzumab vs Bendamustine + Rituximab

Table A4 Results referring to clinical question 2 ACALA + obinutuzumab vs. B + R without p17/del53								
Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	

**Table A4 Results referring to clinical question 2 ACALA + obinutuzumab vs. B + R without p17/del53**

Median OS vs. B+R ITT	MAIC [43]: Alliance (A041202) [15] and NMA [44]; Alliance (A041202) [15], MaBle [28]	NA NA	NA NA	NA NA	HR=0.55(MAIC) HR=0.36(NMA)	(0.20-1.50) (0.12-1.05)	$p = 0.24$ NA	<ul style="list-style-type: none"> <li>• NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers</li> <li>• MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison.</li> <li>• . OS without p17/del53 vs. B + R is not available. Data from ITT populations are used</li> </ul>
Median OS without p17/del53 (ITT)	ELEVATE [6]	NR	NA	NA	HR=0.47	(0.21-1.06)	$p = 0.0577$	Median OS is not reached in ELEVATE and is not available for the population without p17/del53. However the ITT data should be representative for the patient group without p17/del53



**Table A4 Results referring to clinical question 2 ACALA + obinutuzumab vs. B + R without p17/del53**

OS rate at 3 years ITT vs. B+R	ELEVATE [6], Narrative ; Alliance (A041202) [15] CLL-10 [26]	94.9% 90.5–97.3) (ELEVATE) 92% (CLL10)	NA	NA	NA	NA	NA	OS rate at 3 years without p17/del53 vs. B + R is not available. Lack of mature data makes a narrative comparison in conclusive
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**Table A4 Results referring to clinical question 2 ACALA + obinutuzumab vs. B + R without p17/del53**

PFS vs. B+R . ITT	MAIC [43]: Alliance (A041202) [15] and NMA [44]; Alliance (A041202) [15], MaBle [28]	NA NA	NA NA	NA NA	HR= 0.21 (MAIC) HR=0.08 (NMA)	(0.10-0.43) (0.04–0.16)	p < 0.001. NA	<ul style="list-style-type: none"> <li>• NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers</li> <li>• MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison</li> <li>• PFS is not available in patients without p17/del53</li> </ul>
PFS rate at 3 years. ITT	ELEVATE [6]	89.6% (82.0–94.1)	NA	NA	NA	NA	NA	The reported PFS rate is from the ITT population but should be representative for the group without p17/del53

**Table A4 Results referring to clinical question 2 ACALA + obinutuzumab vs. B + R without p17/del53**

PFS rate at 2 years without p17/del53 vs. B+R	ELEVATE [6] Narratie: CLL-10 [26] MABLE [28]	92,7%(82.0-94.1) (ELEVATA ITT) 79% (CLL-10) 79%(MABLE)	NA	NA	NA	NA	NA	Narrative/naive comparison.
Grade 3 or more AEs. vs B+R. ITT	ELEVATE [6] Narratie: CLL-10 [26] MABLE [28]	70.2% (ELEVATE) 84% (CLL-10) 75% (MABLE)	NA	NA	NA	NA	NA	Narrative/naive comparison. Grade 3 or more AEs is not reported for the populations without p17/del53 but data from ITT should be representative for the group without p17/del53
HQoL. ITT population vs. B+R	ELEVATE [6]	- 1.87 0.51	NA	p=0.2898 P=0.8510	NA	NA	NA	EORTC QLQ-C30 HQoL data are not available for the populations without p17/del53 and we cannot compare HQoL data vs B+R studies due to different tools and lack of data

ACALA = acalabrutinib, O=obinutuzumab, Cl= chlorambucil, B=bendamustine, R=rituximab

**Clinical question 3. Acalabrutinib vs Ibrutinib**
**Table A4 Results referring to clinical question 3 Acalabrutinib vs Ibrutinib 1L with del17p/Tp53-ELEVATE-TN and Ahn**

Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
2-year PFS Tp53 Acala vs ibr	ELEVATE [6] Narrative; Ahn [16]	-11%	NA	NA	NA	NA	NA	Narrative/naive comparison. Tp53 population of ELEVATE vs del17p/Tp53 population in Ahn.
2-year PFS del17	ELEVATE [6] Narrative; Ahn [16]	-8%	NA	NA	NA	NA	NA	Narrative/naive comparison. Del17p population of ELEVATE vs del17p/Tp53 population in Ahn.
Grade 3 or more AEs Acala vs Ibrutinib	ELEVATE [6] Narrative; Ahn* [16]	-4,3%	NA	NA	NA	NA	NA	Narrative/naive comparison. Grade 3 or more AEs. In ELEVATE-TN is not reported for the populations with del17p/Tp53 in In the Ahn study it is reported for the Tp53 population.
HQoL	Narrative; Ahn [16]	NA	NA	NA	NA	NA	NA	EORTC QLQ-C30 HQoL data are not available for the comparator

ACALA = acalabrutinib, ibr =ibrutinib

\*Adverse events in Ahn study at 24months is for the Tp53 population and AE for Acalabrutinib at 28.1 months follow up is for the whole population.

## Clinical question 3. Acalabrutinib vs Ibrutinib RESONATE

Table A4 Results referring to clinical question 3 Acalabrutinib vs Ibrutinib 1L with del17/Tp53								
Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
PFS. ITT population	NMA [44]; RESONATE-2 [13], Alliance (A041202) [15], Tedeschi [25]	NA	NA	NA	HR= 0.35	(0.18; 0.66)	NA	NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers

**Table A4 Results referring to clinical question 3 Acalabrutinib vs Ibrutinib 1L with del17/Tp53**

PFS. ITT population	MAIC [43]; RESONATE-2 [13], Alliance (A041202) [15]	NA	NA	NA	HR=0.92	(0.44; 1.95)	P=0.83	MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison
2-year PFS Tp53 Acala vs ibr	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	NA	NA	NA	NA	NA	NA	Narrative/naïve comparison. No 2-year PFS rate for RESONATE-2
2-year PFS del17	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	NA	NA	NA	NA	NA	NA	Narrative/naïve comparison. No 2-year PFS rate for RESONATE-2
OS. ITT population	MAIC [43]; RESONATE-2 [13], Alliance (A041202) [15]	NA	NA	NA	HR= 0.73	(0.27; 2.02)	NA	MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison

**Table A4 Results referring to clinical question 3 Acalabrutinib vs Ibrutinib 1L with del17/Tp53**

OS. ITT population	NMA [44]; RESONATE-2 [13], Alliance (A041202) [15], Tedeschi [25]	NA	NA	NA	HR=0.44	(0.16; 1.27)	NA	NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers
Grade 3 or more AEs Acala vs Ibrutinib	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	-33,3%	NA	NA	NA	NA	NA	Narrative/naive comparison.  Grade 3 or more AEs not reported for the populations with del17p/Tp53 but are based on whole population in both studies
HQoL	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	NA	NA	NA	NA	NA	NA	Narrative/naive comparison.  EORTC QLQ-C30 HQoL data are not available for the comparator

Clinical question 4. Acalabrutinib + obinutuzumab vs Ibrutinib

**Table A4 Results referring to clinical question 4 Acalabrutinib + obinutuzumab vs Ibrutinib 1L with del17/Tp53**

Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis [6, 16, 43, 44]	Difference	CI	P value	Difference	CI	P value	
PFS, ITT	MAIC [43]; RESONATE-2 [13], Alliance (A041202) [15]	NA	NA	NA	HR=0.61	(0.24; 1.55)	P=0.81	PFS data from ITT population. MAIC ITT
PFS, ITT	NMA [44]; RESONATE-2 [13], Alliance (A041202) [15], Tedeschi [25]	NA	NA	NA	HR=0.19	(0.09; 0.38)	NA	PFS data from ITT population. NMA ITT
2-year PFS Tp53 Acala vs ibr	ELEVATE [6] Narrative; Ahn [16]	13%	NA	NA	NA	NA	NA	Narrative/naive comparison. Tp53 population of ELEVATE vs del17p/Tp53 population in Ahn.
2-year PFS del17	ELEVATE [6] Narrative; Ahn [16]	6%	NA	NA	NA	NA	NA	Narrative/naive comparison. Del17p population of ELEVATE vs del17p/Tp53 population in Ahn.



**Table A4 Results referring to clinical question 4 Acalabrutinib + obinutuzumab vs Ibrutinib 1L with del17/Tp53**

Grade 3 or more AEs Acala vs Ibrutinib	ELEVATE [6] Narrative; Ahn* [16]	16,2%	NA	NA	NA	NA	NA	Narrative/naive comparison.  Grade 3 or more AEs. In ELEVATE-TN is not reported for the populations with del17/Tp53 in In the Ahn study it is reported for the Tp53 population.
OS ITT	NMA [44]; RESONATE-2 [13], Alliance (A041202) [15], Tedeschi [25]	NA	NA	NA	HR:0.35	(0.12; 1.04)	NA	NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers
OS ITT	MAIC [43]; RESONATE-2 [13], Alliance (A041202) [15]	NA	NA	NA	HR:0.88	(0.31; 2.52)	p=0.81	MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison
HQoL	ELEVATE [6] Narrative; Ahn [16]	NA	NA	NA	NA	NA	NA	Narrative/naive comparison.  EORTC QLQ-C30 HQoL data are not available for the comparator

**Table A4 Results referring to clinical question 4 Acalabrutinib + Obinutuzumab vs Ibrutinib 1L with del17/Tp53**

Results per outcome:								
	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis	
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
2-year PFS Tp53 Acala vs ibr	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	NA	NA	NA	NA	NA	NA	Narrative/naive comparison. No 2-year PFS rate for RESONATE-2
2-year PFS del17	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	NA	NA	NA	NA	NA	NA	Narrative/naive comparison. No 2-year PFS rate for RESONATE-2
PFS. ITT population	NMA [44]; RESONATE-2 [13], Alliance (A041202) [15], Tedeschi [25]	NA	NA	NA	HR= 0.35	(0.18; 0.66)	NA	NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers

**Table A4 Results referring to clinical question 4 Acalabrutinib + Obinutuzumab vs Ibrutinib 1L with del17/Tp53**

PFS. ITT population	MAIC [43]; RESONATE-2 [13], Alliance (A041202) [15]	NA	NA	NA	HR=0.92	(0.44; 1.95)	P=0.83	MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison
Grade 3 or more AEs Acala vs Ibrutinib	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	-12,8%	NA	NA	NA	NA	NA	Narrative/naive comparison. Grade 3 or more AEs not reported for the populations with 17pdel/Tp53. Data is based on whole population
OS ITT	NMA [44]; RESONATE-2 [13], Alliance (A041202) [15], Tedeschi [25]	NA	NA	NA	HR:0.35	(0.12; 1.04)	NA	NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers

**Table A4 Results referring to clinical question 4 Acalabrutinib + Obinutuzumab vs Ibrutinib 1L with del17/Tp53**

OS ITT	MAIC [43]; RESONATE-2 [13], Alliance (A041202) [15]	NA	NA	NA	HR:0.88	(0.31; 2.52)	p=0.81	MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison
HQoL	ELEVATE [6] Narrative; RESONATE-2 [14], [13]	NA	NA	NA	NA	NA	NA	Narrative/naive comparison. EORTC QLQ-C30 HQoL data are not available for the comparator

**Clinical question 5 . Acalabrutinib vs Ibrutinib R/R**
**Table A4 Results referring to clinical question 5 acalabrutinib vs ibrutinib R/R CLL**

Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	

**Table A4 Results referring to clinical question 5 acalabrutinib vs ibrutinib R/R CLL**

Median OS vs. B+R or I-R ITT	ASCEND [9]	2%	NA	NA	HR=0.84	0.42-1.66	NA	Number of patients that had died. ASCEND publication
Median OS vs. ibrutinib	ASCEND [9] Narrative; RESONATE [21]	NR vs 67.7 months at 6 years post randomization	NA	NA	NA	NA	NA	Narrative/naive comparison. Lack of mature data for acalabrutinib makes a narrative comparison inconclusive
OS rate at 12m vs BR or I-R	ASCEND [9]	3%	NA	NA	NA	NA	NA	Patients alive at 12 months
OS rate at 12m vs ibrutinib	ASCEND [9] Narrative; RESONATE [21]	4%	NA	NA	NA	NA	NA	Narrative/naive comparison.
OS vs ibrutinib	MAIC [43]; RESONATE [19]	NA	NA	NA				MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison
PFS ITT	ASCEND [9]	NR vs 16.5 m	NA	NA	HR=0.31	0.20- 0.49	$P < .0001$	Median follow-up of 16.1 months (range, 0.03-22.4 months)

**Table A4 Results referring to clinical question 5 acalabrutinib vs ibrutinib R/R CLL**

PFS vs ibrutinib	MAIC [43]; RESONATE [19] and NMA [44]; RESONATE [19], HELIOS [30], Huang [36]	NA	NA	NA	<div style="background-color: black; height: 15px; width: 100%;"></div> HR=0.79 (NMA)	0.40-1.54		<ul style="list-style-type: none"> <li>NMA combines the results of multiple RCTs, connected via common comparators, to get an overall estimate of relative effect for each comparator versus another in the network (e.g., OR, RR or difference in change from baseline). NMAs allow for simultaneous comparisons of treatments with comparators from multiple trials and maintain the within-trial randomization from RCTs. The limitation of NMAs is the risk of bias due to heterogeneity across trials in characteristics considered to be effect modifiers</li> <li>MAICs adjust for heterogeneity in RCT patient populations by adjusting population characteristics in one trial, forming an effective sample size, to match the population characteristics in another trial. Thus, this methodology requires access to individual patient data (IPD) from one of the trials in the comparison</li> </ul>
Grade 3 or more AEs. vs B+R. and IR ITT	ASCEND [9]	45% vs I-R -2% vs BR	NA	NA	NA	NA	NA	

**Table A4 Results referring to clinical question 5 acalabrutinib vs ibrutinib R/R CLL**

Any SAEs vs ibrutinib	MAIC [43]; RESONATE [19]	12,50 %	(-27.66; 2.65)	NA				The MAIC has used OR as relative results. This has been recalculated to RR using the formula in the Metodehåndbog. OR was 0.6 and the ACR was 45 events out of 104 from the Huang 2018 trial
AE Grade 3 or more	MAIC [43]; RESONATE [19]	3.05 %	(-19.38; 13.30)	NA				Calculated by AstraZeneca  The MAIC has used OR as relative results. This has been recalculated to RR using the formula in the Metodehåndbog. OR was 0.9 and the ACR was 86 events out of 104 from the Huang 2018 trial
HQoL. ITT population vs. BR/IR	ASCEND [9]	Mean[SD](24 weeks): +7.4 [1.8] vs +6.7 [1.8], Mean [SD](48 weeks): +7.2 [1.9] vs +3.7 [2.1]	See to the left	p=0.73(24 weeks) p=0.15(48 weeks)	NA	NA	NA	GHS)/health-related quality of life (HRQoL) of the EORTC QLQ-C30 scale
HQoL. ITT population vs. ibrutinib	ASCEND [9] Narrative; RESONATE [21]	NA	NA	NA	NA	NA	NA	HQoL is not calculated in a way that allows any narrative comparison with ibrutinib

**Table A4 Results referring to clinical question 5 acalabrutinib vs ibrutinib R/R CLL**

Results per outcome:								Methods used for quantitative synthesis
		Absolute difference in effect			Relative difference in effect			
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
Median PFS(IRC assessed)	ELEVATE RR [9]	0	NA	NA	HR=1.0	(0.79; 1.27)	NA	IRC-assessed PFS, was assessed first for noninferiority. The gate-keeping strategy was implemented to control the family-wise error rate at the 0.05 level given the multiple testing approach for primary and secondary end points. If acalabrutinib was noninferior to ibrutinib on the primary end point (upper bound of HR twosided 95% CI below 1.429), acalabrutinib superiority on the secondary end points was tested at a two-sided 0.05 significance level in the following prespecified order: (1) incidence of any-grade atrial fibrillation, (2) incidence of grade 3 or higher infections, (3) incidence of Richter transformation, and (4) OS.
Investigator assessed PFS	ELEVATE RR [9]	1.8 m	NA	NA	HR=0.90	(0.69; 1.16)	NA	Between-group differences were assessed using two-sided Cochran-MantelHaenszel tests adjusted for del(17)(p13.1) status (yes or no) and number of prior therapies (1-3 v 4 or more) for all secondary end points
PFS 17p and/or TP53	ELEVATE RR [9]	NA	NA	NA	HR=1.01	(0.74; 1.37)	NA	



**Table A4 Results referring to clinical question 5 acalabrutinib vs ibrutinib R/R CLL**

ORR	ELEVATE RR [9]	4 %	(-2.9; 10.9)	0.2503	RR=0.83	(0.59; 1.15)	NA	RR calculated by AstraZeneca
Median OS	ELEVATE RR [9]	4%	NA	NA	HR=0.82	(0.59; 1.15)	NA	Kaplan-Meier methods and a stratified log-rank test
Grade 3 or more TEAE	ELEVATE RR [9]	6.1%	NA	NA	RR=0.92	(0.83; 1.02)	NA	RR calculated by AstraZeneca
Grade 3 or more STEAE	ELEVATE RR [9]	5.1%	NA	NA	RR=0.90	(0.76; 1.07)	NA	RR calculated by AstraZeneca

Company Submission to Medicinrådet

**Calquence® (acalabrutinib) as monotherapy  
for the treatment of patients with CLL in  
Denmark who have received at least one prior  
therapy**

Cost per patient and budget impact analyses

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## Abbreviations

Abbreviation	Description
AE	Adverse event
AIC	Akaike information criterion
AIP	Apotekets indkøbspris
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCR	B-cell receptor
BIC	Bayesian information criterion
BIM	Budget impact model
BI	Budget impact
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
BR	Bendamustine + rituximab
CIRS	Cumulative illness rating scale
CLL	Chronic Lymphocytic Leukemia
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FCR	Fludarabine, cyclophosphamide and rituximab
HR	Hazard ratio
IGHV	Immunoglobulin heavy chain gene
IR	Idelalisib + rituximab
IV	Intravenous
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PFS	Progression free survival
PF	Progression free
PSM	Partitioned survival model
PU	Previously untreated
R/R	Relapsed/refractory
SD	Standard deviation
TLS	Tumor lysis syndrome

## Summary

### Objective

The objective of this economic evaluation is to present cost per patient and budget impact analyses to support reimbursement decision in Denmark for acalabrutinib (Calquence®) – a Bruton's tyrosine kinase inhibitor (BTKi) approved as a treatment for treatment relapsed/refractory patients with chronic lymphocytic leukaemia (R/R CLL). According to the Danish Medicines Council protocol, relevant comparators for acalabrutinib identified in this setting are ibrutinib and venetoclax + rituximab.

### Methods

A three state partitioned survival model was used to estimate the lifetime costs of treatment. A matching-adjusted indirect comparison (MAIC), as well as the head-to-head ELEVATE-RR study, indicates that in patients with R/R CLL, acalabrutinib is associated with similar efficacy to both ibrutinib and venetoclax + obinutuzumab. Accordingly, equivalent progression-free and overall survival was assumed between the three treatments when estimating costs, based on an extrapolation of the ELEVATE-RR data. A budget impact analysis appended to the cost-per-patient model was used to estimate the budget consequences of introducing acalabrutinib for R/R CLL patients in Denmark. Results in the cost-per-patient analysis are presented from a Danish societal perspective, with a healthcare payer perspective adopted for the budget impact analysis.

### Results

In the cost per patient analysis, the average cost per patient over 30 years is DKK [REDACTED] for acalabrutinib, DKK [REDACTED] for ibrutinib therapy, and DKK 3.256.801 for venetoclax + rituximab. The drug acquisition constituted a major part of the costs in both comparisons.

In the budget impact analysis, the base case results in the R/R patient population suggest that introducing acalabrutinib is likely to be cost saving for the Danish healthcare system.

## 1 Introduction

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in adults. Danish statistics for CLL indicate that approximately 450 new cases per year are registered, with the incidence around 6-7 per 100.000 inhabitants per year. It is also estimated that approximately 4.000 inhabitants currently live with the disease. The median age at diagnosis is 70 years, and typically twice as many men as women are diagnosed with this cancer (LYFO database, 2018; NORDCAN, 2019).

As the cancer type originates from the bone marrow and further the B-cells, Bruton tyrosine kinase (BTK) has been identified as a key component of the B-cell receptor (BCR) signalling pathway and evidence suggests that a blockade of BTK activity by potent pharmacologic inhibitors attenuates BCR signalling and induces cell death (CLL gruppen, 2019).

CLL is clinically detected by coincidence after a blood test, as it is often asymptomatic at the time of diagnosis. A clinical assessment will be performed, focusing on the disease stage and risk profile, which includes cytogenetic changes and immunoglobulin heavy-chain variable region (IGHV)-mutation-status. In addition, patient-specific factors, such as performance status, comorbidity (cumulative illness rating scale (CIRS), age, and preferences are examined (CLL gruppen, 2019).

The objectives in treating patients with CLL is to maintain and prolong the symptom-free period and delay disease progression. For CLL patients in Denmark who are relapsed or refractory (R/R) and have previously received at least one treatment, either ibrutinib or venetoclax in combination with rituximab are used (CLL gruppen, 2019)

## 2 Objectives

The European Medicines Agency has approved acalabrutinib (CALQUENCE®) for following indications:

- in combination with obinutuzumab, or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukaemia (PU CLL); and
- as monotherapy for the treatment of patients with CLL who have received at least one prior therapy (R/R CLL)

The objective of this evaluation is to present cost per patient and budget impact (BI) analyses for acalabrutinib-based therapies to support reimbursement decisions for acalabrutinib in Denmark. The following three patient populations were considered in the Danish Medicines Council's protocol:

- PU CLL FCR (fludarabine, cyclophosphamide and rituximab) ineligible patients without 17p deletion/TP53 mutation (in this document, we refer to this population as "patients without 17p deletion/TP53 mutation")
- PU high risk CLL patients with 17p deletion / TP53 mutation (in this document, we refer to this population as "patients with 17p deletion/TP53 mutation")
- Patients with R/R CLL

This submission includes two separate reports assessing the economic implications. This report considers acalabrutinib for the treatment of patients with R/R CLL, whereas acalabrutinib for the treatment of patients with PU CLL is considered in a separate report.

In the cost per patient analysis, the costs per patient were compared between acalabrutinib and comparators in R/R CLL. The cost per patient analysis represents the total costs of disease for selected treatments within

a selected time horizon. Scenario analyses and deterministic sensitivity analyses were performed to assess uncertainty in the analysis.

In the budget impact analysis, the projected healthcare expenditure of adopting acalabrutinib into the formulary is compared with projected expenditure in the same group of patients without the adoption of acalabrutinib. Thus, the base case results of the BI analysis represent the annual incremental costs of introducing acalabrutinib in the Danish setting of CLL treatment. Furthermore, a scenario analysis is performed to investigate the sensitivities in the market share.

### 3 Intervention

Calquence is an orally administered medicine, where each hard capsule contains 100 mg of acalabrutinib. The recommended dose is 100 mg acalabrutinib twice daily (equivalent to a total daily dose of 200 mg). The dose interval is approximately 12 hours. Treatment with Calquence should be continued until disease progression or unacceptable toxicity (Calquence SmPC).

Calquence is a selective irreversible BTK inhibitor, specifically designed to improve upon the safety and efficacy of first generation BTK inhibitors, which also irreversibly inhibit alternative kinase targets, which potentially compromise its therapeutic index. The safety and efficacy of acalabrutinib monotherapy or in combination with obinutuzumab as a first line therapy in previously untreated patients has been evaluated in the ELEVATE-TN trial; whereas the ASCEND and ELEVATE-RR trials have studied the safety and efficacy profile of acalabrutinib as therapy in relapsed/refractory (R/R) patients. ELEVATE-TN, ELEVATE-RR and ASCEND are open-label Phase III, global, randomised and multicentre studies of Calquence (Sharman et al, 2020; Byrd 2021; Ghia et al, 2020).

On the 9th of December 2020, the Danish Medicine Council published a protocol to evaluate the added value of acalabrutinib monotherapy or in combination with obinutuzumab to patient population with and without 17p deletion/TP53 mutation in 1L, and acalabrutinib monotherapy for R/R patient population that previously have received at least one treatment option independent of the 17p deletion/TP53 mutation (Medicinerådet, 2020). This document concerns acalabrutinib monotherapy (referred to as “acalabrutinib”).

### 4 Study Characteristics

The ASCEND phase 3 randomised clinical trial established the efficacy and safety of acalabrutinib monotherapy in patients with R/R CLL by comparing to an investigators' choice of idelalisib + rituximab (IR) or bendamustine + rituximab (BR). There were no restrictions on patient eligibility based on age or comorbidities, as may be considered for first line treatment. The primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS), with overall survival (OS) and overall response rate (ORR) as key secondary endpoints. A total of 310 patients were randomized to receive acalabrutinib ( $n = 155$ ) versus idelalisib + rituximab and bendamustine + rituximab ( $n = 155$ ). Idelalisib + rituximab was the investigators' preferred choice with 119 patients randomised to receive this treatment compared to 36 patients who were to receive bendamustine + rituximab. Median age at baseline was 67 years, 67% of patients were men, 11% had del 17p/TP53 mutations, and more than half had received two or more previous therapies.

Further evidence for acalabrutinib in R/R CLL patients was obtained from the non-inferiority study, ELEVATE-RR. In this phase 3 randomised clinical trial, acalabrutinib monotherapy was compared to ibrutinib monotherapy in terms of the efficacy and safety. The key inclusion criteria were patients with previously treated CLL and 17p deletion or 11p deletion and ECOG PS (Eastern Cooperative Oncology Group



Performance Status) of equal or less than 2. The primary endpoint was to assess whether acalabrutinib is non-inferior to ibrutinib with respect to IRC-assessed PFS in subjects with R/R CLL with high-risk prognostic markers. The evaluation of safety and OS were the key secondary endpoints. A total of 533 patients were randomized to receive acalabrutinib (n = 268) versus ibrutinib (n = 265). Median age at baseline was 66 years, 71,1% of patients were men, 50,8% had 17p deletion and/or TP53 mutation, and more than half had received two or more previous therapies.

Since neither idelalisib + rituximab and bendamustine + rituximab are recommended for R/R CLL patients in Danish clinical practice, the ELEVATE-RR study as well as indirect treatment comparisons of acalabrutinib compared to commonly used treatments in the Danish setting (ibrutinib and venetoclax + rituximab) form the basis of this submission.

Two indirect treatment comparisons were conducted, using both network meta-analysis (NMA) and matching-adjusted indirect comparison (MAIC) methods. Both analyses were based on data from ASCEND study for acalabrutinib, and a systematic review was performed to identify randomised controlled trials (RCTs) in R/R CLL for relevant comparators. The results of the indirect comparisons are currently unpublished, but the study reports of the analyses can be found appended to this report. An overview of relevant clinical trials included in the indirect treatment analyses that are relevant for the current cost and budget impact analyses are shown in Table 1.

**Table 1.** *Trials included in the NMA and MAIC*

Author, Year	Population	Trial Name	Sample Size	Phase	Intervention	Comparator	Median Follow-Up
Brown, 2018	R/R CLL	RESONATE	391	3	Ibrutinib	Ofanutuzumab	19 months
Ghia, 2020	R/R CLL	ASCEND	310	3	Acalabrutinib	Idelasib + Rituximab, Bendamustine + Rituximab	16,1 months
Seymour, 2018	R/R CLL	Murano	389	3	Venetoclax + Rituxmab	Bendamustine + Rituximab	23 months (NMA)
Kater, 2019							36 months (MAIC)

## 5 Comparators

According to the Danish Medicines Council protocol, the added value of acalabrutinib in patients with R/R CLL should be evaluated in comparison with ibrutinib and venetoclax + rituximab combination therapy.

## 6 Perspective

The perspective used in the cost per patient model is a societal perspective with limitations, excluding productivity losses and cross-sectional costs based on the method guideline by the Danish Medicines Council. In the BI analysis, a healthcare payer perspective was used.

## 7 Time Horizon

The Danish Medicines Council does not state a time horizon in their protocol for evaluation of the added value of acalabrutinib (Medicinrådet, 2020). However, relevant time horizons were determined in further discussions with The Danish Medicine Council and used in the base case analyses.

In the cost per patient analysis, a lifetime horizon was used, as per the application guideline, to fully capture all relevant costs of treatment. The cohorts are modelled until a time point when <5% of the population is alive which was assumed to represent a lifetime horizon. The time point used was 30 years and was selected based on the review of previous models and long-term survival for R/R CLL patients in the model. As some level of uncertainty remains regarding the choice of time horizon, scenario analyses have been conducted to explore the impact of shorter time horizons.

For the BI analysis, a time horizon of 5 years was used to show the budget consequence with and without the uptake of acalabrutinib. This time horizon was also agreed with the Danish Medicines Council.

## 8 Discounting

As outlined in the method guideline, a 3,5% discount rate per annum was applied in modelling the added value of acalabrutinib over lifetime horizon in the cost per patient analysis. No discounting was applied in the budget impact model.

## 9 Patient Population

The population for the analysis is aligned with the patient cohort enrolled in the ELEVATE-RR study (patients with previously treated CLL). **Table 2** provides an overview of the baseline characteristics of the trial population. The mean age of 65,4 years and proportion of females (28,9%) sourced from ELEVATE-RR study were utilised in the cost per patient model. However, if the ELEVATE-RR study is not selected for the survival outcomes the target population for the analysis is aligned with the patient cohort enrolled in the ASCEND study (patients with R/R CLL), as the ELEVATE-RR study only randomised patients with 17p deletion or 11q deletion and therefore the higher prevalence of adverse cytogenetics leading to a poorer prognosis may be correlated with other baseline characteristics (**Table 3**).

**Table 2.** Baseline patient characteristics in the ELEVATE-RR trial

Characteristic		Acalabrutinib N= 268	Ibrutinib N= 265	Overall N= 533
Age (years)	Mean (SD)	65.5 (9.3)	65.3 (9.6)	65.4 (9.4)
	Median (Min – Max)	66 (41 – 89)	65 (28 – 88)	66 (28 – 89)
Sex	Male	185 (69.0%)	194 (73.2%)	379 (71.1%)
	Female	83 (31.0%)	71 (26.8%)	154 (28.9%)
ECOG	0	116 (43.3%)	126 (47.5%)	242 (45.4%)
	1	131 (48.9%)	117 (44.2%)	248 (46.5%)
	2	20 (7.5%)	22 (8.3%)	42 (7.9%)
Rai Stage	0	4 (1.5%)	5 (1.9%)	9 (1.7%)
	I	56 (20.9%)	48 (18.1%)	104 (19.5%)
	II	70 (26.1%)	71 (26.8%)	141 (26.5%)
	III	40 (14.9%)	46 (17.4%)	86 (16.1%)
	IV	91 (34.0%)	88 (33.2%)	179 (33.6%)

<b>17p del status</b>	Yes	121 (45.1%)	120 (45.3%)	241 (45.2%)
	No	146 (54.5%)	145 (54.7%)	291 (54.6%)
<b>IGHV</b>	Mutated	44 (16.4%)	28 (10.6%)	72 (13.5%)
	Unmutated	220 (82.1%)	237 (89.4%)	457 (85.7%)
	Missing	4 (1.5%)	0 (0%)	4 (0.8%)
<b>Number of Prior Lines of Therapy</b>	Median (Min – Max)	2 (1 – 9)	2 (1 – 12)	2 (1 – 12)
	1	132 (49.3%)	126 (47.5%)	258 (48.4%)
	2	67 (25.0%)	74 (27.9%)	141 (26.5%)
	3	35 (13.1%)	37 (14.0%)	72 (13.5%)
	≥4	33 (12.3%)	28 (10.6%)	61 (11.4%)

Source: AstraZeneca, ACE-CL-006 Clinical Study Protocol. 2021.

Note: Some columns may not sum to 100% due to rounding

**Table 3. Baseline patient characteristics in the ASCEND trial**

<b>Characteristic</b>		<b>Acalabrutinib N=155</b>	<b>IR / BR N=155</b>	<b>Overall N=310</b>
<b>Age (years)</b>	Mean (SD)	66.9 (9.9)	67.4 (9.5)	66.8 (9.7)
	Median (Min – Max)	68 (32 – 89)	67 (34 – 90)	67 (32 – 90)
<b>Sex</b>	Male	108 (69.7%)	100 (64.5%)	208 (67.1%)
	Female	47 (30.3%)	55 (35.5%)	102 (32.9%)
<b>ECOG</b>	0	58 (37.4%)	55 (35.5%)	113 (36.5%)
	1	78 (50.3%)	79 (51.0%)	157 (50.6%)
	2	19 (12.3%)	21 (13.5%)	40 (12.6%)
<b>Rai Stage</b>	0	2 (1.3%)	4 (2.6%)	6 (1.9%)
	I	39 (25.2%)	32 (20.6%)	71 (22.9%)
	II	49 (31.6%)	54 (34.8%)	103 (33.2%)
	III	21 (13.5%)	18 (11.6%)	39 (12.6%)
	IV	44 (28.4%)	46 (29.7%)	90 (29.0%)
<b>17p del status</b>	Yes	28 (18.1%)	21 (13.5%)	49 (15.8%)
	No	127 (81.9%)	133 (85.8%)	260 (83.9%)
<b>IGHV</b>	Mutated	33 (21.3%)	26 (16.8%)	59 (19.0%)
	Unmutated	118 (76.1%)	125 (80.6%)	243 (78.4%)
	Missing	3 (1.9%)	2 (1.3%)	5 (1.6%)
<b>Number of Prior Lines of Therapy</b>	Median (Min – Max)	1 (1 – 8)	2 (1 – 10)	2 (1 – 10)
	1	82 (52.9%)	67 (43.2%)	149 (48.1%)
	2	40 (25.8%)	46 (29.7%)	86 (27.7%)
	3	17 (11.0%)	24 (15.5%)	41 (13.2%)
	≥4	16 (10.3%)	18 (11.6%)	34 (11.0%)

Source: AstraZeneca, ACE-CL-309 Clinical Study Protocol. 2016.

Note: Some columns may not sum to 100% due to rounding

## 10 Data Inputs Validated by Clinical Experts

Cost-related inputs were obtained from Medicinpriser.dk for drug acquisition, and DRG tariffs from sundhedsstyrelsen.dk for adverse events (AEs), drug administration, and monitoring in outpatient care. In addition, expert opinions from two clinicians (Aarhus university hospital and Rigshospital) were gathered to understand the current patient dynamics and hospital resources within the Danish haematological departments.

The two clinicians (Nørregaard Bentzen & Curovic Rotbain) were asked to give input on the following:

- Patient distributions across subsequent treatment options (the transition from second line therapy to third line therapy)
- Frequency of treatment monitoring and administration across treatment options
- Proportion of patients expected be treated in the hospital inpatient setting and/or at outpatient care across each identified AE

Their assumptions were used both in the cost per patient and budget impact analyses.

## 11 Methods

### 11.1 Methods of the Cost per Patient Analysis

An overview of the cost per patient analysis structure is presented in **Table 4**. The overview of the BIM is presented in section 10.2.1.

**Table 4.** Characteristics of the cost per patient analysis in R/R CLL

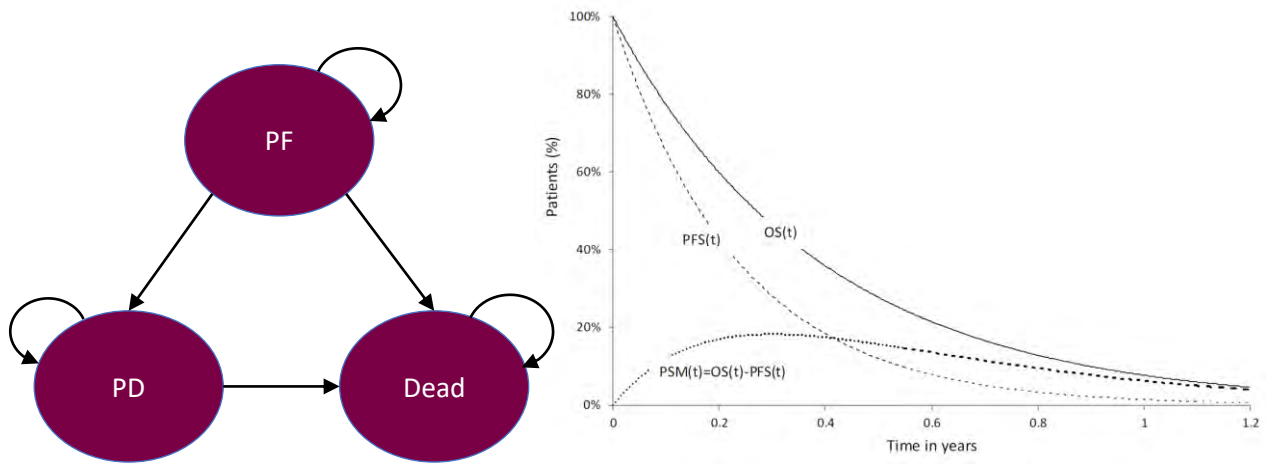
Model Characteristics	Details
Eligible Population	R/R CLL patients (2L treatment)
Country	Denmark
Intervention	Acalabrutinib
Comparator(s)	– Ibrutinib – Venetoclax + Rituximab
Perspective	Societal perspective with limitations, excluding productivity losses and cross-sectional costs based on the method guideline by the Danish Medicines Council.
Time Horizon	30 years (lifetime)
Discounting	3,5 %
Method	Partitioned survival model
Parametric Curve, PFS	Intervention: – Acalabrutinib: Extrapolation of acalabrutinib and ibrutinib arms pooled together using generalized gamma distribution Comparators: – Ibrutinib: Extrapolation of acalabrutinib and ibrutinib arms pooled together using generalized gamma distribution – Venetoclax + Rituximab: Assumption of equal efficacy
Parametric Curve, OS	Intervention: – Acalabrutinib (ibrutinib as baseline): Extrapolation of acalabrutinib and ibrutinib arms pooled together using exponential distribution Comparators: – Ibrutinib: Extrapolation of acalabrutinib and ibrutinib arms pooled together using exponential distribution – Venetoclax + Rituximab: Assumption of equal efficacy
Drug Wastage Included	No
Costs	2L: – Drug acquisition – Drug administration – Drug monitoring – Management of Grade $\geq 3$ AEs – Patient costs Subsequent therapy: – Drug acquisition – Drug administration

Model Characteristics	Details
	<ul style="list-style-type: none"> <li>- Drug monitoring</li> <li>- Patient costs</li> </ul>
Outcomes	Incremental cost per patient

### 11.1.1 Modelling in the Cost per Patient Analysis

The cost per patient model has a conventional three-state structure based on disease progression. **Figure 1** describes the underlying disease progression pathway in the model which includes three mutually exclusive health states: progression-free (PF), progressed disease (PD), and dead.

*Figure 1. CLL Disease progression model structure and underlying transitions*



The cohort in the model are initially in a progression-free state, from which they can either progress or die. The PD state is assumed to capture the clinical outcomes experienced by patients as they undergo subsequent lines of treatment. After entering PD, the cohort can either stay in that health state or transition to the death state. The death state is an absorbing state, meaning that patients are assumed to occupy this state indefinitely.

The cost per patient analysis is implemented using a partitioned survival model (PSM). In partitioned survival modelling, the state occupancy of the simulated cohort is estimated by extrapolating trial data for the cumulative probability of PFS and OS to a lifetime. The cycle length used in the model is 28 days. In each cycle, the curves are used to estimate:

1. The proportion of patients who are alive and have not progressed (Figure 1, under the PFS(t) dotted line)
2. The proportion of patients who have progressed but have not yet died (Figure 1, between the PFS(t) and OS(t) lines)
3. The proportion of patients who have died (Figure 1, under the PSM(t) dotted line)

The two health states of PF and PD are associated with different costs. The costs captured in the model include drug costs (acquisition, administration and monitoring), disease monitoring costs (routine scans and patient follow-ups), AE costs, and subsequent treatment costs.

The three-state model, based around disease progression, has become the norm in oncology and has been used in several previous models in R/R CLL, and PFS was the primary endpoint of the ELEVATE-RR trial for

acalabrutinib. Therefore, a model focusing on disease progression was considered the appropriate framework for the analysis. A partitioned survival framework was favoured for this model as opposed to other commonly used approaches in oncology, such as a state transition model, given the ease of implementation and the maturity of the data inputs.

PFS and OS data from the ELEVATE-RR trial were considered separately. The partitioned survival framework permits this as PFS and OS curves are extrapolated independently, without explicitly considering the underlying patient transitions. The key limitation of this approach is that it does not directly account for how disease progression, a purported prognostic event, may influence survival. This can lead to intrinsic uncertainties in the extrapolation of overall survival, where it is based on the continuation of observed trends rather than clinical rationale or prognostic markers. Partitioned survival models typically provide good predictions of endpoints for the within-trial period, however data maturity and/or external validation are required to ensure the logic of outcomes (NICE DSU, 2017).

### 11.1.2 Indirect Treatment Comparison

To date, there have been no published head-to-head RCTs comparing the efficacy of acalabrutinib vs venetoclax + rituximab in patients with R/R CLL. The ELEVATE-RR trial is a head-to-head RCT comparing the efficacy of acalabrutinib vs ibrutinib, in the subset of the R/R CLL population with high-risk prognostic markers. Network meta-analysis (NMA) methods can have limitations where there are cross-trial differences or a lack of a common comparator. Therefore, matching-adjusted indirect comparison (MAIC) was conducted to compare the relevant therapies. This section summarises the key information from MAIC, and further details are provided in the Appendix (*MAIC report R/R CLL*).

Two MAICs (against ibrutinib and venetoclax + rituximab) were conducted. In these analyses, the patient-level data from the ASCEND trial for acalabrutinib was adjusted in order to match the baseline characteristics of the comparator trials (REASONATE [ibrutinib] and MURANO [venetoclax + rituximab]). Using the adjusted acalabrutinib and comparator data, hazard ratios for acalabrutinib were estimated. The comparators and respective sources used to estimate survival curves for the analysis are as shown in Table 1 above. PFS, OS, and ORR were compared between ASCEND and REASONATE intervention arms (acalabrutinib and ibrutinib, respectively) and between the ASCEND and MURANO intervention arms (acalabrutinib and venetoclax + rituximab, respectively) before and after baseline matching.

In the comparison between acalabrutinib and ibrutinib, all matched baseline characteristics were balanced (i.e., statistically equivalent) between trials after matching. Differences in PFS between the two treatments were not statistically significant before matching (hazard ratio of acalabrutinib vs. ibrutinib [HR]: ■■■■,  $p =$  ■■■■), and remained so after matching, (HR: ■■■■,  $p =$  ■■■■). Differences in OS between the two trials were not statistically significant before or after matching (HR: ■■■■,  $p =$  ■■■■ and HR: ■■■■,  $p =$  ■■■■, respectively). There were no statistical differences in ORR either before or after matching (Before: ■■■■% vs. ■■■■%; odds ratio [OR], ■■■■;  $p =$  ■■■■. After: ■■■■% vs. ■■■■%; OR, ■■■■,  $p =$  ■■■■).

In comparison of acalabrutinib vs. venetoclax + rituximab, all matched baseline characteristics were balanced (i.e., statistically equivalent) between trials after matching. Although PFS was significantly higher for acalabrutinib relative to venetoclax + rituximab before matching (HR: ■■■■,  $p =$  ■■■■), this difference was not significant post matching (HR: ■■■■,  $p =$  ■■■■). Differences in OS between the two trials were not statistically significant before or after matching (HR: ■■■■,  $p =$  ■■■■ and HR: ■■■■,  $p =$  ■■■■, respectively). There were also no statistical differences in ORR either before or after matching (Before: ■■■■% vs. ■■■■%; OR, ■■■■,  $p =$  ■■■■; after: ■■■■% vs. ■■■■%; OR ■■■■,  $p =$  ■■■■).

The MAIC analyses indicate that in patients with R/R CLL, acalabrutinib is associated with comparable efficacy (PFS, OS and ORR) to both ibrutinib and venetoclax + rituximab.

### 11.1.3 Estimation of Survival Curves for Acalabrutinib and Comparators

The ELEVATE-RR trial included both acalabrutinib and ibrutinib and therefore can directly inform extrapolations of both treatments. As the trial was designed as a non-inferiority study, and demonstrated this was the case with a IRC-assessed PFS HR of 1.00 (95% CI 0.79 to 1.27), it is not possible to infer any differences in PFS between the treatments. Therefore, data from the two treatment arms were pooled together and analysed to provide the survival inputs for the model for both acalabrutinib and ibrutinib. The indirect treatment comparison in section 11.1.2. also demonstrated that acalabrutinib has comparable efficacy and survival outcomes to ibrutinib in the R/R CLL setting.

The PFS and OS curves for use in the model were estimated assuming equivalent efficacy for all treatments included in the analysis on the basis of the hazard ratios and confidence intervals obtained from MAICs and the ELEVATE-RR outcomes. As outlined in section 11.1.2 (Indirect treatment comparison), the MAIC analyses indicated that in patients with R/R CLL, acalabrutinib is associated with comparable efficacy (PFS, OS and ORR) to both ibrutinib and venetoclax + rituximab, and it was therefore assumed that all three treatments have comparable efficacy. Hence, the hazard ratios for PFS and OS were set to 1. The pooled patient-level survival data for acalabrutinib and ibrutinib was used as a baseline given this provided the most robust PFS and OS data.

Survival curves were extrapolated from the ELEVATE-RR trial (Byrd et al., 2021) for acalabrutinib and ibrutinib in R/R CLL, with curves for venetoclax + rituximab being modelled relative to this. Curve selection was based on NICE DSU guidance regarding the selection of extrapolation method (NICE, 2013). This process involved:

- Visual inspection of survival curve fit to Kaplan Meier (KM) data from the phase III clinical trial
- Inspection of log-cumulative hazard plots (to assess the behaviour of the hazard over time)
- Statistical model fit, via measures such as Akaike’s Information Criterion (AIC)/Bayesian Information Criterion (BIC)

The survival modelling methods and selected extrapolation are summarized in **Table 5**. More detailed description about the curve selection was presented in the Appendix (*Estimation of survival curves 2L*).

**Table 5. Overview of base case settings**

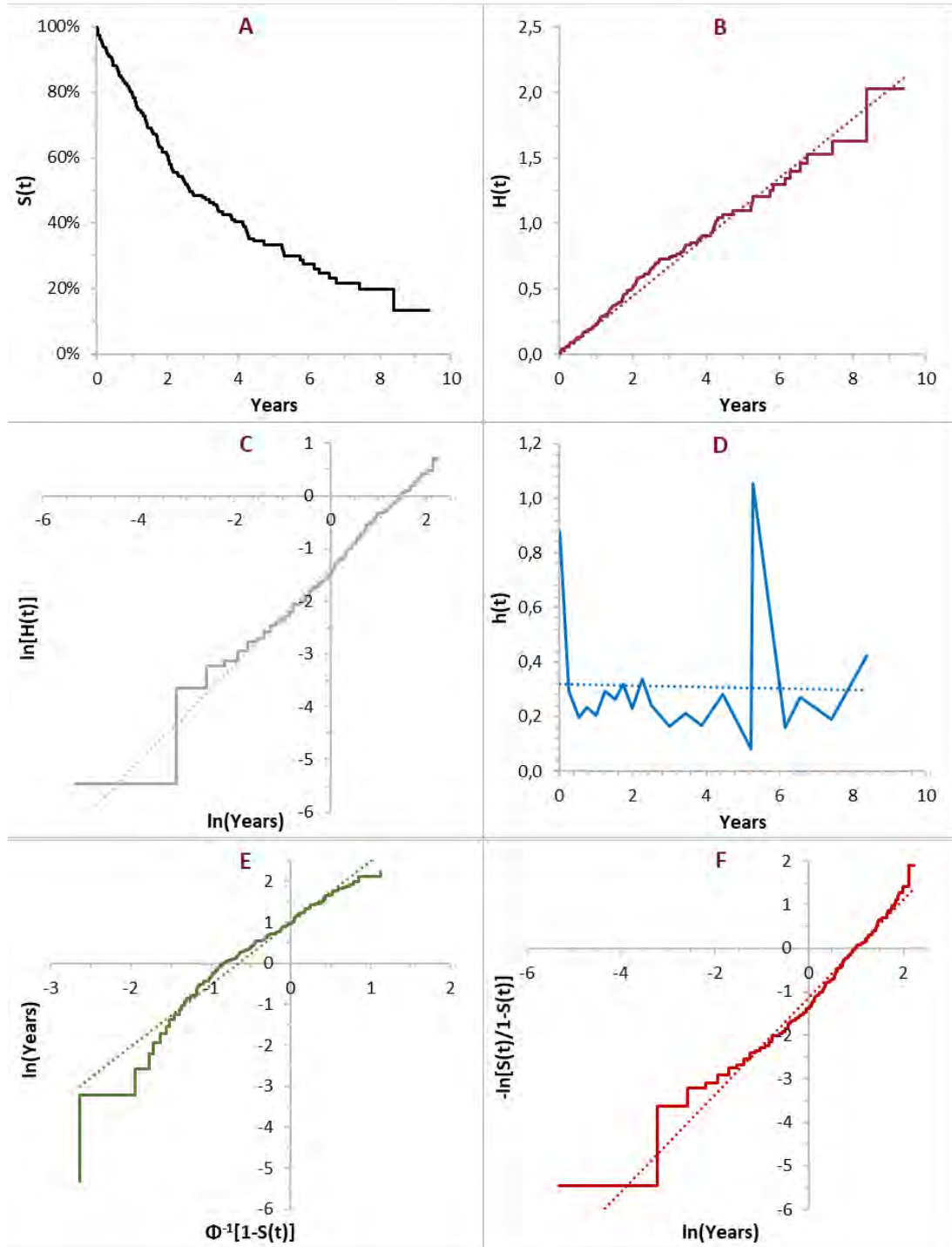
Survival Curves		
	PFS	OS
Ibrutinib Survival Distribution	Generalized Gamma	Exponential
HR for Acalabrutinib vs. Ibrutinib	1*	1*
HR for Venetoclax + Rituximab vs. Ibrutinib	1**	1**

\* Acalabrutinib and ibrutinib have comparable efficacy, which has been demonstrated by the ELEVATE RR trial and the MAIC analysis (11.1.2). The survival curves used for ibrutinib are derived from the extrapolation of the acalabrutinib and ibrutinib pooled survival data and therefore the same curves should be used for both treatments.

\*\* MAIC analyses indicated that in patients with R/R CLL, acalabrutinib is associated with similar efficacy (PFS, OS and ORR) to ibrutinib and venetoclax + rituximab.

The choice to use the exponential function to inform the long-term hazards of death in CLL also gains some external support. Long-term follow-up of 234 CLL patients in the UK receiving a range of different second line treatments (including chlorambucil, FCR, FC, bendamustine, ibrutinib, and alemtuzumab) using data from the Haematological Malignancy Research Network (HMRN 2017) was found to best be modelled with an exponential distribution, thus supporting its plausibility in CLL and for patients receiving acalabrutinib and other targeted therapies in the R/R setting (see **Figure 2**).

**Figure 2.** Comparison of different parametric fits to long-term survival data in R/R CLL from the UK HMRN registry, showing: (A) the Kaplan-Meier of overall survival, (B) the cumulative hazard plot (exponential distribution), (C) the log cumulative hazard plot (Weibull), (D) the instant hazard plot (Gompertz), (E) the probit survival plot (lognormal), and (F) the logit survival plot (loglogistic).





## 11.2 Methods of the Budget Impact Analysis

### 11.2.1 Overview of the Budget Impact Analysis

To analyse the budget consequence of implementing acalabrutinib therapy, two scenarios of CLL market were compared: one being a market without acalabrutinib and the other being a market with acalabrutinib. Each scenario considers the national and CLL population sizes, patient eligibility, and market shares of available treatments. In addition, cost data related to drug acquisitions and healthcare resources of drug administration, disease management, AEs, and treatment monitoring were included, all within a Danish setting. Based on these data, the following estimating steps were made leading to the BI results:

- Total eligible population for 2L CLL treatment in Denmark.
- Number of eligible patients in 2L receiving each therapeutic option every year, estimated by multiplying the eligible population with the market share estimates for each treatment option.
- Calculate the total BI by estimating the difference in total costs between the markets with or without acalabrutinib.

The model structure is aligned with the Danish Medicines Council guideline and follows standard format of calculating the budget impact of new treatments. An overview of the model structure is provided in **Table 6**.

**Table 6.** Characteristics of the budget impact analysis

Model Characteristics	Details
Eligible Population	R/R CLL patients (2L treatment)
Country	Denmark
Intervention	Acalabrutinib
Comparator(s)	– Ibrutinib – Venetoclax + Rituximab
Perspective	Danish healthcare payer perspective
Time Horizon	5 years
Method	Open cohort comprising incident patients only
Market Share	Market share following the adoption of acalabrutinib in 2L treatment for R/R CLL patients
Costs	– Drug acquisition – Drug administration – Drug monitoring – Disease management – Management of Grade $\geq$ 3 AEs – Subsequent therapy (inc. acquisition, administration, and monitoring)
Drug Wastage Included	No
Outcomes	– Budget without acalabrutinib – Budget with acalabrutinib – Incremental budget impact of acalabrutinib
Scenario Analyses	Budget with smaller market share (reduction of 40% for acalabrutinib) in R/R CLL

## 12 Budget Impact Model Inputs

The budget impact analysis was based upon the cost per patient analysis, taking relevant modelled costs over time for each treatment and combining these with estimates of patients initiating each treatment to determine budget impact. Therefore, costing sources are aligned with those of the cost per patient analysis. Further inputs were required to estimate the eligible patient population and market share of treatments.

## 12.1 Eligible Population

The target population eligible for acalabrutinib in 2L were calculated in line with the Danish Medicines Council's protocol for acalabrutinib. The protocol indicates that between 65 and 70 patients initiate second line therapy for CLL each year in Denmark. Based on the estimated annual incidence of new CLL cases in Denmark (7,74 per 100.000; DLG/LYFO, 2019), annual national population growth (0,46% per annum; Statistics Denmark, 2021), and the estimated initiation of first line therapy (33,2%; Medicinrådet, 2020), a prevalent first line population was estimated. Using Danish data on mortality in the first line treatment setting (11,6% per annum; Curovic Rotbain et al, 2020), a progression rate of 8,7% per annum would imply that 65 to 69 patients initiate second line therapy per year, in line with the protocol Danish Medicines Council.

## 12.2 Market Share

In the BIM, two different scenarios for market share were considered. One representing the current standard of care in Denmark (scenario without acalabrutinib) and the other when treatment with acalabrutinib is reimbursed (scenario with acalabrutinib). Venetoclax + Rituximab was approved by the Danish Medicines Council for the treatment of R/R CLL in December 2019. Thus, in the scenario without acalabrutinib the market share for venetoclax + rituximab is assumed to still be increasing due to its relatively recent introduction, from 60% in 2022 to 90% in 2025, while the market share for ibrutinib will be reduced, accordingly. However, if acalabrutinib is approved it is assumed to negatively impact the market share of both of the current treatment options as the market share for acalabrutinib is assumed to increase from 20% in 2022 to 40% in 2024 and 2025.

Market shares were applied to the number of patients eligible for second line treatment to estimate the number of patients receiving each treatment. The market share for each treatment option at second line is presented in **Table 7**.

*Table 7. Market shares*

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>R/R 2L</b>										
<b>Acalabrutinib</b>	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>Ibrutinib</b>	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>Venetoclax + Rituximab</b>	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%

## 13 Treatment Duration

The treatment duration of each treatment option was used to estimate the drug acquisition, administration, monitoring, and AE costs. In turn, cost implications of subsequent therapies for R/R patients who progress to 3L are included.

### 13.1 Second-Line Treatments

While some treatment durations are informed by progression free survival (PFS), others are informed by fixed durations of a maximum number of cycles. The venetoclax + rituximab regimen is composed of two drugs used in a finite duration, as noted in the product resume from European Medicines Agency (EMA). For this treatment, patients are assumed to discontinue treatment at disease progression, death, or the maximum number of treatment cycles (24 months of venetoclax and six cycle of rituximab).

Given both acalabrutinib and ibrutinib are used until progression, the treatment duration for these drugs is equivalent to PFS as modelled. The ELEVATE-RR trial has shown that acalabrutinib and ibrutinib are associated with comparable efficacy (Byrd et al., 2021). This would suggest that reasons for discontinuation due to disease progression would be aligned between treatments. Hence, the treatment duration for both treatments was informed by the PFS curve from the pooled acalabrutinib and ibrutinib ELEVATERR data, extrapolated using generalized gamma model. With regards to potential discontinuations due to unacceptable toxicity, there was no significant differences between the two arms regarding the proportion of observed discontinuations that were attributable to treatment emergent AEs. It was therefore assumed for the purposes of the economic analysis that discontinuations due to unacceptable toxicity would be largely similar.

Venetoclax in combination with rituximab has a fixed number of cycles and thus followed the PFS curve until the maximum number of cycles. Modelled average treatment durations for all regimens for R/R CLL patients are presented in **Table 8**.

**Table 8.** R/R CLL treatment duration

Treatment	Mean Treatment Duration, Months (Cycles)
Acalabrutinib	████ (████)
Ibrutinib	████ (████)
Venetoclax + Rituximab	Venetoclax: █████ (████) Rituximab: █████ (████)

## 13.2 Subsequent Treatment Duration

Patients who progress after 2L treatments were assumed to either receive ibrutinib, venetoclax + rituximab, or acalabrutinib as a subsequent treatment. The duration of 3L treatment options for patients who progress after 2L were assumed to be the same as the duration in 2L (presented in **Table 8**).

The patient distribution for subsequent treatment is presented in **Table 9**. The assumptions were based on expert opinions (Nørregaard Bentzen & Curovic Rotbain) and the market shares presented in section 11.2.

**Table 9.** Percentage of patients receiving 3L treatment in the R/R CLL population

2L Therapy	Patients Receiving Subsequent Therapy at 3L		
	Acalabrutinib	Ibrutinib	Venetoclax + Rituximab
Acalabrutinib	0	0%	100%
Ibrutinib	0%	0%	100%
Venetoclax + Rituximab	80%	20%	0%

## 14 Costs Inputs

### 14.1 Drug Acquisition

Acquisition costs were applied in the models as a cost per cycle for each treatment until progression or until the maximum number of administrations have been reached. Acquisition costs for each treatment option were calculated based on dosing regimen as administration frequency per cycle and cost per dose. **Table 10** shows the drug information including formulations, pack sizes, strength, price (pharmacy purchase price, AIP)

per pack and mg, as well as unit price were sourced from Danish Medicines Agency 2021 (Medicinepriser.dk). In instances where multiple pack prices were available, the pack with the lowest cost per mg was used.

Drug wastage was not included in the base case. Drug wastage is not anticipated to affect the results for oral therapies as, whilst whole packs of tablets will be dispensed in practice, pack sizes are largely aligned with model cycles. As treatment discontinuation is considered to be continuous in line with progression-free survival for most oral therapies, minor deviations in tablet consumption by pack are assumed to average out with time. Drug wastage is potentially a greater issue for parenterally administered drugs, where the required dose per body surface area or weight is unlikely to correspond with full vials, though dose banding or vial sharing can occur in practice and reduce the likelihood of wastage. Excluding drug wastage is likely to be a conservative assumption against acalabrutinib as wastage is most likely to occur with intravenously administered therapies (venetoclax + rituximab) as it captures potential cost savings by vial sharing that could occur with comparator IV therapies rather than the orally administered acalabrutinib. Drug wastage (unused vials) was considered in a scenario analysis. Drug wastage was estimated by calculating the required dose per administration based on the dosing regimen and patient weight/body surface area, where required. This was then compared to the number of whole vials or tablet packs that would be needed to deliver the required dose (e.g., a dose of 950 mg of rituximab at 500 mg/m<sup>2</sup> for a patient with a BSA of 1.9 m<sup>2</sup> would require two 500 mg vials).

**Table 10. Drug information**

	Formulation	Strength	Pack Size	AIP	AIP/Unit
<b>Acalabrutinib</b>	Tablet	100 mg	60	45.224,19	753,74
<b>Ibrutinib</b>	Capsule	140 mg	90	45.124,73	501,39
			120	57.321,65	477,68
	Tablet	140mg	28	14.038,8	501,39
	Tablet	280mg	28	28.077,61	1.002,77
	Tablet	420mg	28	42.116,41	1.504,16
<b>Venetoclax</b>	Tablet	10 mg	14	500,13	35,72
	Tablet	50 mg	7	1.250,33	178,62
	Tablet	100 mg	7	2.500,64	357,23
	Tablet	100 mg	14	5.001,28	357,23
	Tablet	100 mg	112	40.010,34	357,24
<b>Rituximab</b>	IV	100 mg	2	2.675,8	1.337,90
	IV	500 mg	1	6.687	6.687,00

As some treatment doses are body weight and surface area (BSA) specific, the drug acquisition costs in these were sourced from ASCEND study and are presented in **Table 11**.

**Table 11. Population demographics in the analysis**

Characteristic	R/R CLL
Weight (kg)	77.84
Body Surface Area (m <sup>2</sup> )	1.90

Source: ACE-CL-309 Clinical Study Report (Patient baseline characteristics - Overall)

The information on administration frequency and dosing regimens were sourced from the respective EMA SmPCs. **Table 12** summarizes the treatment dosing and administration frequency implemented in the model for R/R CLL patients.

**Table 12. Treatment dosing and administration**

	Administration Method	Dose per Administration	Admin Frequency	Weighted Doses	Source
<b>Acalabrutinib</b>	Oral	100mg	2 tablets once daily	0	Calquence SmPC
<b>Ibrutinib</b>	Oral	420mg	3 tablets once daily of 140 mg*	0	Imbruvica SmPC
<b>Venetoclax</b>	Oral	400mg	1 tablet once daily	0	Venclyxto SmPC
<b>Rituximab</b>	IV	First dose at 375 mg/m <sup>2</sup> , subsequent doses at 500 mg/m <sup>2</sup>	Once per cycle for 6 cycles	1,9 m <sup>2</sup> (BSA) ELEVATE	Mabthera SmPC

\*Cost is identical to 1 tablet of 420 mg

The acquisition costs per cycle for R/R CLL treatments were estimated based on drug information and administration regimens and are presented in Table 13.

The estimated acquisition costs were related to doses per cycle. The per cycle dose for acalabrutinib was estimated to be 56, given the administration frequency of twice per day until progression. For ibrutinib and venetoclax, the per cycle dose was estimated to be 28, as they are administered once per day. For rituximab it was estimated 1 dose per cycle for 6 cycles given the treatment duration.

**Table 13. Drug acquisition costs for treatment options of R/R CLL included in the model**

Treatment	Dose per Cycle	Cost per Cycle
<b>R/R CLL</b>		
Acalabrutinib	56	DKK 42.209,24
Ibrutinib	28	DKK 42.116,41
Venetoclax + Rituximab	28	DKK 40.010,34
	1	DKK 12.175,91

Cost per patient model uses estimates calculated per cycle. Hence, the estimates of this table are not in line with the inputs used in the cost per patient model.

## 14.2 Drug Administration

The administration frequencies for each treatment option in R/R CLL were sourced from the respective EMA SmPCs. Since there is a lack of information on where the administrations of the treatments take place, it is assumed that IV treatment (rituximab) was administered in the outpatient care, thus accruing administration costs. Orally administered treatments were assumed to accrue no administration costs. Unit cost for outpatient care resources was sourced from the 2021 Danish DRG tariffs (Sundhedsdatastyrelsen, 2021).

- **Acalabrutinib:** Since acalabrutinib 100 mg is administered orally twice per day until progression or intolerable toxicity, it is assumed that no administration costs accrued.
- **Ibrutinib:** Since ibrutinib is administered orally three times a day until progression or intolerable toxicity, it is assumed that no administration costs accrued.
- **Venetoclax + Rituximab:** Venetoclax is orally administered where patients will receive increasing dose of venetoclax during the ramp-up period every 7<sup>th</sup> day due the risk of developing TLS. After ramp-up period patients start receiving IV treatment of rituximab once every cycle for total of 6 cycles at the outpatient care, resulting in administration costs.

Table 14 shows the administration frequency for each treatment in R/R CLL with a respective treatment duration and the resulting monthly frequency accounting for 28 days in one cycle. The tariff attributed to the

outpatient care resources for IV administrations are shown in Table 15.

Table 14. Hospital resource use

Treatment		Number of Outpatient Care Visits per Cycle
Acalabrutinib	Acalabrutinib	0
Ibrutinib	Ibrutinib	0
Venetoclax + Rituximab	Venetoclax	0
	Rituximab	1x every cycle (for 6 cycles)

Table 15. Outpatient care cost

Hospital Resource	Unit Cost (DKK)	DRG Code	Code Description	Source
Ambulatory visit	3203	17MA98	MDC17 1-dagsgruppe, pat. mindst 7 år	DRG 2021 (Sundhedsdatastyrelsen 2021)

### 14.3 Monitoring Costs

Given the lack of information on drug monitoring frequency in the respective EMA SmPCs of the treatments, the following monitoring frequencies are based on AstraZeneca's assumptions verified by the external clinicians (Nørregaard Bentzen & Curovic Rotbain). Monitoring costs accounted for the monitoring frequency of blood tests that are taken each time an IV treatment is administered (see section 14.2) and until discontinuation of IV treatment (Sydvestjysk Sygehus, 2017). In addition, costs for yearly monitoring frequencies of other tests were included and were accounted for until disease progression.

The blood tests, necessary for patients receiving IV treatment, were assumed to include lymphocyte count, creatinine count, and total blood count. Since IV related combination treatments (venetoclax + rituximab), are administered in outpatient care the blood tests are assumed to be taken in parallel with the administration described in the section 14.2. For example, rituximab treatment is assumed to be administered once per cycle over six cycles, the blood tests are therefore assumed to be done at the same frequency. It should be noted that ongoing disease monitoring is assumed to account for the blood tests that are performed during the treatment period. Therefore, estimated disease monitoring test frequencies must be subtracted from the estimated blood tests for the treatment period to avoid double counting. The administration dependent test frequencies per month for each comparator treatment are shown in **Table 16**.

Table 16. Blood test frequencies over the treatment period estimated per month

Monitoring of Patients on IV Treatment, per cycle		Lymphocyte Count	Creatinine Count	Total Blood Count
Venetoclax + Rituximab	Venetoclax			
	Rituximab	0,69	0,69	0,69

Ongoing disease monitoring consists of blood tests and additional procedures (CT scan, platelet transfusions, bone marrow test, etc.) and is assumed to be performed for each patient once every third month (0,31 times per cycle). This was verified by two external clinicians (Nørregaard Bentzen & Curovic Rotbain). The disease monitoring is assumed to start at the beginning of each therapy and is continued until death. It should be noted that ongoing disease monitoring is assumed for all therapies (both oral and IV). The ongoing monitoring frequency calculated per cycle for each test (applicable to every treatment option) is shown in **Table 17**.

The unit cost for each test required were derived from 2021 DRG tariffs from sundhedsdatastyrelsen.dk. However, cost for blood tests were derived from Rigshospital Labportal. Whilst the costs for blood tests can be considered as an underestimation, it is argued that any other costs will not impact the result, as the frequency related to each treatment and the survival data remain unchanged. The costs for various monitoring tests are shown in Table 18.

**Table 17.** Ongoing disease monitoring frequency estimated per month across treatment options in R/R CLL

Procedure	Lymphocyte Count	Creatinine Count	Full Blood Count	CT Scan	Platelet Transfusion	Bone Marrow Test	Uric Acid	Biopsy
Frequency per Cycle	0,31	0,31	0,31	0,31	0,31	0,31	0,31	0,31

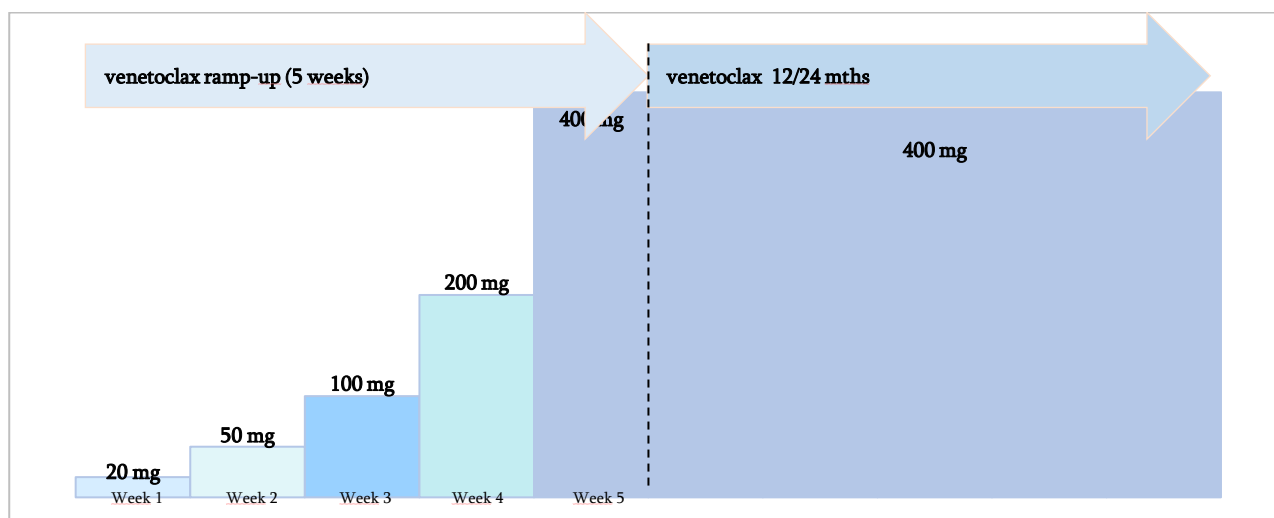
**Table 18.** Monitoring unit costs

Cost Item	Cost (DKK)	Code	Code Description	Source
CT Scan	2007	30PR06	CT-scanning, kompliceret	DRG 2021 (Sundhedsdatastyrelsen 2021)
Blood Transfusion	4628	16PR02	Blood transfusion, Transfusion af blod, øvrig	DRG 2021 (Sundhedsdatastyrelsen 2021)
Platelet Transfusion	6042	16PR01	Transfusion af plasma og/eller behandlet blod	DRG 2021 (Sundhedsdatastyrelsen 2021)
Bone Marrow Test	14526	17PR01	Udtagning af knoglemarv til diagnostisk undersøgelse	DRG 2021 (Sundhedsdatastyrelsen 2021)
Lymphocyte Count	13	Lymfomik	-	Rigshospitalets Labportal, ID: 2466
Uric Acid	28	Urat	-	Rigshospitalets Labportal, ID: 5304
Creatinine Count	28	Crea	-	Rigshospitalets Labportal, ID: 3766
Full Blood Count	71	-	Prøvetagning i AMB, Prisoversigt - Analyser der udføres af KBA i Region Sjælland, KBA	Region Sjælland. Laboratoriemedicinsk Vejledning. ID: 548551
Biopsy	3316	09PR08	Nålebiopsi, overfladisk	DRG 2021 (Sundhedsdatastyrelsen 2021)

#### 14.4 One-Time Monitoring Costs

Monitoring of tumour lysis syndrome (TLS) is needed for all patients initiating of venetoclax treatment (Venclyxto SmPC). The model accounts for TLS prophylaxis associated costs at treatment initiation as the dose of venetoclax is gradually increased during the first five weeks of treatment, from 20mg daily to 400mg daily (**Figure 3**).

**Figure 3.** Dosing scheme for venetoclax in combination with rituximab



According to the SmPC, patients being treated with venetoclax have a risk of developing TLS during the ramp-up period which is associated with increased monitoring frequency. To assess the risk, several blood tests among others are taken in the outpatient care every week when the dose is increased. Thus, it is assumed that patient will be monitored for TLS 5 times during a ramp-up period. A unit cost from 2021 DRG tariffs is attributed for the outpatient care resources required for TLS management and is shown in the **Table 19**. The tariff code is assumed to include blood tests resources.

**Table 19.** DRG tariff of TLS control unit cost

Cost Item	Code	Code Description	Unit Cost (DKK)	Source
TLS Prophylaxis	10MA98	MDC10 1-dagsgruppe, pat. mindst 7 år	1.518	DRG 2021 (Sundhedsdatastyrelsen 2021)

## 14.5 Adverse Events

The costs of managing treatment-emergent adverse events (AEs) are included in the analyses. Only grade  $\geq 3$  AEs that occurred in at least 2% of patients are included in any of the pivotal trials for acalabrutinib, ibrutinib, or venetoclax + rituximab were included. The AE incidence rates applied are presented in **Table 20**. The rates for acalabrutinib and ibrutinib, were sourced from the ELEVATE-RR trial. AE rates for Venetoclax + Rituximab were sourced from published literature reporting results of the MURANO trial.



**Table 20. AE incidence rates for the R/R CLL population**

	Acalabrutinib	Ibrutinib	Venetoclax + Rituximab
Anaemia			11,3 %
Cataract			Not Reported
Atrial Fibrillation			Not Reported
Syncope			Not Reported
Congestive Heart Failure			Not Reported
Diarrhoea			Not Reported
Dyspnoea			Not Reported
Fatigue			Not Reported
Febrile Neutropenia			3,6 %
Hyperglycemia			2,1 %
Hypertension			Not Reported
Urinary Tract Infection			Not Reported
Infusion-Related Reaction			2,1 %
Hypogammaglobulinemia			2,1 %
Acute Kidney injury			Not Reported
Neutropenia			58,8 %
Pyrexia			Not Reported
Thrombocytopenia			5,7 %
Tumour Lysis Syndrome			3,1 %
Sepsis			Not Reported
Hyperuricaemia			Not Reported
Pneumonia			5,2 %
Source	[1]	[1]	[2]

[1] AstraZeneca, ACE-CL-006 (ELEVATE RR) Clinical Study Report. 2021.

[2] Kater et al. 2020

All adverse events were assumed to accrue some healthcare costs, given as by definition grade 3 adverse events of a severity to require investigation or treatment. It is assumed by AstraZeneca that hospital resource use depends on whether an adverse event is treated in an outpatient care or a hospital. This assumption was verified by the external clinicians (Nørregaard Bentzen & Curovic Rotbain). **Table 21** shows the 2021 DRG, code, description and tariffs attributed to each AE. Some of the AEs are assumed to require full hospitalisation (i.e., inpatient stay), whereas other are assumed to be treated in outpatient care. The cost estimates were calculated based on the assumed percentage of patients requiring hospitalisation or outpatient care and the DRG tariffs attributed to each AE, which is shown in **Table 21**. It is also assumed that treatment of certain AEs will require extra blood tests, hence the price of the full blood test is added to the calculation (DKK 71). Eight diagnosis groups were identified related to the AEs. These were diseases in the respiratory organs (=04), circulatory organs (=05MA), digestive organs (=06MA), musculoskeletal system (=08MA), endocrine diseases, nutritional and metabolic diseases (=10MA), haematologic organs (=16MA), infectious and parasitic diseases (=18MA) as well as accidents and poisonings (=21MA). Within these diagnosis groups specific codes related to the hospitalisation and outpatient care (=98) were identified that were corresponding to each AE. **Table 22** shows the percentage of patient requiring hospitalisation and percentage of patient requiring outpatient care for each AE.

Table 21. Resource use unit cost of treating AEs

Adverse Event	Hospital DRG Code	Hospitalisation Description	Tariff	Outpatient Care DRG Code	Outpatient Care Description	Tariff
Anaemia	16MA10	Øvrige sygdomme i blod og bloddannende organer	22.545	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114
Cataract	02MP21	Grå stær operationer, u. generel anæstesi	3.036			
Atrial Fibrillation	05MA07	Hjertearytmi og synkope	15.488	05MA98	MDC05 1-dagsgruppe, pat. mindst 7 år	1.153
Syncope	05MA07	Hjertearytmi og synkope	15.488			
Congestive Heart Failure	05MA04	Hjertesvigt og shock	33.642			
Diarrhoea	06MA11	Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	5.130	06MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	2.277
Dyspnoea	04MA23	Symptomer fra luftveje	19.691	04MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	1.732
Fatigue	04MA02	Søvnapnø	2.382	04MA98	MDC04 1-dagsgruppe, pat. mindst 7 år	1.732
Febrile Neutropenia	16MA03	Granulo- og trombocytopeni	35.483	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114
Hyperglycaemia	10MA06	Andre ernærings- og stofskiftesygdomme	24.306	10MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	1.518
Hypertension	05MA11	Hypertension	14.155			
Urinary Tract Infection	11MA07	Infektioner i nyrer og urinvej, pat. mindst 16 år	24.431	11MA98	Urinvejsinfektion uden angivelse af lokalisation - MDC11 1-dagsgruppe, pat. mindst 7 år	1.906
Infusion-Related Reaction	18MA09	Observation for infektion eller parasitær sygdom	19.185	18MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	2.676
Hypogammaglobulinemia				16MA98	Ikke-familier hypogammaglobulinæmi/MDC16 1-dagsgruppe, pat. mindst 7 år	3.114
Acute Kidney injury	11MA01	Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese	41.799			
Neutropenia	16MA03	Granulo- og trombocytopeni	35.483	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114

Adverse Event	Hospital DRG Code	Hospitalisation Description	Tariff	Outpatient Care DRG Code	Outpatient Care Description	Tariff
Pyrexia	18MA04	Feber af ukendt årsag, pat. mindst 18 år, uden biopsi og/eller scopi	18.889	18MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	2.676
Thrombocytopenia	16MA09	Koagulationsforstyrrelser	25.203	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114
Tumour Lysis Syndrome	10MA06	Andre ernærings- og stofskiftesygdomme	24.306	10MA98	MDC10 1-dagsgruppe, pat. mindst 7 år	1.518
Sepsis	18MA01	Sepsis	42.770			
Hyperuricaemia				23MA98	MDC23 1-dagsgruppe, pat. mindst 7 år	1.626
Pneumonia	04MA13	Lungebetændelse og pleurit, pat. mindst 60 år	36.514			

Table 22. Percentage of patients being treated in inpatient and outpatient care

Adverse Event	Patients Requiring Treatment	Calculation / Total Cost
Anaemia	20% hospitalisation and 80% outpatient care + 3 extra blood tests	$(0,2*22.545) + (0,8*3.114) + (3*71) = 7.213$
Cataract	100% hospitalisation	3.036
Atrial Fibrillation	100 % hospitalisation	15.488
Syncope	100% hospitalisation	15.488
Congestive Heart Failure	100% hospitalisation	33.642
Diarrhoea	70% hospitalisation and 30% outpatient care	$(0,7*5.130) + (0,3*2.277) = 4.274$
Dyspnoea	100% outpatient care	1.732
Fatigue	100% outpatient care	1.732
Febrile Neutropenia	100 % hospitalisation	35.483
Hyperglycaemia	100% outpatient care	1.518
Hypertension	100% hospitalisation	14.155
Urinary Tract Infection	10% hospitalisation and 90% outpatient care	$(0,1*24.431) + (0,9*1.906) = 4.158$
Infusion-Related Reactions	100% outpatient care	2.676
Hypogammaglobulinemia	100% outpatient care	3.114
Acute Kidney injury	100% hospitalisation	41.799
Neutropenia	10% hospitalisation and 90% outpatient care	$(0,1*35483) + (0,9*3114) = 6.351$
Pyrexia	100 % hospitalisation	18.889
Thrombocytopenia	10% hospitalisation and 90% outpatient care + 3 extra blood tests	$(0,1*25203) + (0,9*3114) + (3*71) = 5.536$
Tumour Lysis Syndrome	100 % hospitalisation	24.306
Sepsis	100% hospitalisation	42.770
Hyperuricaemia	100% outpatient care	1.626
Pneumonia	100% hospitalisation	36.514

## 14.6 Subsequent Treatment Costs

Costs accrued for subsequent treatment were included in the analyses. The treatment duration of the subsequent treatments and the subsequent treatment distribution were presented in section 13.2.

As the cost per patient model tracks the survival of each cohort of patients entering the PD health state, subsequent treatment costs were estimated as follows:

- Per cycle costs (and 1st cycle) costs associated with each subsequent treatment option were estimated (incl. acquisition, administration and monitoring costs).
- The per cycle costs for each individual subsequent treatment were multiplied by the treatment duration (**Table 8**).
- The subsequent treatment costs accrued by “new progressors” in each model cycle were a weighted average of the total costs and subsequent treatment distribution (**Table 9**).

## 14.7 Patient Time and Transportation Costs

### 14.7.1 Ongoing Monitoring and Costs Related to Treatment

Patient costs were estimated based on the Danish Medicine Council’s guidelines of unit cost evaluation. The patient costs are calculated based on the number of hospital or clinic visits required for each treatment regimen and included yearly monitoring visits and IV treatment administration and additional monitoring (e.g., blood tests). AE related visits were conservatively excluded. In addition, patient costs associated with IV treatment monitoring visits (administration and monitoring) were not included for patients on subsequent treatments which are administered intravenously. For oral therapies, no additional time or visits were considered for collecting medications from the hospital. Discussions with clinicians have highlighted that patients collect medication during routine hospital visits, which for well-treated CLL patients is typically every 3 months in line with monitoring visits (as noted in Section 14.3 above), and therefore no additional costs for travelling to the pharmacy were included.

The health care visits include the effective time at the outpatient clinic associated with the resource use estimates (**Table 23**), and include the total patient time and transport time. Transport time is assumed to be one hour per visit (30 minutes each way). The average patient time per visit, including waiting time, was assumed to be 5 hours. The monetary value for patient time according to the Danish Medicines Council’s guidelines was DKK 179 per hour. The transport cost was set to DKK 100 (equivalent to 14 km) per visit to the health care clinic and back home.

**Table 23.** Patient time associated with drug monitoring visits

Resource	Time Taken	Sources / Notes
CT Scan	10 to 20 mins	NHS England ( <a href="https://www.nhs.uk/conditions/ct-scan/">https://www.nhs.uk/conditions/ct-scan/</a> )
Blood Transfusion	2 to 4 hours	Memorial Sloan Kettering Cancer Center ( <a href="https://www.mskcc.org/cancer-care/patient-education/about-blood-transfusion">https://www.mskcc.org/cancer-care/patient-education/about-blood-transfusion</a> )
Platelet Transfusion	30 to 60 mins	
Bone Marrow Test Biopsy	30 minutes	Cancer.Net ( <a href="https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/bone-marrow-aspiration-and-biopsy">https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/bone-marrow-aspiration-and-biopsy</a> )
Lymphocyte Count	5 minutes	Assumption based on a single visit to the phlebotomy clinic
Creatinine Count		
Total Blood Count		
Uric Acid		
Waiting Time	25 minutes	Assumption
Travel Time	1 hour	Assumption
Total Time per Visit	6 hours	Calculated

Patient costs were calculated based on the same disease monitoring frequencies by each treatment option as assumed in section 14.3 of monitoring cost. Table 24 presents the patient cost calculation associated with yearly monitoring. The total number of visits was multiplied by the time per visit. The patient time for visits and transport is multiplied with the unit cost for patient time. The total patient costs include the patient time costs and the transport costs. The patient costs associated with yearly monitoring were accounted both for PF and PD health states in the cost per patient model.

Table 24. Estimated patient costs for time and transport for R/R CLL

Cost Unit	Ibrutinib	Acalabrutinib	Venetoclax + Rituximab
<b>Monitoring Frequency (per 28 day cycle)</b>			
CT Scan	0,31	0,31	0,31
Blood Transfusion	0,31	0,31	0,31
Platelet Transfusion	0,31	0,31	0,31
Bone Marrow Test	0,31	0,31	0,31
Lymphocyte Count	0,31	0,31	0,31
Creatinine Count	0,31	0,31	0,31
Total Blood Count	0,31	0,31	0,31
Uric Acid	0,31	0,31	0,31
Biopsy	0,31	0,31	0,31
<b>Number of Visits per Cycle</b>	<b>0,31</b>	<b>0,31</b>	<b>0,31</b>
<b>Patient time consumption (per visit)</b>			
<b>Patient time, visits (hours)</b>	5	5	5
<b>Patient time, transport (hours)</b>	1	1	1
<b>Patient costs (per 28 days cycle)</b>			
<b>Patient time, visits cost (DKK)</b>	895	895	895
<b>Patient time, transport cost (DKK)</b>	179	179	179
<b>Transport cost (DKK)</b>	100	100	100
<b>Total patient cost per cycle*</b>	1174*0,31 = 361,23	1174*0,31 = 361,23	1174*0,77 = 361,23

\*Patient time cost (DKK) + transport cost (DKK)

**Table 25** presents the patient costs associated with administration visits and monitoring assumed for patients on IV treatments (administration and blood tests). To avoid double counting patient costs for the months when patients will also have the ongoing monitoring visits, the frequencies were reduced similarly as presented in section 14.3, assuming that tests and travel costs would only be accrued on the additional visits required. For these visits it was arbitrarily assumed that the time for blood tests (including waiting time) would be around 20 minutes. Patient time for drug administration per treatment cycle was also included, based on the estimated infusion times from the SmPC for each of the IV products. No additional travel time or travel costs were included for drug administration as it was conservatively assumed tests and monitoring would be conducted on the same days as drug administration.

Table 25. Estimated patient costs for time and transport, IV treatment administration visits and monitoring<sup>1</sup>

Cost Unit	Venetoclax + Rituximab
<b>Monitoring frequencies (per month)</b>	
Lymphocytes Count	0,69
Creatinine Count	0,69
Total Blood Count	0,69
<b>Number of Visits per Cycle</b>	<b>0,69</b>
<b>Patient Time Consumption (per visit)</b>	
Patient Time, Visits (hours)	0,33
Patient Time, Transport (hours)	1
<b>Patient Costs (per 28 day cycle)</b>	
Patient Time, Visits (DKK)	60
Patient Time, Transport (DKK)	179
Transport Cost (DKK)	100
Total Patient Cost per Cycle*	339*0,69 = 234,46
<b>Patient Costs for Drug Administration (per 28 day cycle)</b>	
Patient Time, Drug Administration, (hours)	3,08**
Total Patient Cost per Cycle	551,92

<sup>1</sup> The analysis did not consider the patient costs associated with outpatient visits for administration and monitoring (blood tests) of patients on subsequent treatment (IV). This was estimated to have negligible impact on results.

\*Patient time cost (DKK) + transport cost (DKK)

\*\* Based on the SmPC and the modelled patient weight, rituximab would administered over ~3,5 hours in the first cycle and ~3 hours in the subsequent 5 cycles. Minimum estimated time in hospital is 18h30m, distributed over 6 cycles

#### 14.7.2 One-Time Monitoring Patient Costs

Costs for patient time and transport are calculated for patients treated with venetoclax-based treatment (venetoclax + rituximab) due to the ramp-up period using similar approach as presented above. Thus, the total patient cost is calculated based on the 5 times patients will get tested for TLS during the ramp-up period. The total number of visits is multiplied by the time per visit, which is assumed to be 20 minutes including waiting time, and multiplied by the transport time, assumed to be one hour per visit. The 20 minute TLS control visit is assumed to include risk assessment of blood tests. The same monetary value of transport and patient time as in calculations above was utilised. Patient costs during ramp up are shown in Table 26.

Table 26. Patient costs included in the ramp-up for venetoclax-based treatment

Patient Cost Unit	Venetoclax + Rituximab
TLS Prophylaxis: Number of Visits During 1 <sup>st</sup> Cycle	5
Patient Time, Visits (hours)	1,67 (20 min * 5)
Patient Time, Transport (hours)	5 (1 hour *5)
Patient Time, Visits (DKK)	298,33 (179*1,67)
Patient Time, Transport (DKK)	895,00 (179*7,5)
Transport Cost (DKK)	500,00 (100*5)
Total Patient Cost for TLS Prophylaxis (DKK)	<b>1.693,33</b>

## 15 Results

### 15.1 Cost per Patient Analysis

#### 15.1.1 Base Case Results

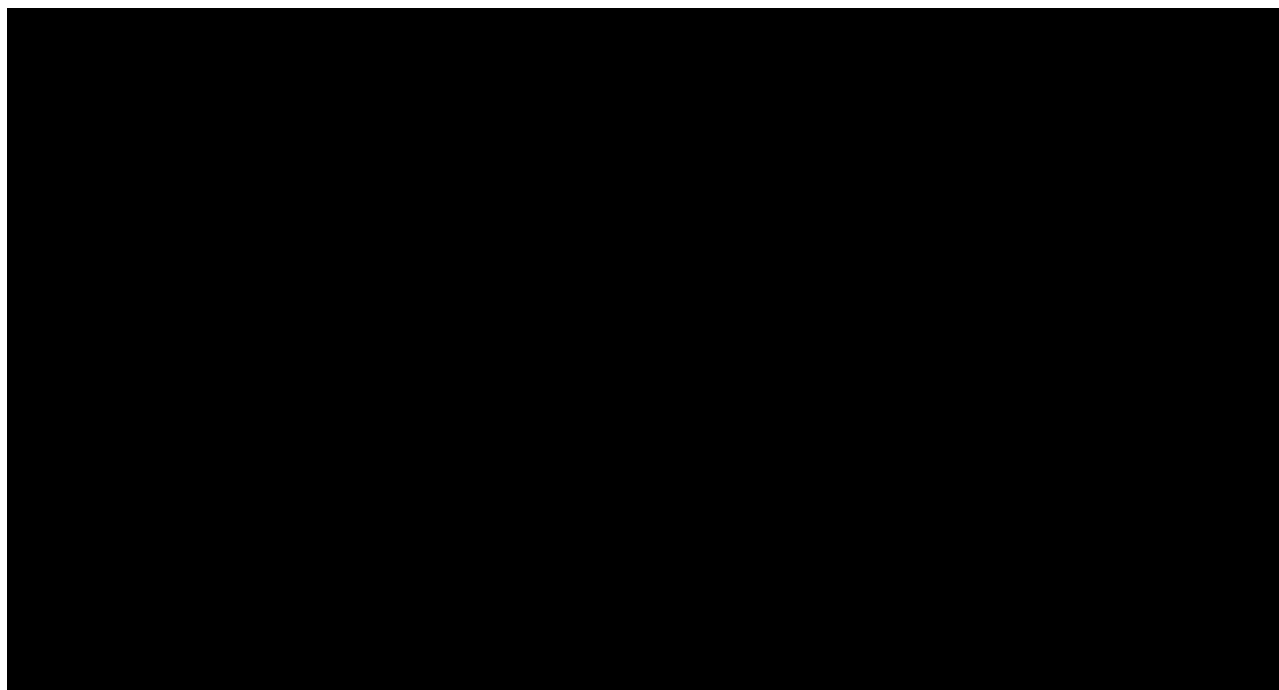
The results of the cost analysis for patients with R/R CLL shows the average costs per patient over 30 years (**Table 27**). The drug acquisition costs constitute a major part of the total costs for acalabrutinib and ibrutinib. For venetoclax + rituximab the drug acquisition is lower due to its fixed-period treatment duration (24 months). The total cost per patient over 30 years is DKK 3.339.384 for acalabrutinib, DKK 3.336.917 for ibrutinib therapy, and DKK 3.256.801 for venetoclax + rituximab. The drug acquisition constituted a major part of the costs in both comparisons. The cost breakdown per patient is presented in **Figure 4** versus ibrutinib and venetoclax + rituximab, respectively.

**Table 27.** Average costs per patient for acalabrutinib versus ibrutinib and venetoclax + rituximab over 30 years

Cost Category	Total Costs per Treatment (DKK)			Incremental Costs (DKK): Acala vs.	
	Acalabrutinib	Ibrutinib	Venetoclax + Rituximab	Ibrutinib	Venetoclax + Rituximab
Disease Management	1.025.712	1.025.712	1.025.712	0	0
Drug Acquisition			939.598		
Drug Administration	0	0	18.660	0	-18.660
Treatment Monitoring*	0	0	8.042	0	-8.042
Adverse Events	11.351	12.245	8.929	-895	2.422
Subsequent Treatments	734.056	734.056	1.210.309	0	-476.253
Patient Costs	39.277	39.277	45.551	0	-6.275
<b>Total Costs</b>			<b>3.256.801</b>		

\* Includes TLS prophylaxis for venetoclax + rituximab only

**Figure 4.** Cost per patient breakdown for acalabrutinib versus ibrutinib over 30 years



## 15.1.2 Scenario Analyses

Scenario analyses for acalabrutinib versus ibrutinib and acalabrutinib versus venetoclax + rituximab were performed for key variables and assumptions in the model (**Table 28** and **Table 29**). The parameters included in the scenario analyses were the discount rate, time horizon, drug acquisition costs, AE costs, patient distribution in subsequent (3L) treatment, and parametric models used for extrapolation of PFS and OS of ibrutinib. Except for the discount rate, time horizon and the choice of the parametric models, all parameters were varied with  $\pm 20\%$ .

When compared with ibrutinib, the results were most sensitive to drug acquisition costs, for both acalabrutinib and ibrutinib, and changes in patient distribution in subsequent treatment, and relatively insensitive to the other parameters. For the comparison with venetoclax + rituximab, the results were most sensitive to changes in the time horizon, and drug acquisition costs, especially for acalabrutinib, and relatively insensitive to the other parameters.

**Table 28.** Scenario analyses for acalabrutinib versus ibrutinib

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acalabrutinib	Ibrutinib		
Base Case		-				-
Discount Rate	3,5 %	0 %				7%
		2 %				3%
		5 %				-3%
Time Horizon	30 years	1 years				-88%
		2 years				-52%
		5 years				-1%
Drug Acquisition Cost: Acalabrutinib	45.224,19 DKK	-20 %				-12.391%
		20 %				12.391%
Drug Acquisition Cost: Ibrutinib	45.124,73 DKK	-20 %				12.364%
		20 %				-12.364%
Total AE Costs*	11.351 DKK for acalabrutinib and 12.245 DKK for ibrutinib	-20 %				7%
		20 %				-7%
Subsequent Treatment Distribution after Ibrutinib	Venetoclax + Rituximab 100%	+ 20% for Acalabrutinib, - 20% for Venetoclax + Rituximab				-3.864%
Extrapolation for PFS	Generalized gamma	Gompertz **				6%
Extrapolation for OS	Exponential	Weibull **				0%

\*Total AEs costs over 30 years

\*\* Second best parametric model based on the AIC and BIC



**Table 29.** Scenario analyses for acalabrutinib versus venetoclax + rituximab

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acalabrutinib	Venetoclax + Rituximab		
Base Case	-	-		3.256.801		
Discount Rate	3,5 %	0 %		3.706.801		24%
		2 %		3.426.907		10%
		5 %		3.112.146		-10%
Time Horizon	30 years	1 years		763.459		-175%
		2 years		1.247.236		-106%
		5 years		1.977.029		605%
Drug Acquisition Cost: Acalabrutinib	45.224,19 DKK	-20 %		3.063.066		-136%
		20 %		3.450.536		136%
Drug Acquisition Cost: Venetoclax	40.010,34 DKK	-20 %		3.083.069		49%
		20 %		3.430.533		-49%
Drug Acquisition Cost: Rituximab	6.687,00 DKK	-20 %		3.242.614		4%
		20 %		3.270.988		-4%
Total AE Costs*	11.351 DKK for Acalabrutinib and 8.929 DKK for Ven + R	-20 %		3.255.015		-1%
		20 %		3.258.587		1%
Subsequent Treatment Distribution after Venetoclax + Rituximab	Acalabrutinib 80%, Ibrutinib 20%	- 20 percentage points for Acalabrutinib, + 20 percentage points for Ibrutinib		3.256.268		1%
		+ 20 percentage points for Acalabrutinib; - 20 percentage points for Ibrutinib		3.257.334		-1%
Extrapolation for PFS	Generalized gamma	Gompertz **		3.321.277		11%
Extrapolation for OS	Exponential	Weibull **		3.324.063		0%

\*Total AEs costs over 30 years

\*\*Second best parametric model based on the AIC and BIC

An additional scenario was investigated considering survival curves extrapolated from the RESONATE trial (Byrd et al, 2019) for ibrutinib in R/R CLL, with curves for both acalabrutinib and venetoclax + rituximab being modelled relative to this. Using an alternative source for PFS and OS compared to ELEVATE-RR was considered relevant as the ELEVATE-RR trial included a higher proportion of patients with 17p deletion than other R/R trials (see **Table 2** and **Table 3**) and therefore they may be expected to have a worse prognosis than the average R/R CLL population. The choice to use RESONATE as the basis for all survival extrapolations was informed by the fact this trial has had the longest published follow-up to date when compared to trials for acalabrutinib or venetoclax + rituximab. Therefore, the data from RESONATE is the most mature, resulting

in the least uncertainty in the long-term estimates of survival when extrapolating. The exponential function was selected to inform the long-term hazards of both progression and death in CLL in this case (see Appendix “*Estimation of Survival Curves 2L*”). The AE incidence rates for this scenario were based on the MAICs conducted for acalabrutinib vs. ibrutinib (ASCEND trial for acalabrutinib and RESONATE trial for ibrutinib) and acalabrutinib vs. venetoclax and rituximab (ASCEND trial for acalabrutinib and MURANO trial for venetoclax and rituximab) after matching (see Appendix “*MAIC report R/R CLL*”).

The model inputs adjusted for this scenario are presented in **Table 30**, **Table 31** and **Table 32** and the results are presented in **Table 33** and **Table 34**.

**Table 30.** Model inputs adjusted for the scenario where the model survival curves are extrapolated based on the RESONATE trial for ibrutinib

Variable	Input	Reference
Proportion of females	33%	ACE-CL-309 Clinical Study Report (Patient baseline characteristics - Overall)
Age at Baseline (years)	67	ACE-CL-309 Clinical Study Report (Patient baseline characteristics - Overall)
Extrapolation for PFS	Exponential	
Duration of ibrutinib and acalabrutinib as subsequent treatments (number of cycles)	█	Model estimate
Duration of venetoclax (as part of the combination venetoclax + rituximab) as subsequent treatments (number of cycles)	█	Model estimate
Duration of rituximab (as part of the combination venetoclax + rituximab) as subsequent treatments (number of cycles)	█	Model estimate

**Table 31.** AE incidence rates for the R/R CLL population treated with acalabrutinib and ibrutinib based on the MAIC

	Acalabrutinib	Ibrutinib	Cost (DKK)
Anaemia	█	█	7.213
Atrial Fibrillation	█	█	15.488
Diarrhoea	█	█	4.274
Fatigue	█	█	1.732
Hypertension	█	█	14.155
Neutropenia	█	█	6.351
Thrombocytopenia	█	█	5.536
Pneumonia	█	█	36.514
Headache	█	█	3.353*
Haemorrhage	█	█	21.420**
Infections	█	█	36.096 ‡

Source for AE incidence rates: Safety outcomes after matching in MAIC of acalabrutinib vs. ibrutinib (see Appendix “MAIC report R/R CLL”).

\* MDC01 1-dagsgruppe, pat. mindst 7 år, Male, 67 Year(s) (DG444) Hovedpine forårsaget af lægemiddel IKA (DRG code: 01MA98)

\*\* Blødning fra mave-tarmkanal, pat. mindst 18 år, u. kompl. bidiag. (Most major bleeds observed in ASCEND were gastrointestinal) (DRG code: 06MA07)

‡ Average of 'Lungebetændelse og pleurit, pat. mindst 60 år' and 'Andre infektioner eller parasitære sygdomme' (DRG code: 04MA13/18MA08) (36.514 DKK, 35.678 DKK)

**Table 32.** AE incidence rates for the R/R CLL population treated with acalabrutinib and venetoclax + rituximab based on the MAIC

	Acalabrutinib	Venetoclax + Rituximab	Cost
Anaemia			7.213
Neutropenia			6.351
Thrombocytopenia			5.536
Tumour Lysis Syndrome			24.306
Pneumonia			36.514
Infections			36.096 ‡

Source: Safety outcomes after matching in MAIC of acalabrutinib vs. venetoclax and rituximab combination therapy (see Appendix "MAIC report R/R CLL").

‡ Average of 'Lungebetændelse og pleurit, pat. mindst 60 år' and 'Andre infektioner eller parasitære sygdomme' (DRG code: 04MA13/18MA08) (36.514 DKK, 35.678 DKK)

**Table 33.** Average costs per patient for acalabrutinib versus ibrutinib over 30 years, for the scenario where ibrutinib survival is based on the RESONATE trial and acalabrutinib survival is considered equal to ibrutinib

Cost Category	Total Costs per Treatment (DKK)		Incremental Costs (DKK): Acala vs.
	Acalabrutinib	Ibrutinib	Ibrutinib
Disease Management	844.532	844.532	0
Drug Acquisition			
Drug Administration	0	0	0
Adverse Events	9.613	15.133	-5.520
Subsequent Treatments	673.030	673.030	0
Patient Costs	32.339	32.339	0
<b>Total Costs</b>			

**Table 34.** Average costs per patient for acalabrutinib versus venetoclax + rituximab over 30 years, for the scenario where ibrutinib survival is based on the RESONATE trial and acalabrutinib and venetoclax + rituximab survival is considered equal to ibrutinib

Cost Category	Total Costs per Treatment (DKK)		Incremental Costs (DKK): Acala vs.
	Acalabrutinib	Venetoclax + Rituximab	Venetoclax + Rituximab
Disease Management	844.532	844.532	0
Drug Acquisition		927.530	
Drug Administration	0	18.448	-18.448
Treatment Monitoring*	0	8.037	-8.037
Adverse Events	8.146	13.728	-5.582
Subsequent Treatments	673.030	1.244.735	-571.704
Patient Costs	32.339	38.562	-6.223
<b>Total Costs</b>		<b>3.095.571</b>	

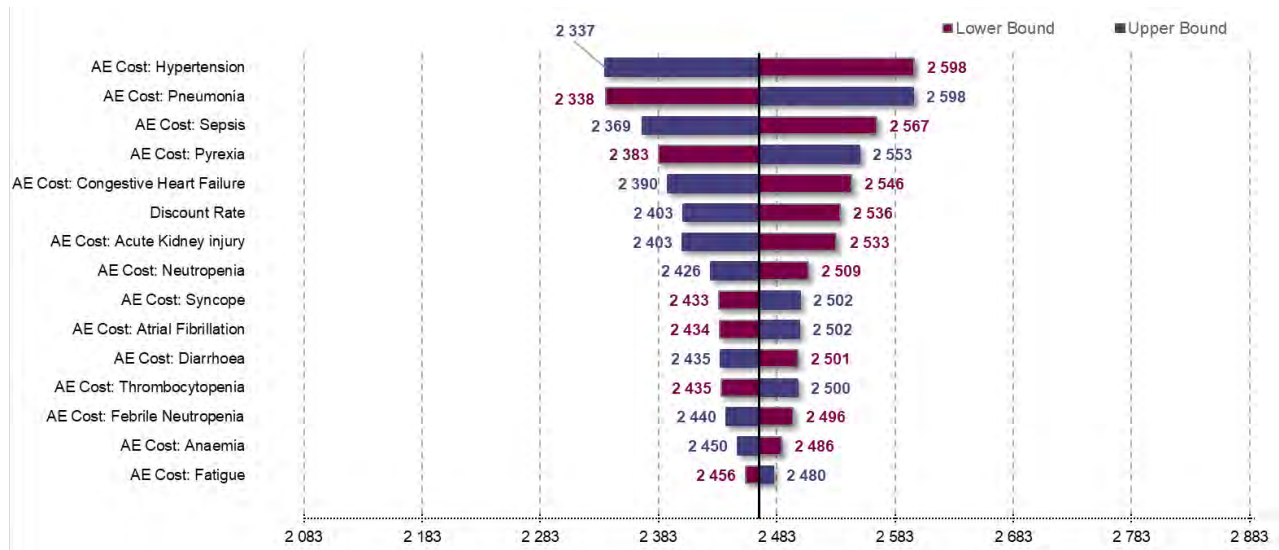
\* Includes TLS prophylaxis for venetoclax + rituximab only

### 15.1.3 Deterministic Sensitivity Analyses

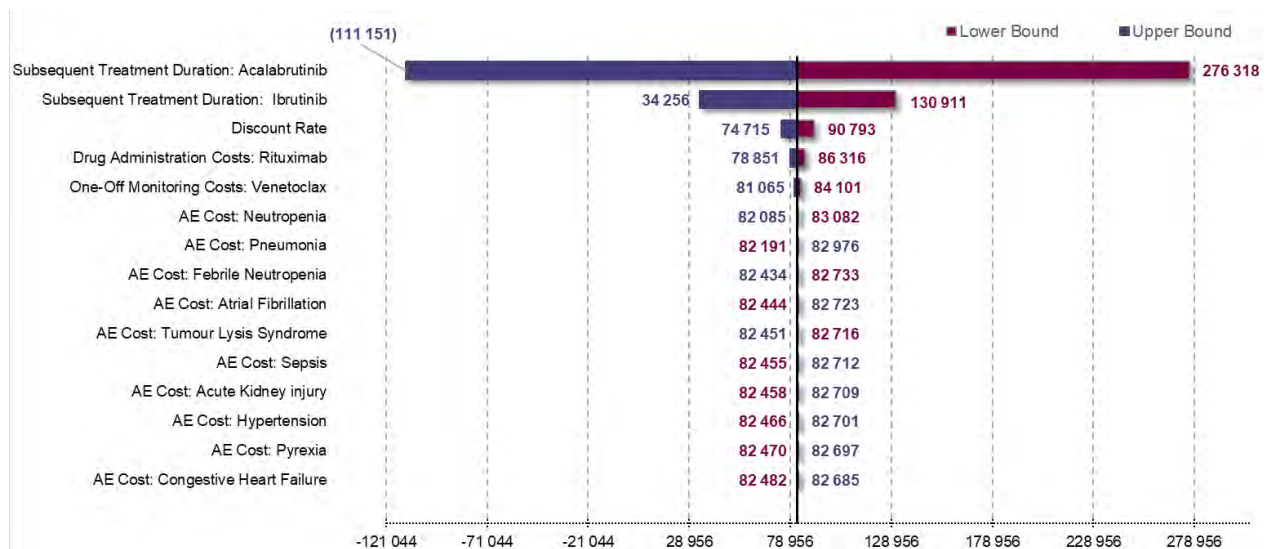
One-way DSA was undertaken by varying each key parameter to its reasonable limits. Most parameters were varied  $\pm 20\%$  of the value used in the main analyses. The parameters are listed in the economic model ("DSA" sheet) and summarized with top 15 parameters in a tornado diagram in **Figure 5** and **Figure 6** for acalabrutinib versus ibrutinib and for acalabrutinib versus venetoclax + rituximab, respectively.

Across scenarios, acalabrutinib had similar costs than ibrutinib, ranging between DKK 2.337 and DKK 2.598 more across the lifetime. The changes in the analysis were relatively small and did not alter conclusions. The parameters associated with the greatest uncertainty in costs were the AE costs and the discount rate. In comparison with venetoclax + rituximab, the model was most sensitive for the duration of treatment for acalabrutinib as a subsequent treatment (**Figure 6**) resulting in incremental costs ranging between DKK -111.151 and DKK 276.318. Results were also sensitive to the duration of treatment for ibrutinib as a subsequent treatment resulting in incremental costs ranging between DKK 34.256 and DKK 130.911.

**Figure 5.** Tornado diagram for acalabrutinib versus ibrutinib



**Figure 6.** Tornado diagram for acalabrutinib versus venetoclax + rituximab



## 15.2 Budget Impact Analysis

For the base case results the model compared two scenarios to assess the budget impact and cost implications of introducing acalabrutinib in patients with R/R CLL:

- Scenario without acalabrutinib: based on the current and forecasted market shares when acalabrutinib is not reimbursed for R/R CLL.
- Scenario with acalabrutinib: based on the current and forecasted market shares when acalabrutinib is introduced by taking market share from other treatments in R/R CLL.

In both scenarios the total number of patients eligible for 2L treatment was estimated to be between 65 in 2022 and 69 in 2026 (Table 35). Using the market share estimates calculations from the scenario with acalabrutinib and the total number of patients eligible in R/R CLL indication, the number of patients starting treatment with acalabrutinib during 2022-2026 were estimated. Then the incremental cost differences in above mentioned scenarios were calculated.

**Table 35.** Number of patients in R/R CLL starting acalabrutinib

	2022	2023	2024	2025	2026
Total Number of 2L CLL Patients	65	66	67	68	69
Patients Starting Acalabrutinib	█	█	█	█	█

The budget impact calculations include cost implications of introducing acalabrutinib in 2L, along with subsequent treatment costs (which may include acalabrutinib for other therapies). The costs included costs for drug acquisition, administration, monitoring, disease management, and AEs. Table 36 presents the results of the budget impact analysis. The results show that reimbursing acalabrutinib is likely to be cost saving to the Danish healthcare system over the initial four years after its introduction.

**Table 36.** Budget impact in R/R CLL starting acalabrutinib

	2022	2023	2024	2025	2026
<b>R/R CLL</b>					
Current Scenario	54.478.440	103.119.486	134.612.475	159.521.677	181.275.612
Scenario with Acalabrutinib	█	█	█	█	█
Incremental Cost of Introducing Acalabrutinib	█	█	█	█	█
Budget Impact (%)	█%	█%	█%	█%	█%

### 15.2.1 Scenario Analysis: Decreased Market Share

A scenario analyses were conducted with the market share for acalabrutinib decreased by 40% compared to the base case analysis. It was instead assumed that this market share would be allocated to venetoclax + rituximab and ibrutinib use would remain constant compared to the base case analysis. The market shares for the scenario analysis are shown in Table 37, and the results of the budget impact analysis using these market shares is shown in Table 38.

The results show that a lower market share for acalabrutinib and a greater uptake of venetoclax + rituximab would lead to less savings over the initial three years after acalabrutinib introduction compared to the base case scenario.

**Table 37.** Scenario analyses: Market shares

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>R/R 2L</b>										
Acalabrutinib	█%	█%	█%	█%	█%	█%	█%	█%	█%	█%
Ibrutinib	█%	█%	█%	█%	█%	█%	█%	█%	█%	█%

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
Venetoclax + Rituximab	█%	█%	█%	█%	█%	█%	█%	█%	█%	█%

**Table 38.** Summary of the incremental results: Sensitivity analysis with decreased market shares in R/R CLL

	2022	2023	2024	2025	2026
<b>R/R CLL</b>					
Current Scenario	54.478.440	103.119.486	134.612.475	159.521.677	181.275.612
Scenario with Acalabrutinib	█	█	█	█	█
Incremental Cost of Introducing Acalabrutinib	█	█	█	█	█
Budget Impact (%)	█%	█%	█%	█%	█%

## 16 Discussion

The cost analyses present the incremental costs of introducing acalabrutinib as a second line treatment for R/R CLL in Denmark. The analyses were based on the ELEVATE-RR trial outcomes and the MAIC analyses (versus ibrutinib and venetoclax + rituximab). These indicated that, in patients with R/R CLL, acalabrutinib is associated with similar efficacy (PFS, OS, and ORR) to ibrutinib and venetoclax + rituximab. Acalabrutinib and ibrutinib have the same mode of action (ATC L01XE; protein kinase inhibitors) and the same approved indications. However, the MAIC analysis showed a more favourable safety profile for acalabrutinib, and in ELEVATE-RR there were statistically significant differences in certain adverse event rates.

The cost per patient analyses included disease management costs, treatment acquisition, administration costs, monitoring costs, patient-related costs and treatment-related AE costs. In the base case analysis, the total cost per patient over 30 years was DKK █ for acalabrutinib compared with DKK █ for ibrutinib. The drug acquisition constituted a major part of the costs and is comparable between acalabrutinib and ibrutinib. The total cost per patient over 30 years for venetoclax + rituximab was DKK 3.256.801, a cost saving of DKK █ when compared to acalabrutinib, which mainly resulted from differences in treatment duration, as venetoclax + rituximab has a fixed-period treatment duration of 24 months compared to acalabrutinib which is continued until disease progression.

Whilst the overall lifetime costs of acalabrutinib may be comparable or higher than those of its comparators, acalabrutinib offers the opportunity to save costs in other areas. The costs of disease management and drug administration/treatment monitoring are considerably lower when treating patients with a BTK inhibitor compared to venetoclax + rituximab. The monitoring cost for venetoclax + rituximab is higher when compared to acalabrutinib, as patients treated with venetoclax have to visit the hospital for TLS control once every week in the first 5 weeks. This risk is also reflected in the AE costs savings for acalabrutinib compared to venetoclax. In addition, it is assumed that blood tests are taken when treated with rituximab. Furthermore, costs for administration are accrued when patients are treated with venetoclax + rituximab, as rituximab is administered via IV infusion.

Acalabrutinib would appear to be the preferred BTKi in clinical practice, given the superior adverse event profile identified in the ELEVATE-RR study and the indirect treatment comparison. In addition, the AEs in the model are calculated as a one-off event at treatment initiation, however there is data to suggest that some AEs can occur later during treatment (i.e., atrial fibrillation for ibrutinib) (Archibald et al, 2020). It is purported that the greater off-target effects seen with ibrutinib increase adverse event risk, and therefore it is likely

that the long-term costs of AEs may be underestimated for ibrutinib in this model, providing a greater benefit of treatment with acalabrutinib.

The budget impact analysis show that reimbursing acalabrutinib is likely to decrease the total expenditure for the care and management of R/R CLL the first four years after its introduction. A scenario analysis was performed to address uncertainties associated with the market shares. The market share was decreased with 40 % in the uptake of acalabrutinib, which resulted in less savings in the first three years. Therefore, a lower market share for acalabrutinib actually increases expenditure and cost savings in the near term could be increased with wider uptake of acalabrutinib.

The treatment duration is a driver for the costs per patient, and in the base case patients will be treated almost two times as long with acalabrutinib and ibrutinib compared to patients treated with venetoclax + rituximab. A scenario analysis explored the impact of the model time horizon on costs per patient. Results showed that in comparison with venetoclax + rituximab, costs per patient with acalabrutinib were lower over the shorter time horizon (2 years) compared to longer time horizon (30 years) resulting in a lower difference in costs. The initial costs savings on acquisition in using a finite regimen like venetoclax + rituximab also appear to be somewhat offset by the higher costs of subsequent treatment, and thus costs of continuous treatment are delayed rather than avoided.

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## 18 Appendices

### MAIC Report R/R CLL

The document was attached to the dossier as a separate document.

### Estimation of Survival Curves 2L

The document was attached to the dossier as a separate document (Estimation of survival curves 2L)

Company Submission to Medicinrådet

Calquence® (acalabrutinib) in combination with obinutuzumab, or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukaemia in Denmark

Cost per patient and budget impact analyses

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## Abbreviations

Abbreviation	Description
Acala	Acalabrutinib
AE	Adverse event
AIC	Akaike information criterion
AIP	Apotekets indkøbspris
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
B	Bendamustine
BCR	B-cell receptor
BIC	Bayesian information criterion
BIM	Budget impact model
BI	Budget impact
BTK	Bruton tyrosine kinase
Chlo	Chlorambucil
CIRS	Cumulative illness rating scale
CLL	Chronic Lymphocytic Leukemia
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FCR	Fludarabine, cyclophosphamide and rituximab
HR	Hazard ratio
Ibru	Ibrutinib
IGHV	Immunoglobulin heavy chain gene
INV	Investigator assessed
IRC	Independent review committee
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
Obin	Obinutuzumab
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PFS	Progression free survival
PF	Progression free
PPS	Post progression survival
PU	Previously untreated
R	Rituximab
R/R	Relapsed/refractory
SD	Standard deviation
TLS	Tumor lysis syndrome
TP	Transition probability

TTDeath	Time to death (pre-progression)
TTP	Time to progression
Ven	Venetoclax

## Summary

### Objective

The objective of this economic evaluation is to present cost per patient and budget impact analyses for acalabrutinib (both as monotherapy and in combination with obinutuzumab) to support reimbursement decisions for acalabrutinib in Denmark. In this analysis, PU CLL FCR ineligible patients (patients without 17p deletion/TP53 mutation) and high risk patients (patients with 17p deletion/TP53 mutation) were considered. Comparators included and defined by the Danish Medicine Council were chlorambucil + obinutuzumab and bendamustine + rituximab for the patient population without high-risk disease and ibrutinib and venetoclax + obinutuzumab for the high-risk population.

### Methods

The cost per patient analysis was based on a three health-state semi-Markov model and was presented from a Danish societal perspective excluding productivity losses and cross-sectional costs. A lifetime horizon of 30 years was utilized in the analysis.

To analyse the budget consequence of introducing acalabrutinib monotherapy and combination with obinutuzumab in the Danish untreated CLL treatment regimen for patients without or with 17p deletion/TP53 mutation, two scenarios in the base case were developed; one being a new scenario where acalabrutinib is introduced and the other being the current scenario where acalabrutinib is not introduced. A healthcare payer perspective was taken where costs related to health care resources and acquisition were included to calculate the incremental cost of introducing acalabrutinib.

### Results

For patients without 17p deletion/TP53 mutation, the average cost per patient over 30 years is DKK 4.918.035 for acalabrutinib monotherapy, DKK 6.505.924 for acalabrutinib + obinutuzumab combination therapy, DKK 2.385.130 for chlorambucil + obinutuzumab therapy, and DKK 1.880.368 for bendamustine + rituximab therapy. The drug acquisition costs constitute a major part of the total costs for acalabrutinib-based therapies.

For patients with 17p deletion/TP53 mutation, the average cost per patient over 30 years is DKK [REDACTED] for acalabrutinib monotherapy, DKK [REDACTED] for acalabrutinib + obinutuzumab combination therapy, DKK [REDACTED] for ibrutinib therapy and DKK [REDACTED] for venetoclax + obinutuzumab therapy. The drug acquisition costs associated with treatment duration contributed to the overall higher costs for acalabrutinib-based therapies and ibrutinib.

In the budget impact analysis base case results for patients without 17p deletion/TP53 mutation showed an increasing incremental budget impact of the uptake of acalabrutinib from 2022 to 2024, which then stabilises from 2024 to 2026. For the patients with 17p deletion/TP53 mutation, the budget impact of introducing acalabrutinib showed to be gradually increasing throughout the 5 year time horizon, up to an overall increase of 16%.



## 1 Introduction

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in adults. Danish statistics for CLL indicate that approximately 450 new cases per year are registered, with the incidence around 6-7 per 100.000 inhabitants per year. It is also estimated that approximately 4.000 inhabitants currently live with the disease. The median age at diagnosis is 70 years, and typically twice as many men as women are diagnosed with this cancer (LYFO database, 2018; NORDCAN, 2019).

As the cancer type originates from the bone marrow and further the B-cells, Bruton tyrosine kinase (BTK) has been identified as a key component of the B-cell receptor (BCR) signalling pathway and evidence suggests that a blockade of BTK activity by potent pharmacologic inhibitors attenuates BCR signalling and induces cell death (CLL gruppen, 2019).

CLL is clinically detected by coincidence after a blood test, as it is often asymptomatic at the time of diagnosis. A clinical assessment will be performed, focusing on the disease stage and risk profile, which includes cytogenetic changes and immunoglobulin heavy-chain variable region (IGHV)-mutation-status. In addition, patient-specific factors, such as performance status, comorbidity (cumulative illness rating scale (CIRS), age, and preferences are examined (CLL gruppen, 2019).

The objectives in treating patients with CLL is to maintain and prolong the symptom-free period and delay disease progression. In that sense, the treatment regimen is risk stratified and divided according to whether patients have cytogenetic changes of deletion 17p/TP53 mutation, since patients with the mutation are associated with poor prognosis compared to those without. First line treatment options (1L) for the previously untreated CLL patient group (PU CLL) without deletion 17p/tp53 mutation include cytostatic drugs in combination with CD-20 antibodies. For the patient populations targeted in these cost analyses these include bendamustine in combination with rituximab (BR) and chlorambucil in combination with obinutuzumab. Patients with mutations and high risk features are insensitive to cytostatic drugs and so they are instead treated with targeted treatment options such as protein kinase inhibitor, ibrutinib or venetoclax in combination with obinutuzumab.

## 2 Objectives

The European Medicines Agency has approved acalabrutinib (CALQUENCE®) for following indications:

- in combination with obinutuzumab, or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukaemia (PU CLL); and
- as monotherapy for the treatment of patients with CLL who have received at least one prior therapy (R/R CLL)

The objective of this evaluation is to present cost per patient and budget impact (BI) analyses for acalabrutinib-based therapies to support reimbursement decisions for acalabrutinib in Denmark. The following three patient populations were considered in the Danish Medicines Council's protocol:

- PU CLL FCR (fludarabine, cyclophosphamide and rituximab) ineligible patients without 17p deletion/TP53 mutation (in this document, we refer to this population as "patients without 17p deletion/TP53 mutation")
- PU CLL high risk CLL patients with 17p deletion/TP53 mutation (in this document, we refer to this population as "patients with 17p deletion/TP53 mutation")
- Patients with R/R CLL

This submission includes two separate reports assessing the economic implications. This report considers acalabrutinib monotherapy and acalabrutinib combination therapy for the treatment of patients with PU CLL. Acalabrutinib monotherapy for the treatment of patients with R/R CLL is considered in a separate report.

In the cost per patient analysis, the costs per patient were compared between acalabrutinib and comparators for patients without 17p deletion/TP53 mutation and with 17p deletion/TP53 mutation. In addition, a scenario is also considered with stratification by whether the patient has a IGHV mutation or not given. IGHV status is prognostic of survival, where patients with unmutated IGHV have a worse prognosis, and the criterion now forms part of the treatment guidelines when selecting first-line therapies for patients with CLL in Denmark (CLL gruppen, 2019). The cost per patient analysis represents the total costs of disease for selected treatments within a selected time horizon. Scenario analyses and deterministic sensitivity analyses were performed to assess uncertainty in the results.

In the BI analysis, the projected health care expenditure of adopting acalabrutinib into the formulary is compared with projected expenditure without the adoption of acalabrutinib. Thus, the base case results of the BI analysis represent the annual incremental costs of introducing acalabrutinib in the Danish setting of CLL treatment. Furthermore, scenario analyses are performed to investigate the sensitivities of the market shares.

It should be noted that although the Danish medicine council identified PU FCR-eligible patients as suitable patient population, this was not included in the analyses. AstraZeneca had responded to the request, noting that data for this population were not available as inclusion criteria for the ELEVATE-TN trial in PU CLL patients excluded those who would typically be eligible for FCR based on age or comorbidities. The argumentation was accepted by the Danish Medicine Council. Hence, only FCR-ineligible and high-risk patients were considered in the analyses.

### 3 Intervention

Calquence is an orally administered medicine, where each hard capsule contains 100 mg of acalabrutinib. The recommended dose is 100 mg acalabrutinib twice daily (equivalent to a total daily dose of 200 mg). Calquence can be used as a monotherapy or in combination with obinutuzumab. Treatment with Calquence should be continued until disease progression or unacceptable toxicity (Calquence SmPC).

Calquence is a selective irreversible BTK inhibitor, specifically designed to improve upon the safety and efficacy of first generation BTK inhibitors, which also irreversibly inhibit alternative kinase targets, which potentially compromise its therapeutic index. The safety and efficacy of acalabrutinib monotherapy or in combination with obinutuzumab as a first line therapy in previously untreated patients has been evaluated in the ELEVATE-TN trial; whereas the ASCEND trial has studied the safety and efficacy profile of acalabrutinib as a second line therapy in relapsed/refractory (R/R) patients. ELEVATE-TN, ASCEND, and ELEVATE-RR are open-label Phase III, global, randomised and multicentre studies of Calquence (Sharman et al, 2020; Ghia et al, 2020; Byrd et al, 2021).

On the 9<sup>th</sup> December 2020, the Danish Medicines Council published a protocol to evaluate the added value of acalabrutinib monotherapy or in combination with obinutuzumab to patient population with and without the deletion 17p/TP53 mutation in 1L, and acalabrutinib monotherapy for R/R patient population that previously have received at least one treatment option independent of the 17p deletion/TP53 mutation (Medicinrådet, 2020).

### 4 Study Characteristics

The efficacy and safety of acalabrutinib with or without obinutuzumab versus chlorambucil plus obinutuzumab (ChIO) was investigated in the ELEVATE-TN randomised controlled trial. A total of 535 PU CLL

patients were included in the study who were FCR-ineligible and aged  $\geq 65$  years or had comorbidities (Cumulative Illness Rating Scale-Geriatric score  $> 6$  or renal dysfunction [CrCl 30–69 mL/min]). These patients were randomised to acalabrutinib plus obinutuzumab ( $n = 179$ ) and acalabrutinib monotherapy ( $n = 179$ ) or chlorambucil + obinutuzumab ( $n = 177$ ). The primary endpoint was progression-free survival (PFS) for acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab, whereas the secondary endpoint was PFS for acalabrutinib monotherapy versus chlorambucil plus obinutuzumab, both as assessed by independent review committee (Sharman et al, 2020).

The ELEVATE-TN study included patients above 65 years, which according to Danish clinical practice would receive either bendamustine + rituximab ( $> 65$  years and CIRS-score  $< 6$ ) or chlorambucil + obinutuzumab (any age, CIRS-score  $> 6$ ). CIRS was however not measured in ELEVATE-TN for patients above 65 years, and therefore patients above 65 years included in ELEVATE-TN could potentially be eligible for both treatments. ELEVATE-TN also included patients below 65 years with a CIRS-score above 6, a group who according to Danish clinical practice would receive chlorambucil + obinutuzumab. Finally, the study allowed patients with del17p (acalabrutinib: 9,5%; acalabrutinib + obinutuzimab: 8,9%) or mutated TP53 (acalabrutinib: 11,7%; acalabrutinib + obinutuzimab: 10,6%), which in Danish clinical practice would receive ibrutinib or venetoclax + obinutuzumab, which was recently approved by Danish Medicines Council (Medicinrådet, 2020).

In addition, two indirect treatment comparisons using both network meta-analysis (NMA) and matching-adjusted indirect comparison (MAIC) methods were performed to compare the efficacy and safety of acalabrutinib monotherapy and acalabrutinib plus obinutuzumab versus bendamustine + rituximab among others. Both analyses were based on data from ELEVATE-TN for acalabrutinib monotherapy and acalabrutinib plus obinutuzumab, and a systematic review was performed to identify randomised controlled trials (RCTs) in first-line CLL for relevant comparators. The results of the ITCs have been published by Davids et al. (2020) and Davids et al. (2021), and the study reports from both the NMA and MAIC are appended to this submission. An overview of relevant clinical trials included in the indirect treatment analyses that are used in the current cost analysis and budget impact are shown in Table 1.

**Table 1.** Trials included in the NMA and MAIC

Author, Year	Population	Trial Name	Sample Size	Phase	Intervention	Comparator	Median Follow-Up
Barr 2018	1L CLL	RESONATE-2	269	3	Ibrutinib	Chlorambucil	29 months
Moreno 2019	1L CLL	iLLUMINATE	229	3	Ibrutinib + Obinutuzumab	Chlorambucil + Obinutuzumab	31.3 months
Woyach 2018	1L CLL	Alliance (A041202)	547	3	Ibrutinib	Ibrutinib + Rituximab, Bendamustine + Rituximab	38 months
Michallet 2018	1L and 2L CLL	MaBLE	241	3b	Bendamustine + Rituximab	Chlorambucil + Rituximab	~ 23.4 months
Goede 2014	1L CLL	CLL11	781	3	Chlorambucil	Rituximab + Chlorambucil, Obinutuzumab + Chlorambucil	30 months
Sharman 2020	1L CLL	ELEVATE-TN	535	3	Acalabrutinib, Acalabrutinib + Obinutuzumab	Chlorambucil + Obinutuzumab	~ 29 months
Fischer 2019	1L CLL	CLL14	432	3	Venetoclax + Obinutuzumab	Chlorambucil + Obinutuzumab	28.1 months
Tedeschi 2019	1L CLL	RESONATE-2 and iLLUMINATE		3 (cross-trial comparison)	Ibrutinib (RESONATE-2)	Chlorambucil + Obinutuzumab (iLLUMINATE)	RESONATE-2: 48.8 months iLLUMINATE: 31.3 months

## 5 Comparators

According to the Danish Medicines Council protocol, relevant comparators were identified to evaluate the clinical added value of acalabrutinib monotherapy and combination in three treatment situations. For FCR ineligible patients without 17p deletion/TP53 mutation, the comparators were identified to be bendamustine + rituximab and chlorambucil + obinutuzumab. For high risk patients with 17p deletion/TP53 mutation, the comparators were identified to be ibrutinib monotherapy and the combination therapy of venetoclax + obinutuzumab that was recently approved by the Danish Medicines Council.

## 6 Perspective

The perspective used in the cost per patient model is a societal perspective with limitations, excluding productivity losses and cross-sectional costs based on the method guideline by the Danish Medicines Council. In the budget impact model (BIM), a healthcare payer perspective was used.

## 7 Time Horizon

The Danish Medicines Council does not state a time horizon in their protocol for evaluation of the added value of acalabrutinib (Medicinrådet, 2020). However, relevant time horizons were determined in further discussions. For the cost per patient analysis, a lifetime horizon was used as per the application guideline to fully capture the costs of the treatments. The cohorts are modelled until a time point when < 5% of the population is alive which was assumed to represent a lifetime horizon. The time point used was 30 years and was selected based on the long-term survival. As some level of uncertainty remains regarding the choice of time horizons, sensitivity analyses have been conducted to explore the impact of shorter time horizons. For BI analysis, a time horizon of 5 years was used to show the budget consequence of acalabrutinib. This time horizon was also agreed with the Danish Medicines Council.

## 8 Discounting

As outlined in the methods guideline, a 3,5% discount rate per annum was applied in modelling the added value of acalabrutinib over lifetime horizon in the cost per patient analysis. No discounting was applied in the budget impact model.

## 9 Patient Population

The target population of the analysis is aligned with the patient cohort enrolled in the ELEVATE-TN study (elderly [ $\geq 65$  years] or unfit patients with PU CLL), who are FCR ineligible. Baseline characteristics of the intent-to-treat (ITT) trial population are presented in Table 2. The mean age of 70 years and proportion of females (38 %) sourced from ELEVATE-TN study were utilised in the cost per patient model.

As well as the ITT population, subgroup analyses are also considered in this report in line with the protocol from Medicinrådet and Danish clinical treatment guidelines. These included stratification by whether high risk or not (deletion 17p and/or TP53 mutation) and whether patients had mutated or unmutated IGHV status.

**Table 2.** Baseline patient characteristics in the ELEVATE-TN trial

Characteristic	Acalabrutinib (n=179)	Acalabrutinib + Obinutuzumab (n=179)	Obinutuzumab + Chlorambucil (n=177)	Total (n=535)
<b>Age (years)</b>				
Mean (SD)	69.8 (7.57)	70.2 (8.02)	70.8 (7.56)	70.3 (7.72)
Median (Min – Max)	70 (44 – 87)	70 (41 – 88)	71 (46 91)	70.0 (41.0, 91.0)
<b>Male</b>	111 (62.0%)	111 (62.0%)	106 (59.9%)	328 (61.3%)
<b>Female</b>	68 (38.0%)	68 (38.0%)	71 (40.1%)	207 (38.7%)
<b>ECOG</b>				
0-1	165 (92.2%)	169 (94.4%)	167 (94.4%)	504 (94.2%)
2	14 (7.8%)	10 (5.6%)	10 (5.6%)	31 (5.8%)
<b>RAI Stage</b>				
0	0	3 (1.7%)	1 (0.6%)	4 (0.7%)
I	48 (26.8%)	54 (30.2%)	50 (28.2%)	152 (28.4%)
II	44 (27.9%)	36 (20.1%)	48 (27.1%)	128 (25.8%)
III	50 (27.9%)	48 (26.8%)	40 (22.6%)	138 (25.8%)
IV	37 (20.7%)	38 (21.2%)	38 (21.5%)	113 (21.1%)
<b>17p deletion</b>				
Yes	16 (8.9%)	17 (9.5%)	16 (9.0%)	49 (9.2%)
No	163 (91.1%)	162 (90.5%)	160 (90.4%)	485 (90.7%)
Missing	0	0	1 (0.6%)	1 (0.2%)
<b>TP53 mutation</b>				
Mutated	19 (10.6%)	21 (11.7%)	21 (11.9%)	95 (17.8%)
Unmutated	160 (89.4%)	158 (88.3%)	1555 (87.6%)	439 (82.1%)
Missing	0	0	1 (0.6%)	1 (0.2%)
<b>17p del or TP53 m.</b>				
Mutated	23 (12.8%)	25 (14.0%)	25 (14.1%)	73 (13.6%)
Unmutated	156 (87.2%)	154 (86.0%)	152 (85.9%)	465 (86.4%)
<b>IGHV</b>				
Mutated	58 (32.4%)	74 (41.3%)	59 (33.3%)	191 (35.7%)
Unmutated	119 (66.5%)	103 (57.35%)	116 (65.5%)	338 (63.2%)
Missing	2 (1.1%)	2 (1.1%)	2 (1.1%)	6 (1.1%)

Source: AstraZeneca, ACE-CL-007 (ELEVATE-TN) Clinical Study Protocol. 2017.

Note: Some columns may not sum to 100% due to rounding

## 10 Data Inputs Validated by Clinical Experts

Cost-related inputs were obtained from Medicinpriser.dk for drug acquisition, and DRG tariffs from sundhedsstyrelsen.dk for adverse events (AEs), drug administration, and monitoring in outpatient care. In addition, expert opinions from Aarhus university hospital and Rigshospitalet were gathered to understand the current patient dynamics and hospital resources within the Danish haematological departments.

Two clinicians (Nørregaard Bentzen & Curovic Rotbain) were asked to give input on the following:

- Patient distributions across subsequent treatment options (the transition from untreated CLL patients to second line therapy)
- Frequency of treatment monitoring and administration across treatment options
- Proportion of patients expected be treated in the hospital inpatient setting and/or at outpatient care across each identified and included AE

Their assumptions were used both in the cost per patient and BI analyses.

## 11 Methods

### 11.1 Methods of the Cost per Patient Analysis

#### 11.1.1 Overview of the Analysis Methods in the Cost per Patient Analysis

An overview of the cost per patient analysis structure is presented in Table 3. The overview of the BIM is presented in section 10.2.1.

**Table 3.** Characteristics of the cost per patient analysis in PU CLL

Model Characteristics	Details
Eligible Population	<ul style="list-style-type: none"> <li>– PU CLL FCR ineligible patients without 17p deletion/TP53 mutation</li> <li>– PU CLL high risk CLL patients with 17p deletion/TP53 mutation</li> </ul>
Country	Denmark
Intervention	Patients without and with 17p deletion/TP53 mutation: <ul style="list-style-type: none"> <li>– Acalabrutinib</li> <li>– Acalabrutinib + obinutuzumab</li> </ul>
Comparator(s): Base Case	Patients without 17p deletion/TP53 mutation: <ul style="list-style-type: none"> <li>– Chlorambucil + obinutuzumab</li> <li>– Bendamustine + rituximab</li> </ul> Patients with 17p deletion/TP53 mutation: <ul style="list-style-type: none"> <li>– Ibrutinib</li> <li>– Venetoclax + Obinutuzumab</li> </ul>
Comparator(s): Scenario Analyses	Patients with IGHV mutation: <ul style="list-style-type: none"> <li>– Chlorambucil + obinutuzumab</li> <li>– Bendamustine + rituximab</li> </ul> Patients without IGHV mutation: <ul style="list-style-type: none"> <li>– Chlorambucil + obinutuzumab</li> <li>– Bendamustine + rituximab</li> </ul>
Perspective	Societal perspective with limitations, excluding productivity losses and cross-sectional costs based on the method guideline by the Danish Medicine Council.
Time Horizon	30 years (lifetime)
Discounting	3,5 %
Method	3-health state semi-Markov model
Parametric Curves, TTP	<u>Patients without 17p deletion/TP53 mutation</u> Intervention: <ul style="list-style-type: none"> <li>– Acalabrutinib: Gompertz</li> <li>– Acalabrutinib + obinutuzumab: Weibull</li> </ul> Comparators: <ul style="list-style-type: none"> <li>– Chlorambucil + obinutuzumab: Lognormal</li> <li>– Bendamustine + rituximab: HRs from MAIC, using acalabrutinib + obinutuzumab as a baseline curve.</li> </ul> <u>Patients with 17p deletion/TP53 mutation</u> Intervention: <ul style="list-style-type: none"> <li>– Acalabrutinib: Weibull</li> <li>– Acalabrutinib + obinutuzumab: Weibull</li> </ul> (combined curves for mono and combo)  Comparators: <ul style="list-style-type: none"> <li>– Ibrutinib: HRs from ITT MAIC (set to 1)</li> <li>– Venetoclax + obinutuzumab: HRs from ITT MAIC (set to 1)</li> </ul> <u>Patients with mutated IGHV</u> Intervention: <ul style="list-style-type: none"> <li>– Acalabrutinib: Weibull</li> <li>– Acalabrutinib + obinutuzumab: Weibull</li> </ul>

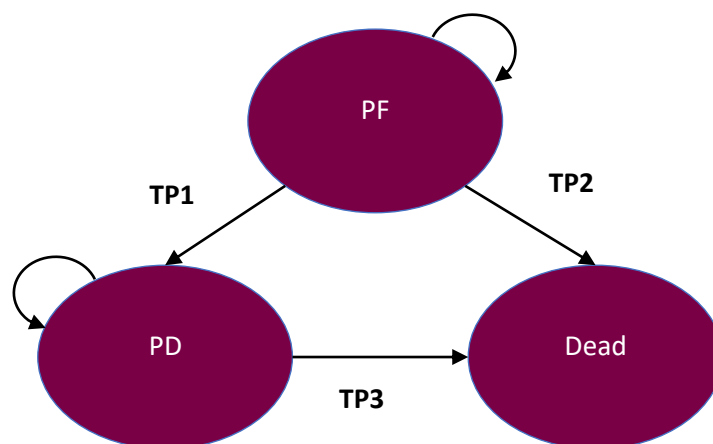
Model Characteristics	Details
	<p>Comparators:</p> <ul style="list-style-type: none"> <li>- Chlorambucil + obinutuzumab: Lognormal</li> <li>- Bendamustine + rituximab: HRs from NMA, using acalabrutinib + obinutuzumab as a baseline curve.</li> </ul> <p><u>Patients with unmutated IGHV</u></p> <p>Intervention:</p> <ul style="list-style-type: none"> <li>- Acalabrutinib: Weibull</li> <li>- Acalabrutinib + obinutuzumab: Weibull</li> </ul> <p>Comparators:</p> <ul style="list-style-type: none"> <li>- Chlorambucil + obinutuzumab: Lognormal</li> <li>- Bendamustine + rituximab: HRs from NMA, using acalabrutinib + obinutuzumab as a baseline curve.</li> </ul>
Parametric Curves, TTD	<p><u>Patients without 17p deletion/TP53 mutation</u></p> <p>Intervention:</p> <ul style="list-style-type: none"> <li>- Acalabrutinib: Exponential</li> <li>- Acalabrutinib + obinutuzumab: Exponential</li> </ul> <p>Comparators:</p> <ul style="list-style-type: none"> <li>- Chlorambucil + Obinutuzumab: Exponential</li> <li>- Bendamustine + rituximab: HRs from MAIC</li> </ul> <p><u>Patients with 17p deletion/TP53 mutation</u></p> <p>Intervention:</p> <ul style="list-style-type: none"> <li>- Acalabrutinib: Exponential</li> <li>- Acalabrutinib + obinutuzumab: Exponential (combined curves for mono and combo)</li> </ul> <p>Comparators:</p> <ul style="list-style-type: none"> <li>- Ibrutinib: HRs from MAIC (set to 1)</li> <li>- Venetoclax + obinutuzumab: HRs from MAIC (set to 1)</li> </ul> <p><u>Patients with mutated IGHV</u></p> <p>Intervention:</p> <ul style="list-style-type: none"> <li>- Acalabrutinib: Exponential</li> <li>- Acalabrutinib + obinutuzumab: Exponential</li> </ul> <p>Comparators:</p> <ul style="list-style-type: none"> <li>- Chlorambucil + Obinutuzumab: Exponential</li> <li>- Bendamustine + rituximab: HRs from NMA</li> </ul> <p><u>Patients with unmutated IGHV</u></p> <p>Intervention:</p> <ul style="list-style-type: none"> <li>- Acalabrutinib: Exponential</li> <li>- Acalabrutinib + obinutuzumab: Exponential</li> </ul> <p>Comparators:</p> <ul style="list-style-type: none"> <li>- Chlorambucil + Obinutuzumab: Exponential</li> <li>- Bendamustine + rituximab: HRs from NMA</li> </ul>
Parametric Curves, PPS	<p>Intervention:</p> <ul style="list-style-type: none"> <li>- Acalabrutinib: ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)</li> <li>- Acalabrutinib + obinutuzumab: ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)</li> </ul> <p>Comparators:</p> <ul style="list-style-type: none"> <li>- Chlorambucil + Obinutuzumab: ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)</li> <li>- Bendamustine + rituximab: ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)</li> <li>- Ibrutinib: ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)</li> <li>- Venetoclax + obinutuzumab: ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)</li> </ul>
Drug Wastage Included	No
Costs	<p>1L:</p> <ul style="list-style-type: none"> <li>- Drug acquisition</li> <li>- Drug administration</li> </ul>

Model Characteristics	Details
	<ul style="list-style-type: none"> <li>- Drug monitoring</li> <li>- Adverse event cost</li> <li>- Patient costs</li> <li>- Management of Grade <math>\geq 3</math> AEs</li> </ul> Subsequent therapy (2L): <ul style="list-style-type: none"> <li>- Drug acquisition</li> <li>- Drug administration</li> <li>- Drug monitoring</li> <li>- Patient costs</li> </ul>
Outcome(s)	Incremental cost per patient

### 11.1.2 Modelling in the Cost per Patient Analysis

The cost per patient model uses a semi-Markov structure, based on three mutually exclusive health states: progression-free (PF), progressed disease (PD), and dead. Figure 1 describes the disease progression pathway in the model. Unlike a conventional Markov, the semi-Markov model captures and follows each cohort of patients entering the PD state in each cycle using tunnel states. This technique allows the model to track the survival of each cohort entering the PD state using time-dependent transition probabilities (if deemed appropriate based on the underlying data).

*Figure 1. CLL Disease progression model structure*



A semi-Markov approach was favoured over a partitioned survival model in this setting due to the relative immaturity of the overall survival data. The primary endpoint for the ELEVATE-TN trial was progression-free survival, for which acalabrutinib demonstrated significantly reduced hazards when compared to chlorambucil + obinutuzumab (Sharman et al, 2020). Conversely, a limited number of death events were observed during follow-up in ELEVATE-TN, particularly for patients receiving acalabrutinib-based regimens. Therefore, extrapolating survival on this endpoint purely using the trial data is likely to lack validity. The use of a semi-Markov model permits the integration of external data into the model, leveraging more mature sources to improve the validity of long-term estimates. For the purposes of modelling it was assumed survival post-progression would largely be influenced by the subsequent treatment received. By using a semi-Markov approach, the overall survival data from the pivotal trial of the therapy most likely to be used post-first line progression (i.e., in relapsed or refractory CLL) with a given treatment could be considered a proxy for post-progression survival at first line, assuming treatment sequences as may be used in clinical practice.

By using external data to inform post-progression survival, selection effects and informative censoring on the ELEVATE-TN data can be avoided. Given the limited trial follow-up and the low number of observed death



events, extrapolating post-progression survival (or even overall survival) from ELEVATE-TN could be biased as only the patients with the worst prognosis (who progressed the quickest) would be available for extrapolation of survival post-progression. As noted in Technical Support Document 19 from the NICE Decision Support Unit, this downward bias is greater for more efficacious therapies pre-progression (NICE DSU, 2017a). Therefore, using external data in a semi-Markov model is assumed to be the least biased approach in this scenario.

The DSU also note that whilst the partitioned survival approach is “intuitive, easy to implement, and generally predicts trial endpoints well for the within-trial period...it may not provide the ideal modelling approach to inform extrapolation due to the lack of structural relationship between modelled endpoints” (NICE DSU 2017b, p.53). Extrapolating within-trial trends without considering the underlying disease process may not produce appropriate extrapolations. Consequently, the DSU argue that the simplicity does not provide a sufficient basis for justifying use of the approach. However, it does assume an explicit link between disease progression and survival. This has been demonstrated in treatment with a BTKi (Burger et al, 2019), and can be seen with other first-line treatments in CLL (Goede et al, 2014), where an extension to PFS is also associated with extended OS when data is mature enough to estimate this.

State occupancy was modelled at four-week intervals (28 days) over the course of the time horizon. A four-week cycle length was used as it is the common denominator between treatment cycle duration and the annual time horizons required for the economic analysis.

The total costs of treatments were estimated by combining the proportion of patients in each health state over time, with the costs assigned to each state. The health states included within the model describe the following disease stages:

- **PF:** All patients start in the progression-free state and remain in this state until disease progression or death. First-line treatment is initiated upon entry to the model (and the progression-free state) and is continued until either progression, death, or the maximum number of treatment cycles for the specific regimen.
- **PD:** The PD state captures patients who have progressed on their first line therapy prior to death. Once in the PD state, patients receive subsequent treatment.
- **Death:** The death state is an absorbing state, meaning that patients transitioning to this health state are assumed to occupy it indefinitely

The transition probabilities (TPs) as shown in Figure 1 are time-dependent. As disease progression and pre-progression death are competing, mutually exclusive, events, TP1 and TP2 were modelled using competing risks models. The use of competing risks models was necessary given that patients could either progress or die before progression when transitioning from the progression-free health state, and the independent extrapolation of time to progression or deaths before progression (assuming that patients would be censored for one event when experiencing the other) would produce incorrect results. Competing risks are events that can alter the probability of the occurrence of another event, including completely precluding it, which is distinct from censoring in that censoring merely prevents observation of the event of interest at the time at which it occurs. Therefore, failure to account for competing risks by censoring patients would mean in the extrapolation that any patient who died prior to progression could subsequently experiencing a progression event. The TPs within the model are described in further detail below:

- **TP1 (TTP):** TP1 governs transitions from the PF to PD state and is modelled using time to progression (TTP) data. TTP patient-level data from ELEVATE-TN was extrapolated to derive TP1 for acalabrutinib monotherapy, acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab. For bendamustine

+ rituximab, TP1s were derived through application of HRs (derived via either NMA or MAIC) to baseline acalabrutinib curves from the ELEVATE-TN trial patient-level data.

- **TP2 (TTDeath):** The transition from PF to Death state (TP2) is modelled using time to pre-progression death (TTDeath) data. TTDeath patient-level data from ELEVATE-TN were extrapolated to derive TP2 for acalabrutinib monotherapy, acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab. For bendamustine + rituximab, TP2 was derived through application of HRs (derived via either NMA or MAIC) to the baseline acalabrutinib TTDeath curve derived from the ELEVATE-TN trial patient-level data. To ensure survival did not exceed that expected for the general population, TP2 was restricted by the general population mortality in Denmark which was applied as a competing risk.
- **TP3 (PPS):** TP3 captures the risk of death at any time in patients with progressed disease. TP3 was estimated using post-progression survival (PPS) data. PPS was modelled from R/R clinical studies. As with TP2, the general population mortality in Denmark was applied as a competing risk to prevent survival exceeding that of the general population.

### 11.1.3 Indirect Treatment Comparison

To evaluate the relative costs of the acalabrutinib based therapy compared with the current standard of care not included in the ELEVATE-TN study, the network meta-analysis (NMA) and the matching-adjusted indirect comparison (MAIC) were conducted.

The cost per patient model included time-to-progression (TTP) curve and time-to-death (TTDeath) curve derived from PFS in the ELEVATE study. The HRs from the NMA and MAIC (PFS) were therefore not aligned with the endpoints used in the model. Accordingly, the PFS HRs were applied to both TTP and TTDeath on the assumption that PFS observed in trials captures both of these events. This assumption was necessary, as TTP and TTDeath endpoints were not reported in the literature, thus making an indirect treatment comparison on these endpoints unfeasible. TTDeath curves from the ELEVATE-TN trial were informed by a very low number of events. Although the HRs estimated in the NMA and MAIC were based on immature Kaplan-Meier (KM) data, for comparisons with chemo-immunotherapies the HR was applied for the model time horizon as long-term data from the RESONATE-2 trial shows a sustained efficacy benefit of BKTi over chemo-immunotherapy over a 5-year follow-up period (Burger et al, 2019).

Both acalabrutinib monotherapy and combination therapy were used as reference treatments in ITCs. In contrast to the ELEVATE-TN study where the primary efficacy endpoint was independent review committee (IRC) assessed PFS, only investigator (INV) assessed PFS was measured in the ALLIANCE and MaBLE studies (ibrutinib, ibrutinib + rituximab, bendamustine + rituximab, chlorambucil + rituximab), which were essential to results from ELEVATE-TN with other relevant treatments. Thus, INV assessed PFS was used to generate the hazard ratios (HR) in the NMA and MAIC. The HRs of acalabrutinib-based therapies versus comparators are shown in Table 4.

**Table 4.** HRs applied to acalabrutinib baseline TTP and TTDeath curves from the NMA and MAIC

Comparator	PFS HR (95% CI) vs. Acalabrutinib Monotherapy		PFS HR (95% CI) vs. Acalabrutinib + Obinutuzumab	
	NMA	MAIC	NMA	MAIC
Bendamustine + Rituximab	5,34 (2,83 – 10,20)	2,63 (1,39 – 5,00)	7,06 (3,53 – 13,97)	4,76 (2,33 – 10,00)
Ibrutinib	1,64 (0,87 – 3,12)	1,09 (0,51 – 2,27)	2,16 (1,09 – 4,28)	1,64 (0,65 – 4,17)
Venetoclax + Obinutuzumab	2,13 (1,12 – 4,10)	0,81 (0,37 – 1,75)	2,80 (1,40 – 5,62)	1,28 (0,55 – 3,03)

Acalabrutinib-based therapy showed trends for superior efficacy to all comparators but the results were not consistently statistically significant in comparison with ibrutinib and venetoclax + obinutuzumab. Accordingly, efficacy was considered equal between ibrutinib, venetoclax + obinutuzumab, and acalabrutinib monotherapy in the model in the subgroup with 17p deletion/TP53 mutation, which compared these therapies. This is supported by further subgroup analyses in the NMA. Subgroups of high risk patients (with 17p deletion, 11q deletion, TP53 mutation, or without IGHV mutation) were included in ELEVATE-TN. The PFS benefit for acalabrutinib was consistent across all prespecified subgroups. The subgroup NMA for the first line population with a 17p deletion showed that acalabrutinib was associated with comparable PFS versus ibrutinib + obinutuzumab, HR [redacted] ([redacted], [redacted]). The comparison was characterized by wide credible intervals likely due to small sample sizes. Given that it was not possible to obtain population specific HRs for the patients with 17p deletion/TP53 mutation, the HRs from ITT population had to be utilised to draw inferences on comparative efficacy and thus these would suggest that equal efficacy can be assumed between acalabrutinib monotherapy and the comparators in the high risk subgroup.

In comparison with bendamustine + rituximab, the MAIC method, which resulted in conservative estimates against the acalabrutinib based therapy, was used in the cost per patient base case analysis. The NMA results were considered in the sensitivity analysis. As bendamustine + rituximab is a combination therapy, where a chemotherapeutic agent is discontinued after a finite time, it was therefore considered more comparable to acalabrutinib + obinutuzumab than monotherapy. Hence, the baseline data of acalabrutinib + obinutuzumab was utilized in the comparison with acalabrutinib based therapy and bendamustine + rituximab (see more details in section 10.1.4). For the scenario analysis subgroups stratifying patients by the presence of IGHV mutation, HRs from the MAIC were not available, and so HRs from the NMA were utilised in these analyses.

#### 11.1.4 Estimation of Survival Curves for Acalabrutinib-Based Therapies and Comparators

The ELEVATE-TN study provided survival data up to a limited follow-up time. To apply a lifetime perspective in the cost per patient analysis, extrapolation beyond the trial follow-up period was required. The following summarizes the survival curve selection for acalabrutinib and comparators in the PU patient populations identified by the Danish Medicines Council:

- Patients without 17p deletion/TP53 mutation (ITT)
- Patients with 17p deletion/TP53 mutation
- Scenario analysis population: patients without IGHV mutation
- Scenario analysis population: patients with IGHV mutation

Survival curves for all endpoints were fitted using standard parametric models: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma. For treatments included in the ELEVATE-TN study, survival curves were fitted to patient level data, based on Decision Support Unit (DSU) guidance from the National Institute for Health and Care Excellence (NICE, 2013). For other treatments, the KM curves were digitised using standard methods (Guyot et al, 2012) and used to inform indirect treatment comparisons.

For all curves presented in the following sections, the following key criteria were applied:

- Clinical plausibility of long-term extrapolation
- Visual inspection of survival curve fit to KM data from the ELEVATE-TN trial
- Inspection of log-cumulative hazard plots (to assess the behaviour of the hazard over time)
- Statistical model fit, via measures such as Akaike's Information Criterion (AIC) / Bayesian Information Criterion (BIC)

The comparison of acalabrutinib and acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab was based on the data from ELEVATE-TN trial. PFS assessed by IRC from ELEVATE-TN was used as it was the primary efficacy endpoint in the study.

As outlined in the section 10.1.3 (Indirect treatment comparison), the MAIC analyses indicated that, acalabrutinib-based therapy is associated with similar efficacy (PFS, OS and ORR) to ibrutinib and venetoclax + obinutuzumab. In the absence of HRs for the patients with 17p deletion/TP53 mutation equal efficacy between acalabrutinib monotherapy and comparators was assumed (HRs set to 1), as outlined above. To increase the sample size for this subgroup the acalabrutinib and acalabrutinib + obinutuzumab arms from the ELEVATE trial were combined for the analyses.

The survival modelling methods and selected extrapolation are summarized in Table 5 and Table 6 for patients without 17p deletion/TP53 mutation and with 17p deletion/TP53 mutation, respectively. More detailed description about the curve selection is presented in Appendix (*Estimation of survival curves 1L*). The overview of the settings for survival curve extrapolation in patient population with IGHV mutation and without IGHV mutation is presented in Appendix (*Overview of the scenario analysis settings for survival curve extrapolation in patient population with/without IGHV mutation*).

For post-progression survival, it was assumed this would be equal for all first line treatments as all patients are assumed to receive a novel target therapy (either BTKi or BCL2) at second line (see Table 14), and the efficacy of novel therapies in previously treated CLL patients is considered to be equal (see Byrd et al., 2021 and the appended MAIC in R/R CLL, "*Matching-adjusted indirect comparisons of efficacy and tolerability outcomes with acalabrutinib versus selected comparators for patients with relapsed/refractory chronic lymphocytic leukemia*"). As noted above, given the limited number of deaths observed in the ELEVATE-TN study it was determined that data should be sourced elsewhere, to avoid extrapolating post-progression survival from a highly restricted number of patients who survived beyond disease progression. Upon request from Medicinrådet, this has been modelled using the overall survival data from the ELEVATE-RR trial. AstraZeneca has chosen to pool the survival data for acalabrutinib monotherapy and ibrutinib monotherapy given these treatments are non-inferior to each other. Whilst this patient population may have a worse prognosis than the general second line CLL population in Denmark given the higher prevalence of cytogenetic abnormalities such as del(17p), TP53mut, or del(11q) in this trial (45%, 40% and 64% in ELEVATE-RR vs. 16%, 24% and 27% in ASCEND, respectively), it has previously been demonstrated that survival outcomes in patients with these cytogenetic abnormalities are not substantially worse than patients without when treated with a BTKi compared to when treated with legacy therapies (Munir et al., 2019). As a scenario, post-progression survival using a pooled analysis of the ELEVATE-TN post-progression data and the ASCEND OS data as the source is presented.

This assumption also applies to acalabrutinib-based therapy and ibrutinib in the subgroup of patients with 17p deletion/TP53 mutation, as all these patients are also assumed to receive a novel therapy (venetoclax + rituximab) at second line and the ELEVATE-RR data provides the best source of long-term survival of patients with high risk features. Whilst patients receiving venetoclax + obinutuzumab at first line were considered most likely to receive a BTKi at second line based on clinician feedback, to date there is no evidence of differential overall survival between acalabrutinib and venetoclax + obinutuzumab (see the NMA and MAIC reports appended to this document). Therefore, in the interests of fairness, equal post-progression survival is assumed between these treatments. A scenario analysis is considered where the post-progression survival following venetoclax + rituximab is based on BTKi therapy (the RESONATE trial for ibrutinib).

**Table 5. Base case survival curve extrapolations in patients without 17p deletion/TP53 mutation (ITT\*)**

<b>Acalabrutinib Monotherapy</b>	
TTP Distribution	Gompertz
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)
<b>Acalabrutinib + Obinutuzumab</b>	
TTP Distribution	Weibull
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)
<b>Chlorambucil + Obinutuzumab</b>	
TTP Distribution	Lognormal
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)
<b>Bendamustine + Rituximab (ITC)</b>	
TTP/TTDeath Source	MAIC HR applied to both TTP/TTDeath using acalabrutinib combination therapy as the baseline
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)

\*Modelled with the data of ITT population.

**Table 6. Base case survival curve extrapolations in patients with 17p deletion/TP53 mutation\***

<b>Acalabrutinib Monotherapy*</b>	
TTP Distribution	Lognormal
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)
<b>Acalabrutinib + Obinutuzumab*</b>	
TTP Distribution	Lognormal
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)
<b>Ibrutinib</b>	
TTP/TTDeath Source	Assumption of equal efficacy vs acalabrutinib monotherapy based on MAIC results
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)
<b>Venetoclax + Obinutuzumab</b>	
TTP/TTDeath Source	Assumption of equal efficacy vs acalabrutinib monotherapy based on MAIC results
PPS Source	ELEVATE-RR (Pooled Acalabrutinib / Ibrutinib OS)

\*Modelled with the data of 17p deletion/TP53 mutation using pooled data of acalabrutinib monotherapy and combination therapy arm.

## 11.2 Methods of the Budget Impact Analysis

### 11.2.1 Overview of the Budget Impact Analysis

To analyse the budget consequence of implementing acalabrutinib with or without obinutuzumab therapy, two scenarios of the CLL market were compared: one being a market without acalabrutinib (neither monotherapy or combination therapy) and the other being a market with acalabrutinib (either as monotherapy, combination therapy, or with both available). Each scenario considers the national and CLL population sizes, patient eligibility, and market shares of available treatments. In addition, cost data related to drug acquisition and healthcare resources of drug administration, disease management, AEs, and treatment monitoring were included, all within a Danish setting. Based on these data, the following steps of calculations were made leading to the BI results:

- Eligible population for acalabrutinib with or without obinutuzumab in patients with/without 17p deletion/TP53 mutation in PU CLL treatment.

- Number of eligible patients with/without 17p deletion/TP53 mutation receiving each therapeutic option, estimated by multiplying the eligible population for patients with/without 17p deletion/TP53 mutation with the market shares for each treatment option.
- Calculate the total BI by estimating the difference in total costs between the markets with or without acalabrutinib.

The model structure is closely aligned with the Danish Medicines Council guideline and follows standard format of calculating the budget impact of new treatments. An overview of the model structure is provided in Table 7.

**Table 7. Characteristics of the BI analysis**

Model Characteristics	Details
Eligible Population	<ul style="list-style-type: none"> <li>– PU CLL FCR-ineligible patients without 17p deletion/TP53 mutation</li> <li>– PU CLL high-risk CLL patients with 17p deletion/TP53 mutation</li> </ul>
Country	Denmark
Intervention(s)	<ul style="list-style-type: none"> <li>– Acalabrutinib</li> <li>– Acalabrutinib + obinutuzumab</li> </ul>
Comparator(s)	<p><u>Patients without 17p deletion/TP53 mutation:</u></p> <ul style="list-style-type: none"> <li>– Chlorambucil + Obinutuzumab</li> <li>– Bendamustine + Rituximab</li> </ul> <p><u>Patients with 17p deletion/TP53 mutation:</u></p> <ul style="list-style-type: none"> <li>– Ibrutinib</li> <li>– Venetoclax + Obinutuzumab</li> </ul>
Perspective	Healthcare payer perspective
Time Horizon	5 years
Method	Open cohort comprising incident patients only
Market Share	Market shares following the adoption of acalabrutinib +/- obinutuzumab in 1L treatment for patients with and without 17p deletion/TP53 mutation
Costs	<ul style="list-style-type: none"> <li>– Drug acquisition</li> <li>– Drug administration</li> <li>– Drug monitoring</li> <li>– Disease management</li> <li>– Management of Grade <math>\geq 3</math> AEs</li> <li>– Subsequent therapy (inc. acquisition, administration, and monitoring)</li> </ul>
Drug Wastage Included	No
Outcomes	<ul style="list-style-type: none"> <li>– Budget without acalabrutinib</li> <li>– Budget with acalabrutinib</li> <li>– Incremental budget impact of acalabrutinib</li> </ul>
Scenario Analyses	<ul style="list-style-type: none"> <li>– Budget with smaller market share (reduction of 40% for acalabrutinib-based therapies) in untreated CLL without 17p deletion/TP53 mutation</li> <li>– Budget with smaller market share (reduction of 40% for acalabrutinib-based therapies) in untreated CLL with 17p deletion/TP53 mutation</li> </ul>

## 12 Budget Impact Model Inputs

The budget impact analysis was based upon the cost per patient analysis, taking relevant modelled costs over time for each treatment and combining these with estimates of patients initiating each treatment to determine budget impact. Therefore, costing sources are aligned with those of the cost per patient analysis.

Further inputs were required to estimate the eligible patient population and market share of treatments.

## 12.1 Eligible Population

The target populations eligible for acalabrutinib with or without obinutuzumab were estimated in line with the protocol published by the Danish Medicines Council for the assessment of acalabrutinib. The annual incidence rate was set to be 7,74 per 100.000 people based on the average annual reported incidence of CLL in Denmark between 2016 and 2019 (DLG/LYFO, 2019). This resulted in 454 incident diagnosed CLL cases in Denmark in the first year of the BI analysis, increasing to 463 by year 5 after accounting for expected population growth. According to the Danish Medicine Council, approximately 150 CLL patients initiate first line therapy each year and so it was assumed that 33.2% of incident cases would be symptomatic CLL patients who are eligible for 1L treatment each year. Furthermore, the protocol states that 90% of these would be patients without 17p deletion/TP53 mutation, and who are eligible for chemoimmunotherapy. However, as FCR eligible patients are out of scope in the current analysis, the proportion of patients eligible for chemoimmunotherapy but who would be ineligible for FCR needs to be estimated. It has previously been estimated that 20% of patients without 17p deletion/TP53 mutation at first line would receive FCR (RADS, 2016).

**Table 8.** Total number of patients that are eligible for acalabrutinib across the time horizon

Parameter	Year 1 (2022)	Year 2 (2023)
Population of Denmark [1,2]	5 866 980	5 894 040
Annual incidence of CLL (per 100.000) [3]	7,74	7,74
Newly diagnosed CLL patients	454	456
Untreated CLL patients eligible for treatment [4]	33,2%	33,2%
Patients starting 1L treatment	151	151
<b>Patients without 17p deletion/TP53 mutation</b>		
Proportion untreated CLL without 17p deletion/TP53 mutation [4]	90%	90%
Patients starting chemoimmunotherapy	136	136
Proportion untreated CLL without 17p deletion/TP53 mutation starting FCR [5]	20%	20%
<b>FCR-ineligible patients starting treatment</b>	<b>109</b>	<b>109</b>
<b>Patients with 17p deletion/TP53 mutation</b>		
Proportion untreated CLL with 17p deletion/TP53 mutation [4]	10%	10%
<b>High risk patients starting treatment</b>	<b>15</b>	<b>15</b>

[1]: Statistics Denmark. Population at the first day of the quarter (Q1 2021)

[2]: Average annual population growth from first day of year 2017 to 2021, obtained from Statistics Denmark

[3]: LYFO database. 2018

[4]: Medicinrådet. 2020

[5]: RADS. 2016

## 12.2 Market Share

In the BIM, two different scenarios for market share were considered. One representing the current standard of care in Denmark (scenario without acalabrutinib +/- obinutuzumab) and the other when treatment with acalabrutinib +/- obinutuzumab is reimbursed (scenario with acalabrutinib +/- obinutuzumab). The scenarios with acalabrutinib is further divided into three scenarios, showing market shares for acalabrutinib monotherapy, acalabrutinib + obinutuzumab and acalabrutinib +/- obinutuzumab. Since AstraZeneca does not have access to sales per indications the market shares for the intervention and comparators were based on AstraZeneca's assumptions.

The current clinical practice for patients without 17p deletion/TP53 mutation is bendamustine + rituximab for the elderly patient population with good performance status (or the younger patients with poor performance status), and chlorambucil + either rituximab and obinutuzumab for patients with poor performance status. According to the Danish Medicine Council the considered comparators to acalabrutinib +/- obinutuzumab are chlorambucil + obinutuzumab and bendamustine + rituximab. The market shares were

assumed to be higher for bendamustine + rituximab, than for chlorambucil + obinutuzumab. The uptake of acalabrutinib +/- obinutuzumab is assumed to increase over the 5-year horizon and take market shares from both chlorambucil + obinutuzumab and bendamustine + rituximab.

For patients with 17p deletion/TP53 mutation venetoclax + obinutuzumab was recently approved by the Danish Medicine Council. The uptake of this treatment option is therefore assumed to be increasing over 5 years (■%-■%), in turn negatively impacting the use of ibrutinib (■%-■%). This was in line with venetoclax + obinutuzumab application (Medicinrådet, 2020). Both the increased market shares for venetoclax + rituximab and the reduced market shares for ibrutinib was assumed in accordance with the feedback from external clinicians and the venetoclax + obinutuzumab application (Medicinrådet, 2020). The uptake of acalabrutinib +/- obinutuzumab in 2022 was assumed to further impact the market share of the current treatment options. During 2022-2026 the uptake of acalabrutinib +/- obinutuzumab is assumed to take market shares from both ibrutinib and venetoclax + obinutuzumab.

It should be noted that the reimbursement process of ibrutinib + rituximab in 1L indications is ongoing in the Danish Medicine Council. If approved, there will be an impact on the assumed market shares in 1L.

The market shares for each treatment option are presented in Table 9 for the scenario with acalabrutinib monotherapy, in Table 10 for the scenario with acalabrutinib + obinutuzumab, and in Table 11 for the scenario with both acalabrutinib monotherapy and acalabrutinib + obinutuzumab.

**Table 9. Market shares for the scenario with acalabrutinib monotherapy**

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>Without 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Bendamustine + Rituximab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Chlorambucil + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>With 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Venetoclax + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Ibrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%



**Table 10.** Market shares for the scenario with acalabrutinib + obinutuzumab

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>Without 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Bendamustine + Rituximab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Chlorambucil + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>With 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Venetoclax + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Ibrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%

**Table 11.** Market shares for the scenario with both acalabrutinib +/- obinutuzumab

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>Without 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Bendamustine + Rituximab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Chlorambucil + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>With 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Venetoclax + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Ibrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%

### 13 Treatment Duration

The treatment duration of each treatment option was used to estimate the drug acquisition, administration, monitoring, and AE costs. In turn, cost implications of subsequent therapies for untreated patients who progress to 2L. While some treatment durations are informed by progression free survival (PFS), others have fixed durations of a maximum number of cycles (e.g., chemoimmunotherapies and venetoclax-based

combination treatments). These were informed with treatment stopping rules based on the respective product's SmPC for implementation in the model. For finite regimens, patients are assumed to discontinue treatment at disease progression, death, or the maximum number of treatment cycles.

### 13.1 First-Line Treatments

The treatment duration was used to estimate total treatment-related costs. Treatment duration for all treatment options for untreated CLL patients are presented in Table 12. It should be noted that for combination chemoimmunotherapy with fixed duration, only the duration of the longest treatment according to the stopping rule is presented in the table. Although acalabrutinib is a continuous treatment, for combination therapy the obinutuzumab treatment is accounted for at 7,36 months (8 doses), with adjustment additional adjustment for disease progression or death. The same treatment duration of obinutuzumab is set for chlorambucil + obinutuzumab and venetoclax + obinutuzumab.

The duration of ibrutinib therapy was assumed to be equal to acalabrutinib. This is as both drugs have the same mechanism of action and both have product labels that permit them to be used until disease progression or unacceptable toxicity. The results of the indirect treatment comparisons have shown that acalabrutinib and ibrutinib are associated with comparable efficacy with regards to progression-free survival (HR 0,92; 95% CI 0,44 to 1,95). This would suggest that reasons for discontinuation due to disease progression would be aligned between treatments. With regards to potential discontinuations due to unacceptable toxicity, after 29 months of follow-up in the RESONATE-2 trial of ibrutinib in previously untreated CLL patients, 16 of the 136 patients (12%) randomised to receive ibrutinib had discontinued due to adverse events (Barr et al, 2018). This compares to 16 of the 179 (9%) receiving acalabrutinib in ELEVATE-TN (median follow-up 28,3 months). It was therefore assumed for the purposes of the economic analysis that discontinuations due to unacceptable toxicity would be largely similar.

**Table 12.** Untreated CLL treatment duration

Treatment	Mean Duration (months)	Source
Acalabrutinib	Without del(17p): 69,41 With del(17p): █████	PFS was sourced from the parametric extrapolation of Kaplan-Meier estimates conducted on the patient level data from the ELEVATE trial
Acalabrutinib + Obinutuzumab	Without del(17p): 109,67 With del(17p): █████	PFS was sourced from the parametric extrapolation of Kaplan-Meier estimates conducted on the patient level data from the ELEVATE trial
Chlorambucil + Obinutuzumab	7,29	This treatment has a fixed duration of 6 cycles of 28 days. However, obinutuzumab dose is administered 3x in the 1 <sup>st</sup> cycle and then once in the remaining cycles. To account for this, the average number of doses per month was estimated and calibrated the treatment duration in order to reach the correct dose of obinutuzumab which is approx. 8/1,09 = 7,36 month. Chlorambucil is administered for 6 cycles, equivalent to a treatment duration of 5,52 months.
Bendamustine + Rituximab	5,42	The treatment has a fixed duration of 6 cycles of 28 days, therefore setting the treatment durations to 5,52 months.
Ibrutinib	█████	The duration of ibrutinib treatment was assumed to be the same as that of acalabrutinib monotherapy.
Venetoclax + Obinutuzumab	11,63	This treatment has a fixed duration of 12 cycles of 28 days, inc. 6 cycles in combination with obinutuzumab followed by 6 cycles of venetoclax as a single agent. Patients receive 100 mg of obinutuzumab on Cycle 1 Day 1, followed by 900 mg, and 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent cycle. The 5-week venetoclax dose-titration begins on Cycle 1 Day 22 and continues through Cycle 2 Day 28. After completing the dose-titration schedule, patients receive 400 mg of venetoclax once daily from Cycle 3 Day 1 of obinutuzumab to the last day of Cycle 12. Therefore, to reach the maximum dose of venetoclax 400 mg per dose in a pack size of 112 tablets was used to calculate number of tablets needed for 30,44 days per month

## 13.2 Subsequent Treatment Duration

Patients who progress after 1L treatments are recommended to either receive ibrutinib, or venetoclax + rituximab (Medicinerådet, 2020), along with acalabrutinib which is also aligned with the protocol (Medicinerådet, 2020).

The mean duration of ibrutinib and acalabrutinib as subsequent treatments was set to be the mean PFS sourced from R/R cost per patient analysis. In the R/R cost per patient analysis, PFS data from ELEVATE-RR were utilized and extrapolated using exponential model fitted to the patient-level data. Given that acalabrutinib was demonstrated to be non-inferior to ibrutinib in the trial, the pooled data across treatment arms from the primary endpoint of independent review committee (IRC) assessed PFS was used to estimate time on treatment for therapies used until progression. Venetoclax + rituximab has a fixed duration of therapy and therefore treatment stopping was assumed based on the dosing regimen from product resume of EMA, following the time until disease progression curve up to a maximum of 24 months. Table 13 shows the mean treatment duration of 2L subsequent treatment alternatives for PU CLL patients who progressed.

**Table 13.** Subsequent treatment duration for 2L in the untreated CLL population

Subsequent Treatment	Mean Treatment Duration (Cycles)
Acalabrutinib	
Ibrutinib	
Venetoclax + Rituximab	22,05 cycles of venetoclax + 5,83 cycles of rituximab*

\*Restricted mean PFS for 26 cycles of venetoclax and 6 cycles of rituximab

To estimate total costs of subsequent treatment for each model comparator, the patient distributions of the subsequent treatments are presented in Table 14. The assumptions on the patient distributions were based on expert opinions (Nørregaard Bentzen & Curovic Rotbain) and the market shares presented in section 11.2.

**Table 14.** Patient distribution in subsequent treatment for 2L in the untreated CLL population

1L Therapy	Patients Receiving Subsequent Treatment at 2L (%)		
	Acalabrutinib	Ibrutinib	Venetoclax + Rituximab
Acalabrutinib	0	0	100%
Acalabrutinib + Obinutuzumab	0	0	100%
Chlorambucil + Obinutuzumab	40%	5%	55%
Bendamustine + Rituximab	40%	5%	55%
Ibrutinib	0%	0	100%
Venetoclax + Obinutuzumab	70%	20%	10%

## 14 Costs Inputs

### 14.1 Drug Acquisition

Acquisition costs were applied in the models as a cost per cycle for each treatment until progression or until the maximum number of administrations have been reached. Acquisition costs for each treatment option were calculated based on dosing regimen as administration frequency per cycle and cost per dose. For this purpose, drug information including formulations, pack sizes, strength, price (pharmacy purchase price, AIP) per pack and mg, as well as unit price were sourced from Medicinpriser.dk (Medicinerådet, 2021) (Table 15). In instances where multiple pack prices were available, the pack with the lowest cost per mg was used.

In the base case, drug wastage was not included. Drug wastage is not anticipated to affect the results for oral therapies as, whilst whole packs of tablets will be dispensed in practice, pack sizes are largely aligned with model cycles. As treatment discontinuation is considered to be continuous in line with progression-free survival for most oral therapies, minor deviations in tablet consumption by pack are assumed to average out

with time. Drug wastage is potentially a greater issue for parenterally administered drugs, where the required dose per body surface area or weight is unlikely to correspond with full vials, though dose banding or vial sharing can occur in practice and reduce the likelihood of wastage. Excluding drug wastage is likely to be a conservative assumption against acalabrutinib as it captures potential cost savings by vial sharing that could occur with comparator IV therapies rather than the orally administered drugs. Drug wastage (unused vials) was considered in a scenario analysis. Drug wastage was estimated by calculating the required dose per administration based on the dosing regimen and patient weight/body surface area, where required. This was then compared to the number of whole vials or tablet packs that would be needed to deliver the required dose (e.g., a dose of 950 mg of rituximab at 500 mg/m<sup>2</sup> for a patient with a BSA of 1.9 m<sup>2</sup> would require two 500 mg vials).

**Table 15. Drug information**

Drug	Formulation	Strength	Pack Size	AIP	AIP/Unit
<b>Acalabrutinib</b>	Tablet	100 mg	60	45224,19	753,74
<b>Ibrutinib</b>	Capsule	140 mg	90	45124,73	501,39
			120	57321,65	477,68
	Tablet	140mg	28	14038,8	501,39
	Tablet	280mg	28	28077,61	1002,77
	Tablet	420mg	28	42116,41	1504,16
<b>Venetoclax</b>	Tablet	10 mg	14	500,13	35,72
	Tablet	50 mg	7	1250,33	178,62
	Tablet	100 mg	7	2500,64	357,23
	Tablet	100 mg	14	5001,28	357,23
	Tablet	100 mg	112	40010,34	357,24
<b>Obinutuzumab</b>	IV	1000 mg	1	25627,07	25627,07
<b>Chlorambucil</b>	Tablet	2 mg	25	527,00	21,08
<b>Bendamustine</b>	IV	2,5 mg/ml	125	367,00	2,94
	IV	2,5 mg/ml	200	1100,00	5,50
	IV	2,5 mg/ml	500	1174,00	2,35
<b>Rituximab</b>	IV	100 mg	2	2675,80	1337,90
	IV	500 mg	1	6687,00	6687,00

Further, as some treatment doses are body weight and surface area (BSA) specific, these were sourced from ELEVATE-TN study and are presented in Table 16.

**Table 16. Patient characteristics**

Patient Characteristic	PU CLL
Weight (kg)	78,9
BSA (m <sup>2</sup> )	1,9

Source: ACE-CL-007 Clinical Study Report

The information on administration frequency and dosing regimens were sourced from the respective EMA SmPCs. Table 17 summarizes the treatment dosing and administration frequency implemented in the models for previously untreated CLL patients.

**Table 17. Treatment dosing and administration**

	Administration Method	Dose per Administration	Admin Frequency	Weighted Doses	Source
<b>Acalabrunib</b>	Oral	100mg	2 tablets once daily	0	Calquence SmPC
<b>Ibrutinib</b>	Oral	420mg	3 tablets once daily of 140 mg*	0	Imbruvica SmPC
<b>Venetoclax</b>	Oral	400mg	1 tablet once daily (titration at treatment initiation, see section 13.4)	0	Venclyxto SmPC
<b>Rituximab</b>	IV	First dose at 375 mg/m <sup>2</sup> , subsequent doses at 500 mg/m <sup>2</sup>	Once per cycle for 6 cycles	1,9 m <sup>2</sup> (body surface area) ELEVATE	Mabthera SmPC
<b>Obinutuzumab</b>	IV	Loading dose of 100mg + 900mg + 1000mg + 1000mg in cycle 1 and then dose of 1000 mg IV once every 28 days for a total of 6 cycles	Once per cycle for 6 cycles	0	Gazyvaro SmPC
<b>Chlorambucil</b>	Oral	Dose of 0.5 mg/kg administered orally once every two weeks (day 1 and 15) for 6 cycles (section 5.1 SmPC)	Twice per cycle for 6 cycles	78,9 kg (body weight) ELEVATE	Gazyvaro SmPC
<b>Bendamustine</b>	IV	Dose of 100 mg/m <sup>2</sup> (Day 1 and 2 of each cycle for 6 cycles)	Twice per cycle	1,9 m <sup>2</sup> (body surface area) ELEVATE	Bendamustine "Fresenius Kabi" SmPC

\*Cost is identical to 1 tablet of 420 mg

The acquisition costs per cycle for treatments were estimated based on drug information and administration regimens and are presented in Table 18.

The estimated acquisition costs were related to doses per cycle. The per cycle dose for acalabrutinib was estimated to be 56, given the administration frequency of twice per day until progression. For ibrutinib and venetoclax, the monthly dose was estimated to be 28, as they are administered once daily. Venetoclax has an up titration at treatment initiation, see section 13.4. As both chlorambucil and obinutuzumab have a fixed treatment duration, the dose per cycle was estimated to be two and one for 6 cycles, respectively. For bendamustine it was estimated two doses per cycle, when considering the administration frequency of twice per cycle. For rituximab it was estimated one dose per month for 6 cycles given the treatment duration.

**Table 18.** Drug acquisition costs for treatment options of PU CLL included in the model

Regimen	Drug	Dose per cycle	Cost per cycle
<b>PU CLL without 17p deletion/TP53 mutation</b>			
Acalabrutinib	Acalabrutinib	56	DKK 42.209,24
Acalabrutinib + Obinutuzumab	Acalabrutinib Obinutuzumab	56 1	DKK 42.209,24 DKK 25.627,07
Chlorambucil + Obinutuzumab	Chlorambucil Obinutuzumab	2 1	DKK 831,61 DKK 25.627,07
Bendamustine + Rituximab	Bendamustine Rituximab	2 1	DKK 1.004,11 DKK 12.175,91
<b>PU CLL with 17p deletion/TP53 mutation</b>			
Venetoclax + Obinutuzumab	Venetoclax Obinutuzumab	28 1	DKK 40.010,34 DKK 25.627,07
Ibrutinib	Ibrutinib	28	DKK 45.124,73
<b>R/R CLL (Subsequent Treatments)</b>			
Venetoclax + Rituximab	Venetoclax Rituximab	28 1	DKK 40.010,34 DKK 15.456,45

\*Cost per patient model uses the same estimates but applies a calculation per cycle (28 days cycle length).

## 14.2 Drug Administration

The administration frequencies for each treatment option were sourced from the respective EMA SmPCs. Since there is a lack of information on where the administrations of the treatments take place, it is assumed that IV related treatments were administered in the outpatient care, thus accruing administration costs. Orally administered treatments were assumed to accrue no administration costs. The assumption to exclude administration costs for orally administered therapies was made on the basis that all treatments (whether administered orally or IV) would require patients to attend an initial outpatient consultation with a haematologist to determine a treatment plan and the course of therapy. Drugs that are administered orally can be assumed to be prescribed in this visit and would not require further health care resources to administer. Conversely, an IV therapy requiring nurse time to administer the drugs. Therefore, there is assumed to be not incremental costs of initiating therapy with an oral treatment and so these were excluded. Unit cost for outpatient care resources was sourced from the 2021 Danish DRG tariffs (Sundhedsdatastyrelsen, 2021).

- **Acalabrutinib:** Since acalabrutinib 100 mg is administered orally twice per day until progression or intolerable toxicity, it is assumed that no administration costs accrued.
- **Acalabrutinib + Obinutuzumab:** Acalabrutinib 100 mg is administered twice daily starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab is administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. During Cycle 2 patient receive obinutuzumab 3 times (accounting 100mg on Day 1 and 900mg on Day 2 as one day, and at day 8 and 15) followed by 1,000mg on Day 1 of Cycles 3 up to 7, with 28 days between. In other word, patients receive 8 IV administrations of obinutuzumab at the outpatient care in total for 6 cycles in a year.
- **Ibrutinib:** Since ibrutinib is administered orally three times a day until progression or intolerable toxicity, it is assumed that no administration costs accrued.
- **Bendamustine + Rituximab:** It is assumed that patients receive IV treatment of rituximab once every cycle and twice every cycle of bendamustine. It is further assumed that on day 1 both bendamustine and rituximab are administered and on day 2 only bendamustine is administered. Thus, it is assumed that rituximab accrues no administration costs. In total it is assumed that patients will receive 12 administrations of IV during 6 cycles of 28 days.

- Chlorambucil + Obinutuzumab: As in acalabrutinib + obinutuzumab combination treatment, it is assumed that treating with obinutuzumab will lead to 8 outpatient care visits in the first year. Chlorambucil is assumed to accrue no administration costs during the 6 cycles of treatment.
- Venetoclax + Obinutuzumab: Treatment with obinutuzumab will lead to 8 outpatient care visits in the first 6 cycles. Venetoclax is assumed to accrue no administration costs as it is an orally administered drug.
- Venetoclax + Rituximab (subsequent treatment): Venetoclax is orally administered and patients will receive increasing dose of venetoclax during the ramp-up period every 7<sup>th</sup> day due the risk of developing TLS. After ramp-up period patients start receiving IV treatment of rituximab once every cycle for total of 6 cycles at the outpatient care, resulting in administration costs.

Table 19 shows the administration frequency for each treatment in PU CLL with a respective treatment duration and the resulting monthly frequency accounting for 28 days in one cycle. The tariff attributed to the outpatient care resources for IV administrations are shown in Table 20.

*Table 19. Hospital resource use*

Treatment		Administration in Total	
		Number of Outpatient Care Visits per Cycle	
<b>Acalabrutinib</b>	Acalabrutinib	0	
<b>Acalabrutinib + Obinutuzumab</b>	Acalabrutinib	0	
	Obinutuzumab	3x first cycle 1x every cycle from 2-6 cycles	
<b>Ibrutinib</b>	Ibrutinib	0	
<b>Venetoclax + Obinutuzumab</b>	Venetoclax	0	
	Obinutuzumab	3x first cycle 1x every cycle from 2-6 cycles	
<b>Chlorambucil + Obinutuzumab</b>	Chlorambucil	0	
	Obinutuzumab	3x first cycle 1x every cycle from 2-6 cycles	
<b>Bendamustine + Rituximab</b>	Bendamustine	2	
	Rituximab	0	
<b>Venetoclax + Rituximab (subsequent treatment)</b>	Venetoclax	0	
	Rituximab	1	

*Table 20. Outpatient care cost*

Hospital Resource	Unit Cost (DKK)	DRG Code	Code Description	Source
Ambulatory visit	3203	17MA98	MDC17 1-dagsgruppe, pat. mindst 7 år	DRG 2021 (Sundhedsdatastyrelsen 2021)

### 14.3 Monitoring Costs

Given the lack of information on drug monitoring frequency in the respective EMA SmPCs of the treatments, the following monitoring frequencies are based on AstraZeneca's assumptions verified by the external clinicians (Nørregaard Bentzen & Curovic Rotbain). Monitoring costs accounted for the monitoring frequency of blood tests that are taken each time an IV treatment is administered (see section 14.2) until discontinuation of IV treatment (Sydvestjysk Sygehus, 2017). In addition, costs for yearly monitoring frequencies of other tests were included and were accounted for until disease progression.

The blood tests, necessary for patients receiving IV treatment, were assumed to include lymphocyte count, creatinine count, and total blood count. Since IV related combination treatments are administered in outpatient care with different frequency during 6 cycles (obinutuzumab, bendamustine and rituximab) the blood tests are assumed to be taken in parallel with the administration frequency described in section 14.2. Since the obinutuzumab treatment component is assumed to be administered eight times during the first six cycles, the blood tests are assumed to be done at each administration (equal to an average per cycle blood test frequency of 1,33). The same assumption was used for the bendamustine + rituximab, where in total 12 blood tests are taken within six cycle (average per cycle blood test frequency of 2). It should be noted that ongoing disease monitoring frequency accounts for the blood tests that are performed during the treatment period. Therefore, estimated ongoing monitoring frequencies (0,31 per cycle for each test) were subtracted from the estimated blood test frequencies of the treatment period, to avoid double counting. The administration-dependent test frequencies per cycle for each comparator treatment are shown in Table 21.

**Table 21.** Blood test frequencies over the treatment period estimated per cycle

Monitoring of Patients on IV treatment, per cycle		Lymphocyte Count	Creatinine Count	Total Blood Count
Acalabrutinib + Obinutuzumab	Acalabrutinib			
	Obinutuzumab	1,03	1,03	1,03
Chlorambucil + Obinutuzumab	Chlorambucil			
	Obinutuzumab	1,03	1,03	1,03
Bendamustine + Rituximab	Bendamustine	1,69	1,69	1,69
	Rituximab			
Venetoclax + Obinutuzumab	Venetoclax			
	Obinutuzumab	1,03	1,03	1,03
Venetoclax + Rituximab (subsequent treatment)	Venetoclax			
	Rituximab	0,69	0,69	0,69

Ongoing disease monitoring consists of blood tests and selected additional procedures (CT scan, platelet transfusion, bone marrow test, etc.), and is assumed to be performed for each patient once every third month (0,31 times per cycle). This was verified by two external Danish CLL clinicians (Nørregaard Bentzen & Curovic Rotbain). The ongoing monitoring is assumed to start at the beginning of each therapy and is continued until death. It should be noted that ongoing disease monitoring is assumed for all therapies (both oral and IV). The ongoing monitoring frequency calculated per cycle for each test (applicable to every treatment option) is shown in Table 22.

The unit cost for each test required were derived from 2021 DRG tariffs from sundhedsdatastyrelsen.dk. However, cost for blood tests were derived from Rigshospital Labportal. Whilst the costs for blood tests can be considered as an underestimation, it is argued that any other costs will not impact the result, as the



frequency related to each treatment and the survival data remain unchanged. The costs for various monitoring tests are shown in Table 23.

**Table 22.** Ongoing monitoring frequency estimated per month across treatments

Procedure	Lymphocyte Count	Creatinine Count	Full Blood Count	CT Scan	Platelet Transfusion	Bone Marrow Test	Uric Acid	Biopsy
Frequency per Cycle	0,31	0,31	0,31	0,31	0,31	0,31	0,31	0,31

\*Cost per patient model (per 28 cycle): 0.31

**Table 23.** Monitoring unit costs

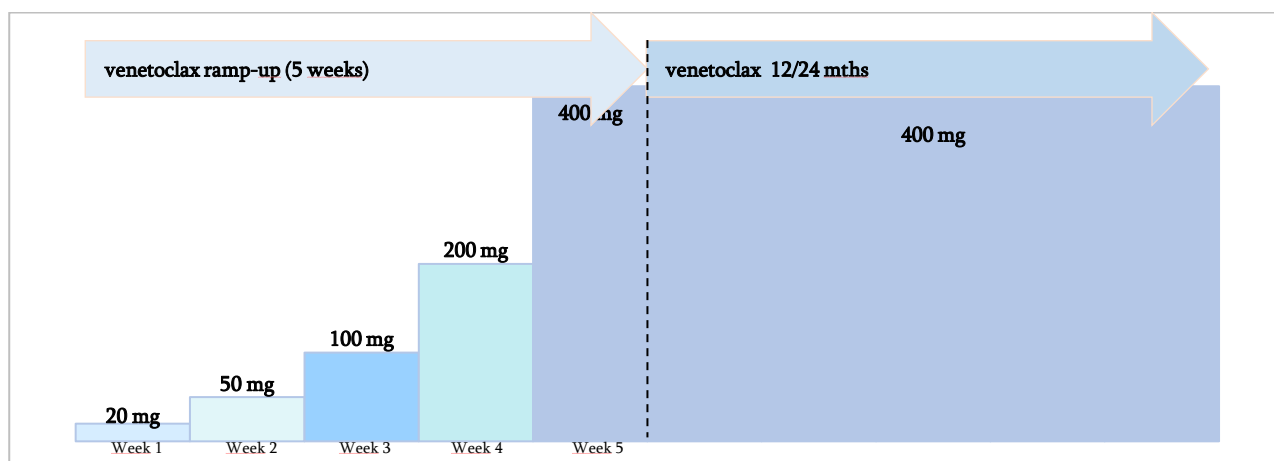
Resource	Cost (DKK)	Code	Code Description	Source
CT Scan	2007	30PR06	CT-scanning, kompliceret	DRG 2021 (Sundhedsdatastyrelsen 2021)
Blood Transfusion	4628	16PR02	Blood transfusion, Transfusion af blod, øvrig	DRG 2021 (Sundhedsdatastyrelsen 2021)
Platelet Transfusion	6042	16PR01	Transfusion af plasma og/eller behandlet blod	DRG 2021 (Sundhedsdatastyrelsen 2021)
Bone Marrow Test	14526	17PR01	Udtagning af knoglemarv til diagnostisk undersøgelse	DRG 2021 (Sundhedsdatastyrelsen 2021)
Lymphocytes Count	13	Lymfomik	-	Rigshospitalets Labportal, ID: 2466
Uric Acid	28	Urat	-	Rigshospitalets Labportal, ID: 5304
Creatinine	28	Crea	-	Rigshospitalets Labportal, ID: 3766
Full Blood Count	71	-	Prøvetagning i AMB, Prisoversigt - Analyser der udføres af KBA i Region Sjælland, KBA	Region Sjælland. Laboratoriemedicinsk Vejledning. ID: 548551
Biopsy	3316	09PR08	Nålebiopsi, overfladisk	DRG 2021 (Sundhedsdatastyrelsen 2021)

#### 14.4 One-Time Monitoring Costs

Monitoring of tumour lysis syndrome (TLS) is needed for all patients initiating venetoclax treatment (Venclyxto SmPC). The analysis accounts for TLS prophylaxis associated costs at treatment initiation as the dose of venetoclax is gradually increased during the first five weeks of treatment, from 20mg daily to 400mg daily (Figure 2).

According to the SmPC, patients being treated with venetoclax have a risk of developing TLS during the ramp-up period which is associated with increased monitoring frequency. To assess the risk, several blood tests among others are taken in the outpatient care every week when the dose is increased. Thus, it is assumed that patients will be monitored for TLS 5 times during the ramp-up period. A unit cost from 2021 DRG tariffs is attributed for the outpatient care resources required for TLS management and is shown in the Table 24 (Sundhedsdatastyrelsen 2020). The tariff code is assumed to include blood tests resources.

**Figure 2.** Dosing scheme for venetoclax in combination with rituximab



**Table 24.** DRG tariff of TLS control unit cost

Resource	Code	Code Description	Unit Cost (DKK)	Source
TLS Prophylaxis	10MA98	MDC10 1-dagsgruppe, pat. mindst 7 år	1518	DRG 2021 (Sundhedsdatastyrelsen 2021)

## 14.5 AE Management

### 14.5.1 AE Unit Costs

The costs of managing drug-related adverse events (AEs) are included in the cost per patient and BI analysis for treatment options in PU CLL population. Only treatment-related Grade  $\geq 3$  AEs that occurred in at least 2% of patients in ELEVATE-TN are included. Further, it is assumed that hospital resource use depends on whether an AE is treated in an outpatient care or a hospital. This assumption was verified by the external clinicians (Nørregaard Bentzen & Curovic Rotbain). Table 25 shows the 2020 DRG, code, description and tariffs attributed to each AE.

Some of the AEs are assumed to require full hospitalisation, whereas other are assumed to be treated in outpatient care. The cost estimates were calculated based on the assumed percentage of patients requiring hospitalisation or outpatient care and the DRG tariffs attributed to each AE, which is shown in Table 25. It is also assumed that treatment of certain AEs will require extra blood tests, hence the price of the full blood test is added to the calculation (DKK 71). It should be noted, that 'ALT/AST increased' adverse event is assumed to not require hospitalisation nor outpatient care, but only blood tests. Five diagnosis groups were identified related to the AEs. These were diseases in the circulatory organs (=05MA), digestive organs (=06MA), hematologic organs (=16MA), infectious and parasitic diseases (=18MA) as well as endocrine diseases, nutritional and metabolic diseases (=10MA). Within these diagnosis groups specific codes related to the hospitalisation and outpatient care (=98) were identified that were corresponding to each AE. Table 26 shows the percentage of patient requiring hospitalization and percentage of patient requiring outpatient care for each AE.

Table 25. Resource use unit cost for treating AEs

Adverse Event	Hospitalisation DRG Code	Hospitalisation Description	Tariff (DKK)	Outpatient Care DRG Code	Outpatient Care Description	Tariff (DKK)	Sources
Abdominal Pain/ Diarrhoea	06MA11	Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	5.103	06MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	2.277	1
Neutropenia	16MA03	Granulo- og trombocytopeni	35.483	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114	1
Leukopenia	16MA03	Granulo- og trombocytopeni	35.483	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114	1
Febrile Neutropenia	16MA03	Granulo- og trombocytopeni	35.483	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114	1
Anaemia	16MA10	Øvrige sygdomme i blod og bloddannende organer	22.545	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114	1
Thrombocytopenia	16MA09	Koagulationsforstyrrelser	25.203	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114	1
Hypotension	05MA15	Observation for sygdom i kredsløbsorganerne	4.684	05MA98	MDC05 1-dagsgruppe, pat. mindst 7 år	1.153	1
Hypertension	05MA11	Hypertension	14.155	05MA98	MDC05 1-dagsgruppe, pat. mindst 7 år	1.153	1
Atrial Fibrillation	05MA07	Hjerterytmi og synkope	15.488	05MA98	MDC05 1-dagsgruppe, pat. mindst 7 år	1.153	1
Tumour Lysis Syndrome	10MA06	Andre ernærings- og stofskiftesygdomme	24.306	10MA98	MDC10 1-dagsgruppe, pat. mindst 7 år	1.518	1
Infections & Infestations	18MA08	Andre infektioner eller parasitære sygdomme	35.768	18MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	2.676	1
Infusion-Related Reactions	18MA09	Observation for infektion eller parasitær sygdom	19.185	18MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	2.676	1
Rash				70AK02	MDC06 1-dagsgruppe, pat. mindst 7 år	481	1
Hyperglycaemia	10MA06	Andre ernærings- og stofskiftesygdomme	24.306	10MA98	MDC06 1-dagsgruppe,	1.518	1

Adverse Event	Hospitalisation DRG Code	Hospitalisation Description	Tariff (DKK)	Outpatient Care DRG Code	Outpatient Care Description	Tariff (DKK)	Sources
					pat. mindst 7 år		
Bleeding				16MA98	MDC06 1-dagsgruppe, pat. mindst 7 år	3.114	1
ALT/AST Increased				Full blood test	Prøvetagning I AMB	71	2
Decreased Neutrophil Count	16MA03	Granulo- og trombocytopeni	35.483	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114	1
Decreased Platelet Count	16MA09	Koagulationsforstyrrelser	25.203	16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	3.114	1

Source: 1. DRG 2020 (Sundhedsdatastyrelsen 2020); 2. Region Sjælland. Laboratoriemedicinsk Vejledning.

**Table 26.** Percentage of patients being treated in inpatient and outpatient care

Adverse Event	Patients Requiring Treatment	Cost Calculation
Abdominal Pain/ Diarrhoea	70% hospitalisation and 30% outpatient care	$(0,7*5130) + (0,3*2277)$
Neutropenia	10% hospitalisation and 90% outpatient care	$(0,1*35483) + (0,9*3114)$
Leukopenia	10% hospitalisation and 90% outpatient care	$(0,1*35438) + (0,9*3114)$
Febrile Neutropenia	100 % hospitalisation	35.483
Anaemia	20% hospitalization and 80% outpatient care + 3 extra blood tests	$(0,2*22545) + (0,8*3114) + (3*71)$
Thrombocytopenia	10% hospitalisation and 90% outpatient care + 3 extra blood tests	$(0,1*22545) + (0,9*3114) + (3*71)$
Hypotension	100 % hospitalisation	4.684
Hypertension	100 % hospitalisation	14.155
Atrial Fibrillation	100 % hospitalisation	15.488
Tumour Lysis Syndrome	100 % hospitalisation	24.306
Infections & Infestations	100 % hospitalisation	35.768
Infusion-Related Reactions	100% outpatient care	2.676
Rash	100% outpatient care	481
Hyperglycaemia	100% outpatient care	1.518
Bleeding	100% outpatient care	3.114
ALT/AST Increased	2x blood tests	$2*71$
Decreased Neutrophil Count	Same assumption as neutropenia	$(0,1*35483) + (0,9*3114)$
Decreased Platelet Count	Same assumption as thrombocytopenia	$(0,1*22.545) + (0,9*3.114) + (3*71)$

## 14.5.2 Adverse Event Incidence Rates

The analysis accounts for the impact of all treatment-related Common Terminology Criteria for Adverse Events (CTCAE) grade  $\geq 3$  AEs that occurred in at least 2% of patients treated with acalabrutinib or any of the comparators. The AE incidence rates applied are presented in Table 27. The rates for acalabrutinib based therapies and chlorambucil + obinutuzumab were sourced from the ELEVATE-TN trial. AE rates for other comparators were sourced from published literature reporting results of relevant clinical trials.

**Table 27.** AE incidence rates for the untreated CLL population

	Acalabrutinib	Acalabrutinib + Obinutuzumab	Chlorambucil + Obinutuzumab	Ibrutinib	Bendamustine + Rituximab	Venetoclax + Obinutuzumab
Abdominal Pain	0.00%	0.00%	0.00%	2.96%	0.00%	0.00%
ALT/AST Increased	0.56%	2.81%	1.78%	0.00%	0.00%	4.25%
Anaemia	6.70%	5.62%	7.10%	5.93%	11.93%	8.02%
Atrial Fibrillation	0	0.6%	0	4.00%	0.00%	0%
Bleeding	1.7%	1.7%	0	6.00%	0.00%	0%
Febrile Neutropenia	1.12%	1.69%	5.33%	2.22%	7.39%	5.19%
Hyperglycaemia	0.00%	0.00%	0.00%	0.00%	0.00%	3.77%
Hypotension	2.25%	2.81%	2.96%	4.44%	10.80%	6.60%
Hypertension	0.56 %	4.49 %	1.78%	3.70%	0.00 %	4.25%
Infections and infestations	14.00%	20.8%	8.3.0%	25.00%	8.52%	17.45%
Infusion-related reaction	0.00%	2.25%	5.33%	0.00%	0.00%	8.96%
Leucopenia	0.00%	0.00%	0.00%	0.00%	0.00%	2.36%
Neutropenia	9.50%	29.78%	41.42%	10.37%	0.00%	52.83%
Neutrophil Count Decreased	0.00%	1.12%	2.96%	0.00%	37.50%	4.25%
Platelet Count Decreased	0.00%	0.00%	0.00%	2.96%	14.20%	0.00%
Rash	0.56%	0.56%	0.00%	2.96%	0.00%	0.00%
Thrombocytopenia	2.79%	8.43%	11.83%	2.22%	0.00%	13.68%
Tumour Lysis Syndrome	0.00%	1.12%	7.69%	0.00%	0.00%	0.00%
Source	[1]	[1]	[1]	[3]	[2]	[4]

[1] AstraZeneca, ACE-CL-007 (ELEVATE-TN) Clinical Study Protocol. 2017. [2] Woyach et al. 2018. [3] Barr et al. 2018. [4] Fischer et al. 2019

## 14.6 Subsequent Treatments

Costs accrued for subsequent treatment were included in the cost per patient and BI analyses. The treatment duration of the subsequent treatments and the subsequent treatment distribution were presented in section 12.2. Costs of subsequent treatments are calculated based on acquisition costs and administration costs related to acalabrutinib monotherapy, ibrutinib, and venetoclax + rituximab, as the expected subsequent treatments for this patient population.

As the cost per patient model tracks the survival of each cohort of patients entering the PD health state, subsequent treatment costs were estimated as follows:

- Per cycle costs (and 1<sup>st</sup> cycle) costs associated with each subsequent treatment were estimated (incl. acquisition, administration and monitoring costs).

- The per cycle costs for each individual subsequent treatment were applied for the defined duration (Table 13, section 12.2). The total subsequent treatment costs applied in each cycle are a weighted average of the per cycle costs and subsequent treatment distribution.
- To reflect the delay between disease progression and subsequent treatment initiation, a treatment free period of 14 cycles was implemented in the analysis.

## 14.7 Patient Time and Transportation Costs

### 14.7.1 Ongoing Monitoring and Costs Related to Treatment

Patient costs were estimated based on the Danish Medicine Council’s guidelines of unit cost evaluation. The patient costs are calculated based on the number of hospital or clinic visits required for each treatment regimen and included ongoing monitoring visits and IV treatment administration and additional monitoring (e.g., blood tests). AE related visits were conservatively excluded. In addition, patient costs associated with IV treatment visits (administration and monitoring) were not included for patients on subsequent treatments which are administered intravenously. For oral therapies, no additional time or visits were considered for collecting medications from the hospital. Discussions with clinicians have highlighted that patients collect medication during routine hospital visits, which for well-treated CLL patients is typically every 3 months in line with monitoring visits (as noted in Section 14.3 above), and therefore no additional costs for travelling to the pharmacy were included.

The health care visits include the effective time at the outpatient clinic associated with the resource use estimates (Table 28), and include the total patient time and transport time. Transport time is assumed to be one hour per visit (30 minutes each way). The average patient time per visit, including waiting time, was assumed to be 5 hours. The monetary value for patient time according to the Danish Medicine Council’s guidelines was DKK 179 per hour. The transport cost was set to DKK 100 (equivalent to 14 km) per visit to the health care clinic and back home.

**Table 28.** Patient time associated with drug monitoring visits

Resource	Time Taken	Sources / Notes
CT Scan	10 to 20 mins	NHS England ( <a href="https://www.nhs.uk/conditions/ct-scan/">https://www.nhs.uk/conditions/ct-scan/</a> )
Blood Transfusion	2 to 4 hours	Memorial Sloan Kettering Cancer Center ( <a href="https://www.mskcc.org/cancer-care/patient-education/about-blood-transfusion">https://www.mskcc.org/cancer-care/patient-education/about-blood-transfusion</a> )
Platelet Transfusion	30 to 60 mins	
Bone Marrow Test	30 minutes	Cancer.Net ( <a href="https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/bone-marrow-aspiration-and-biopsy">https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/bone-marrow-aspiration-and-biopsy</a> )
Biopsy		
Lymphocyte Count	5 minutes	Assumption based on a single visit to the phlebotomy clinic
Creatinine Count		
Total Blood Count		
Uric Acid		
Waiting Time	25 minutes	Assumption
Travel Time	1 hour	Assumption
Total Time per Visit	6 hours	Calculated

Patient costs were calculated based on the same disease monitoring frequencies by each treatment option as assumed in section 14.3 of monitoring cost. Table 29 presents the patient cost calculation associated with yearly monitoring. The total number of visits was multiplied by the time per visit. The patient time for visits and transport is multiplied with the unit cost for patient time. The total patient costs include the patient time costs and the transport costs. The patient costs associated with yearly monitoring were accounted both for PD and PD health states in the cost per patient model.

**Table 29. Estimated patient costs for time and transport, yearly monitoring**

Cost Unit	Acalabrutinib	Acalabrutinib + Obinutuzumab	Chlorambucil + obinutuzumab	Bendamustine + Rituximab	Venetoclax + Obinutuzumab	Ibrutinib
<b>Monitoring frequencies (per 28 day cycle)</b>						
CT Scan	0,31	0,31	0,31	0,31	0,31	0,31
Blood Transfusions	0,31	0,31	0,31	0,31	0,31	0,31
Platelet Transfusion	0,31	0,31	0,31	0,31	0,31	0,31
Bone Marrow Test	0,31	0,31	0,31	0,31	0,31	0,31
Lymphocyte Count	0,31	0,31	0,31	0,31	0,31	0,31
Creatinine Count	0,31	0,31	0,31	0,31	0,31	0,31
Total Blood Count	0,31	0,31	0,31	0,31	0,31	0,31
Uric Acid	0,31	0,31	0,31	0,31	0,31	0,31
Biopsy	0,31	0,31	0,31	0,31	0,31	0,31
<b>Number of Visits per Cycle</b>	<b>0,31</b>	<b>0,31</b>	<b>0,31</b>	<b>0,31</b>	<b>0,31</b>	<b>0,31</b>
<b>Patient time consumption (per visit)</b>						
Patient time, visits (hours)	5	5	5	5	5	5
Patient time, transport (hours)	1	1	1	1	1	1
<b>Patient costs (per 28 days cycle)</b>						
Patient time, visits cost (DKK)	895	895	895	895	895	895
Patient time, transport cost (DKK)	179	179	179	179	179	179
Transport cost (DKK)	100	100	100	100	100	100
<b>Total patient cost per cycle*</b>	<b>1174*0,31 = 361,23</b>	<b>1174*0,31 = 361,23</b>	<b>1174*0,31 = 361,23</b>	<b>1174*0,31 = 361,23</b>	<b>1174*0,31 = 361,23</b>	<b>1174*0,31 = 361,23</b>

\*Patient time cost (DKK) + transport cost (DKK)

Table 30 presents the patient costs associated with administration visits and monitoring assumed for patients on IV treatments (administration and blood tests). To avoid double counting patient costs for the months when patients would also have the ongoing monitoring visits, the same monitoring frequencies were used as presented in section 13.3, assuming that tests and travel costs would only be accrued on the additional visits required. For these visits it was arbitrarily assumed that the time for blood tests (including waiting time) would be around 20 minutes. Patient time for drug administration per treatment cycle was also included, based on the estimated infusion times from the SmPC for each of the IV products. No additional travel time or travel costs were included for drug administration as it was additional assumed tests and monitoring would be conducted on the same days as drug administration.

**Table 30.** Estimated patient costs for time and transport, IV treatment administration visits and monitoring<sup>1</sup>

Cost Unit	Acalabrutinib + Obinutuzumab	Chlorambucil + obinutuzumab	Bendamustine + Rituximab	Venetoclax + Obinutuzumab
<b>Additional Monitoring Frequencies (Admin Visits per 28 day cycle)</b>				
Lymphocyte Count	1,03	1,03	1,69	1,03
Creatinine Count	1,03	1,03	1,69	1,03
Total Blood Count	1,03	1,03	1,69	1,03
<b>Number of Visits per Cycle</b>	<b>1,03</b>	<b>1,03</b>	<b>1,69</b>	<b>1,03</b>
<b>Patient Time Consumption (per visit)</b>				
Patient Time, Visits (hours)	0,33	0,33	0,33	0,33
Patient Time, Transport (hours)	1	1	1	1
<b>Patient Costs (per 28 days cycle)</b>				
Patient Time, Visits (DKK)	60	60	60	60
Patient Time, Transport (DKK)	179	179	179	179
Transport Cost (DKK)	100	100	100	100
Total Patient Cost per Cycle*	339*1,03 = 347,35	339*1,03 = 347,35	339*1,69 = 57313	339*1,03 = 347,35
<b>Patient Costs for Drug Administration (per 28 days cycle)</b>				
Patient Time, Drug Administration, (hours)	6,04**	6,04**	4,08***	6,04**
Total Patient Cost per Cycle	1081,46	1081,46	730,92	1081,46

<sup>1</sup> The analysis did not consider the patient costs associated with outpatient visits for administration and monitoring (blood tests) of patients on subsequent treatment (IV). This was estimated to have negligible impact on results.

\*Patient time cost (DKK) + transport cost (DKK)

\*\* As per the SmPC, obinutuzumab is assumed to be administered over 4 hours on days 1 and 2 of cycle 1 with an IV corticosteroid administered 1 hour prior to infusion (5 hours total), with all subsequent doses (max 8 administrations over 6 cycles) administered over ~3h15m with an oral analgesic administered 30 minutes before infusion (3h45m total). Minimum estimated time in hospital is therefore 36h15m, distributed over 6 cycles

\*\*\* Based on the SmPC, bendamustine is administered over 30-60 minutes (30 mins conservatively assumed) for two days per cycle, and based on the modelled patient weight, rituximab would administered over ~3,5 hours in the first cycle and ~3 hours in the subsequent 5 cycles. Minimum estimated time in hospital is 24h30m, distributed over 6 cycles

## 14.7.2 One-Time Monitoring Patient Costs

Costs for patient time and transport were calculated for patients treated with venetoclax-based treatment (venetoclax + obinutuzumab) due to the ramp-up period using similar approach as presented above. Thus, the total patient cost was calculated based on the 5 times patients will get tested for TLS during the ramp-up period. The total number of visits was multiplied by the time per visit, which was assumed to be 20 minutes including waiting time, and multiplied by the transport time, assumed to be one hour per visit. The 20 minutes TLS control visit was assumed to include risk assessment of blood tests. The same monetary value of transport and patient time as in calculations above was utilised. Patient costs during ramp-up are shown in Table 31.

**Table 31.** Patient costs included in the ramp-up for venetoclax-based treatment

Patient Cost Unit	Venetoclax + Obinutuzumab
TLS Prophylaxis: Number of Visits During 1 <sup>st</sup> Cycle	5
Patient Time, Visits (hours)	1,67 (20 min * 5)
Patient Time, Transport (hours)	5 (1 hour *5)
Patient Time, Visits (DKK)	298,33 (179*1,67)
Patient Time, Transport (DKK)	895,00 (179*7,5)
Transport Cost (DKK)	500,00 (100*5)
Total Patient Cost for TLS Prophylaxis (DKK)	<b>1.693,33</b>



## 15 Results

### 15.1 Cost per Patient Analysis

#### 15.1.1 Base Case Analysis

The results of the cost per patient analysis for patients with untreated CLL shows the average costs per patient over 30 years for patients without 17p deletion/TP53 mutation (Table 32) and for patients with 17p deletion/TP53 mutation (Table 33). The drug acquisition costs constitute a major part of the total costs for acalabrutinib based therapies and ibrutinib.

The total costs per patient (without 17p deletion/TP53 mutation) over 30 years show that acalabrutinib monotherapy is associated with DKK [REDACTED] higher costs per patient than chlorambucil + obinutuzumab, and DKK [REDACTED] higher costs per patient than bendamustine + rituximab. The total costs per patient (without 17p deletion/TP53 mutation) over 30 years show that acalabrutinib + obinutuzumab combination therapy is associated with DKK [REDACTED] higher costs per patient than chlorambucil + obinutuzumab, and DKK [REDACTED] higher costs per patient than bendamustine + rituximab. The cost breakdown per patient without 17p deletion/TP53 mutation is presented in Figure 3.

**Table 32.** Average costs per patient for acalabrutinib based therapies vs chlorambucil + obinutuzumab and rituximab + bendamustine for patients without 17p deletion/TP53 mutation (ITT)

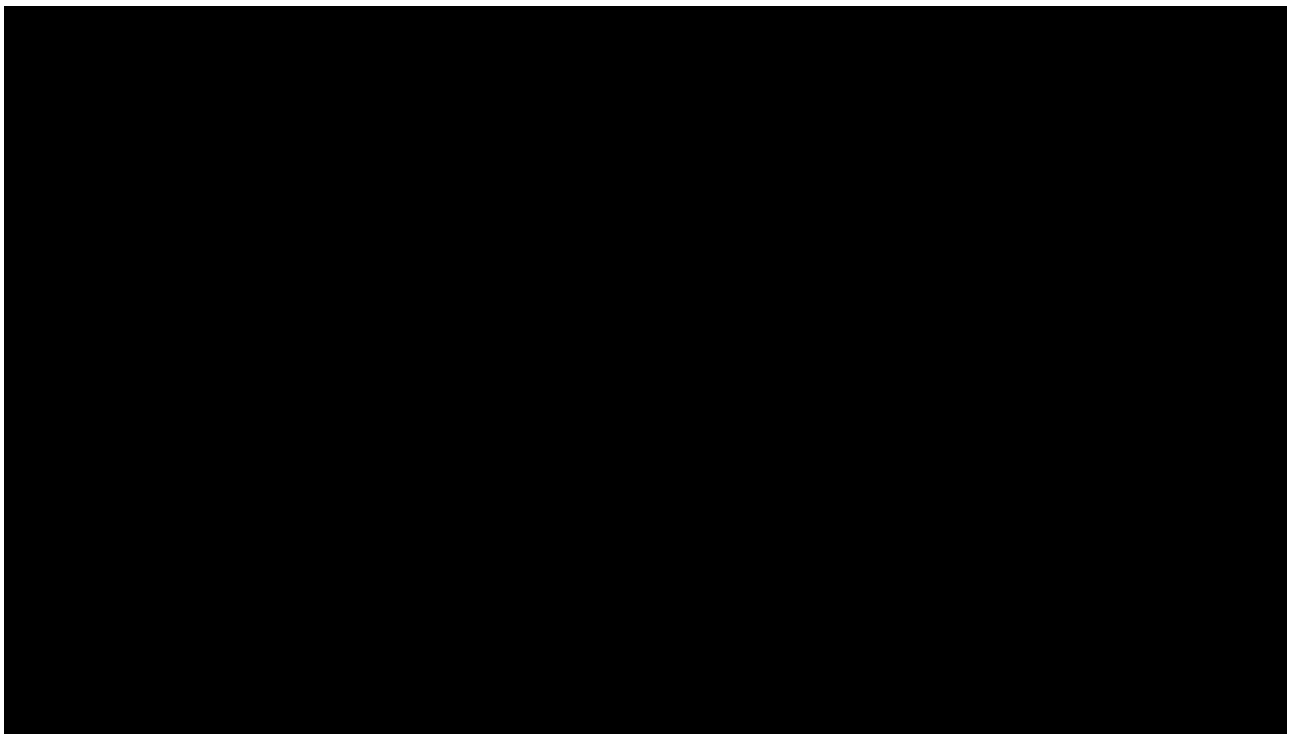
Cost Category	Total Costs per Treatment (DKK)				Incremental Costs (DKK): Acala vs.		Incremental Costs (DKK): Acala + Obin vs.	
	Acala	Acala + Obin	Chlor + Obin	BR	Chlor + Obin	BR	Chlor + Obin	BR
Disease Management	1 336 703	1 469 496	1 125 641	1 005 382	211 063	331 321	343 855	464 113
Drug Acquisition	[REDACTED]	[REDACTED]	208 735	90 215	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Drug Administration	-	33 968	33 823	43 848	-33 823	-43 848	146	-9 880
Treatment Monitoring	-	914	910	1 297	-910	-1 297	4	-384
Adverse Events	6 886	12 125	11 249	10 204	-4 363	-3 317	877	1 922
Subsequent Treatments	622 674	500 473	953 177	683 301	-330 503	-60 627	-452 704	-182 828
Patient Costs	51 185	64 796	51 596	46 120	-411	5 065	13 199	18 676
<b>Total Costs</b>	[REDACTED]	[REDACTED]	<b>2 385 130</b>	<b>1 880 368</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The total costs per patient (with 17p deletion/TP53 mutation) over 30 years show that acalabrutinib monotherapy is associated with DKK [REDACTED] higher costs per patient than venetoclax + obinutuzumab, and cost savings of DKK [REDACTED] when compared to ibrutinib. The total costs per patient (with 17p deletion/TP53 mutation) over 30 years show that acalabrutinib + obinutuzumab combination therapy is associated with DKK [REDACTED] higher costs per patient than venetoclax + obinutuzumab, and DKK [REDACTED] higher costs per patient than ibrutinib. The cost breakdown per patient with 17p deletion/TP53 mutation is presented in Figure 4.

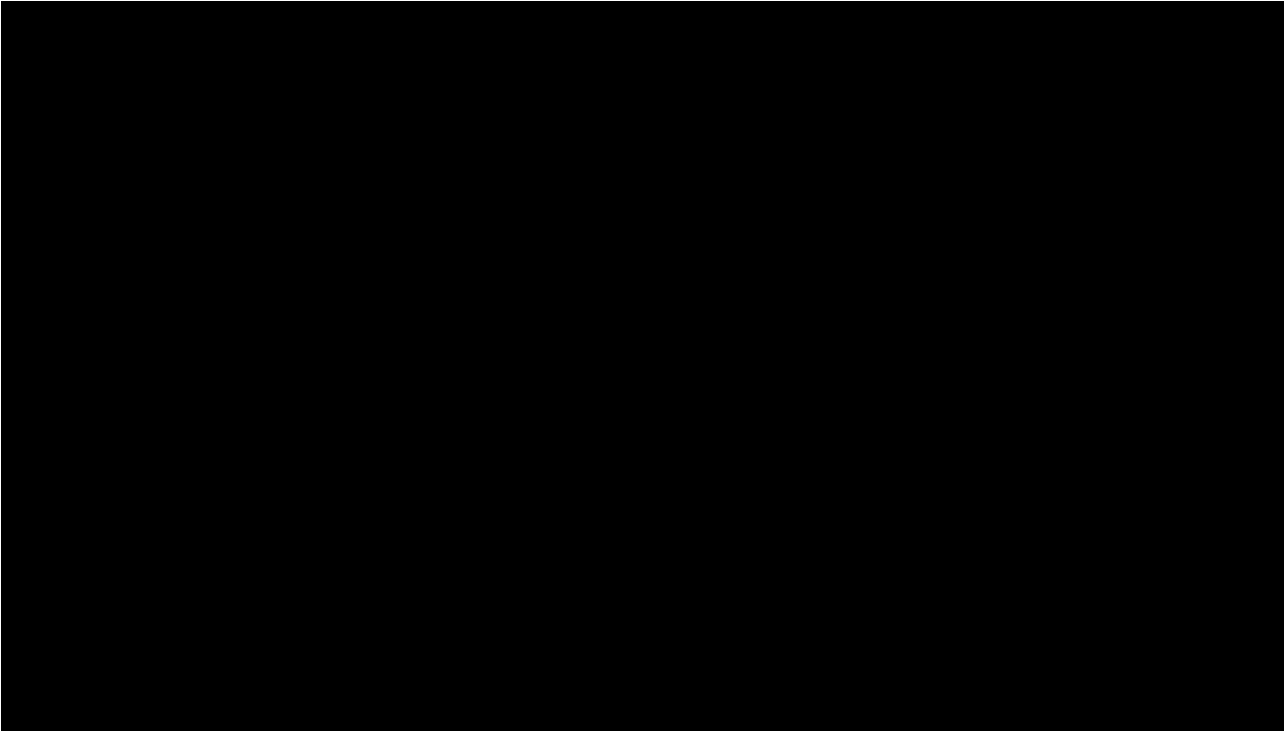
**Table 33.** Average costs per patient for acalabrutinib based therapies vs ibrutinib and venetoclax + obinutuzumab for patient population with 17p deletion/TP53 mutation

Cost Category	Total Costs per Treatment (DKK)				Incremental Costs (DKK): Acala vs.		Incremental Costs (DKK): Acala + Obin vs.	
	Acala	Acala + Obin	Ibrutinib	Ven + Obin	Ibrutinib	Ven + Obin	Ibrutinib	Ven + Obin
Disease Management	1 182 126	1 182 126	1 182 126	1 182 126	-	-	-	-
Drug Acquisition	████████	████████	████████	708 204	████████	████████	████████	████████
Drug Administration	-	33 702	-	33 702	-	-33 702	33 702	-
Treatment Monitoring	-	907	-	8 497	-	-8 497	907	-7 590
Adverse Events	6 886	12 125	12 783	14 407	-5 897	-7 521	-658	-2 282
Subsequent Treatments	571 141	571 141	571 141	898 033	-	-326 892	-	-326 892
Patient Costs	45 266	53 728	45 266	55 421	-	-10 155	8 462	-1 693
<b>Total Costs</b>	████████	████████	████████	<b>2 900 390</b>	████████	████████	████████	████████

**Figure 3.** Cost per patient breakdown over 30 years for patients without 17p deletion/TP53 mutation



*Figure 4. Cost per patient breakdown over 30 years for patients with 17p deletion/TP53 mutation*



#### 15.1.2 Scenario Analyses (Patients without 17p deletion/TP53 mutation)

Scenario analyses for acalabrutinib monotherapy versus chlorambucil + obinutuzumab and bendamustine + rituximab were performed for key variables and assumptions in the model (Table 34 and Table 35). The parameters included in the sensitivity analyses were the discount rate, time horizon, medication wastage, drug acquisition costs, disease management costs, AE costs, patient time and transport costs, patient distribution in subsequent (2L) treatment and parametric models used for extrapolation of PFS and PPS, as well as the modelling approach for PPS. Except for the discount rate, time horizon, medication wastage and the choice of the parametric models, all parameters were varied with  $\pm 20\%$  or percentage points.

The results were most sensitive to drug acquisition costs for acalabrutinib, changes in discount rate, time horizon, extrapolation method of acalabrutinib TTP curve, and the duration of subsequent treatments applied, and relatively insensitive to the other parameters.

**Table 34.** Scenario analyses for acalabrutinib monotherapy versus chlorambucil + obinutuzumab

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference	% Change
			Acala	Chlo + Obin		
Base Case		-		2 385 130		-
Discount Rate	3,5 %	0 %		2 837 267		+19%
		2 %		2 555 823		+7%
		5 %		2 240 473		-7%
Time Horizon	30 years	1 years		407 024		-86%
		2 years		609 855		-69%
		5 years		1 667 855		-50%
Medication Wastage	Excluded	Included		2 388 034		+0%
Drug Acquisition Cost: Acalabrutinib	45,224 DKK	-20 %		2 288 105		-19%
		+ 20 %		2 482 155		+19%
Drug Acquisition Cost: Chlorambucil	527 DKK	-20 %		2 383 975		+0%
		+ 20 %		2 386 285		-0%
Drug Acquisition Cost: Obinutuzumab	25,627 DKK	-20 %		2 344 538		+2%
		+ 20 %		2 425 722		-2%
Administration Cost	3,203 DKK	-20 %		2 376 814		+0%
		+ 20 %		2 393 447		-0%
Disease Management Costs	9,434 DKK	-20 %		2 160 002		-2%
		+ 20 %		2 610 259		+2%
Monitoring Costs for IV Treatments	115 DKK	-20 %		2 384 911		+0%
		+ 20 %		2 385 350		-0%
Total AE Costs*	6,886 DKK for Acala mono and 11,249 DKK for Chlo + Obin	-20 %		2 382 881		+0%
		+ 20 %		2 387 380		-0%
Patient Time & Transport cost	361 DKK	-20 %		2 376 510		-0%
		+ 20 %		2 393 751		+0%
Extrapolation Acala Monotherapy	TTP: Gompertz	Weibull		2 385 130		+55%
	TTD: Exponential	Weibull		2 385 130		-3%
Extrapolation Chlo + Obin	TTP: Log-normal	Gen gamma		2 352 065		+1%
	TTD: Exponential	Weibull		2 395 766		-0%
PPS Source	8. ELEVATE-RR OS	<b>Acala:</b> 4. ELEVATE PPS (Pooled Acalabrutinib arms) + ASCEND OS (IR/BR arm) <b>Chlo + Obin:</b> 2. ELEVATE PPS (O+C arm) + ASCEND OS (Acalabrutinib arm)		2 453 146		-5%
PPS Distribution for Acala Monotherapy and Chlo + Obin	Exponential	Weibull		2 418 140		-1%
		Gen gamma		2 261 883		+2%
Subsequent Treatment Distribution after Acala Monotherapy	Ven + R 100%	- 20% for Ven + R , + 20% for Ibru		2 385 130		+3%

<b>Subsequent Treatment Distribution after Chlo + Obin</b>	Acala 40%, Ibru 5%, Ven + R 55%	- 20 percentage points for Acala, + 20 percentage points for Ibru	██████████	2 384 597	██████████	+0%
		- 20 percentage points for Acala, + 20 percentage points for Ven + R	██████████	2 290 766	██████████	+4%
		+ 20 percentage points for Acala, - 5 percentage points for Ibru and - 15 percentage points for Ven + R	██████████	2 456 037	██████████	-3%
		+ 20 percentage points for Acala, - 20 percentage points for Ven + R	██████████	2 479 495	██████████	-4%
<b>Mean Duration of Subsequent Treatments</b>	██████████ cycles (ELEVATE-RR PFS IRC)	82,73 cycles (ASCEND PFS IRC)	██████████	3 038 222	██████████	-25%

\*Total AEs costs over 30 years

**Table 35. Scenario analyses for acalabrutinib monotherapy versus bendamustine + rituximab**

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acala	BR		
Base Case		-		1 880 368		-
Discount Rate	3,5 %	0 %		2 298 146		+17%
		2 %		2 037 952		+7%
		5 %		1 747 165		-6%
Time Horizon	30 years	1 years		293 380		-85%
		2 years		451 178		-69%
		5 years		1 072 100		-39%
Medication Wastage	Excluded	Included		1 891 313		-0%
Drug Acquisition Cost: Acalabrutinib	45.224 DKK	-20 %		1 810 814		-17%
		20 %		1 949 922		+17%
Drug Acquisition Cost: Bendamustine	367 DKK	-20 %		1 878 993		+0%
		20 %		1 881 743		-0%
Drug Acquisition Cost: Rituximab	6.687 DKK	-20 %		1 859 469		+0%
		20 %		1 901 267		-0%
Administration Cost	3.203 DKK	-20 %		1 870 485		+0%
		20 %		1 890 250		-0%
Disease Management Costs	9.434 DKK	-20 %		1 679 291		-2%
		20 %		2 081 444		+2%
Monitoring Costs for IV Treatments	115 DKK	-20 %		1 880 082		+0%
		20 %		1 880 654		-0%
AE Costs*	6.886 DKK for Acala mono and 10.204 DKK for BR	-20 %		1 878 327		+0%
		20 %		1 882 409		-0%
Patient Time & Transport Cost	361 DKK	-20 %		1 872 668		-0%
		20 %		1 888 068		+0%
Extrapolation Acala Monotherapy	TTP: Gompertz	Weibull		1 880 368		+46%
	TTD: Exponential	Weibull		1 880 368		-3%
Extrapolation BR	HR via MAIC	HR via NMA		1 746 939		+4%
PPS Source	8. ELEVATE-RR OS	<b>Acala:</b> 4. ELEVATE PPS (Pooled Acalabrutinib arms) + ASCEND OS (IR/BR arm)		1 923 855		-3%
		<b>BR:</b> 2. ELEVATE PPS (O+C arm) + ASCEND OS (Acalabrutinib arm)				
PPS Distribution for Acala Monotherapy and BR	Exponential	Weibull		1 900 852		-0%
		Gen gamma		1 799 521		+0%
Subsequent Treatment Distribution after Acala Monotherapy	Ven + R 100%	- 20% for Ven + R , + 20% for Ibru		1 880 368		+3%
Subsequent Treatment Distribution after BR	Acala 40%, Ibru 5%, Ven + R 55%	- 20 percentage points for Acala, + 20 percentage points for Ibru		1 879 986		+0%

		- 20 percentage points for Acala, + 20 percentage points for Ven + R	████████	1 812 721	████████	+2%
		+ 20 percentage points for Acala, - 5 percentage points for Ibru and - 15 percentage points for Ven + R	████████	1 931 198	████████	-2%
		+ 20 percentage points for Acala, - 20 percentage points for Ven + R	████████	1 948 014	████████	-2%
<b>Mean Duration of Subsequent Treatments</b>	██████ cycles (ELEVATE-RR PFS IRC)	82,73 cycles (ASCEND PFS IRC)	████████	2 348 547	████████	-15%

\*Total AEs costs over 30 years

Scenario analyses for acalabrutinib + obinutuzumab combination therapy versus chlorambucil + obinutuzumab and bendamustine + rituximab were performed for key variables and assumptions in the model (Table 36 and Table 37). The parameters included in the sensitivity analyses were the discount rate, time horizon, medication wastage, drug acquisition costs, disease management costs, AE costs, patient time and transport costs, patient distribution in subsequent (2L) treatment and parametric models used for extrapolation of PFS and PPS, as well as the modelling approach for PPS. Except for the discount rate, time horizon, medication wastage and the choice of the parametric models, all parameters were varied with  $\pm 20\%$  or percentage points.

The results were also most sensitive to drug acquisition costs for acalabrutinib, changes in discount rate, time horizon, extrapolation method of acalabrutinib + obinutuzumab TTP curve, and duration of subsequent treatments applied, and relatively insensitive to the other parameters.

**Table 36. Scenario analyses for acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab**

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference	% Change
			Acala + Obin	Chlo + Obin		
Base Case		-		2 385 130		-
Discount Rate	3,5 %	0 %		2 837 267		+28%
		2 %		2 555 823		+10%
		5 %		2 240 473		-9%
Time Horizon	30 years	1 years		407 024		-85%
		2 years		609 855		-75%
		5 years		1 667 855		-60%
Medication Wastage	Excluded	Included		2 388 034		+0%
Drug Acquisition Cost: Acalabrutinib	45.224 DKK	-20 %		2 288 105		-18%
		+ 20 %		2 482 155		+18%
Drug Acquisition Cost: Chlorambucil	527 DKK	-20 %		2 383 975		+0%
		+ 20 %		2 386 285		-0%
Drug Acquisition Cost: Obinutuzumab	25.627 DKK	-20 %		2 344 538		-0%
		+ 20 %		2 425 722		+0%
Administration Cost	3.203 DKK	-20 %		2 376 814		-0%
		+ 20 %		2 393 447		+0%
Disease Management Costs	9.434 DKK	-20 %		2 160 002		-2%
		+ 20 %		2 610 259		+2%
Monitoring Costs for IV Treatments	115 DKK	-20 %		2 384 911		-0%
		+ 20 %		2 385 350		+0%
Total AE Costs*	12.125 DKK for Acala + Obi and 11.552 DKK for Chlo + Obin	-20 %		2 382 881		-0%
		+ 20 %		2 387 380		+0%
Patient Time & Transport cost	361 DKK	-20 %		2 376 510		-0%
		+ 20 %		2 393 751		+0%
Extrapolation Acala + Obin	TTP: Weibull	Gompertz		1 938 806		-2%
	TTD: Exponential	Gompertz		2 052 091		-6%
Extrapolation Chlo + Obin	TTP: Log-normal	Gen gamma		2 352 065		+1%
	TTD: Exponential	Weibull		2 395 766		-0%
PPS Source	8. ELEVATE-RR OS	<b>Acala + Obin:</b> 4. ELEVATE PPS (Pooled Acalabrutinib arms) + ASCEND OS (IR/BR arm)  <b>Chlo + Obin:</b> 2. ELEVATE PPS (O+C arm) + ASCEND OS (Acalabrutinib arm)		2 453 146		-2%
PPS Distribution for Acala + Obin and Chlo + Obin	Exponential	Weibull		2 418 140		-1%
		Gen gamma		2 261 883		+2%
Subsequent Treatment Distribution after Acala + Obin	Ven + R 100%	- 20% for Ven + R , + 20% for Ibru		2 385 130		+2%
Subsequent Treatment Distribution after Chlo + Obin	Acala 40%, Ibru 5%, Ven + R 55%	- 20 percentage points for Acala, +		2 384 597		+0%



		20 percentage points for Ibru				
		- 20 percentage points for Acala, + 20 percentage points for Ven + R	██████████	2 290 766	██████████	+2%
		+ 20 percentage points for Acala, - 5 percentage points for Ibru and - 15 percentage points for Ven + R	██████████	2 456 037	██████████	-2%
		+ 20 percentage points for Acala, - 20 percentage points for Ven + R	██████████	2 479 495	██████████	-2%
<b>Mean Duration of Subsequent Treatments</b>	██████████ cycles (ELEVATE-RR PFS IRC)	82,73 cycles (ASCEND PFS IRC)	██████████	3 038 222	██████████	-16%

\*Total AEs costs over 30 years

**Table 37. Scenario analyses for acalabrutinib + obinutuzumab versus bendamustine + rituximab**

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acala + Obin	BR		
Base Case		-		1 880 368		-
Discount Rate	3,5 %	0 %		2 298 146		+25%
		2 %		2 037 952		+10%
		5 %		1 747 165		-8%
Time Horizon	30 years	1 years		293 380		-84%
		2 years		451 178		-74%
		5 years		1 072 100		-52%
Medication Wastage	Excluded	Included		1 891 313		-0%
Drug Acquisition Cost: Acalabrutinib	45.224 DKK	-20 %		1 810 814		-17%
		20 %		1 949 922		+17%
Drug Acquisition Cost: Obinutuzumab	25.627 DKK	-20 %		1 880 368		-1%
		20 %		1 880 368		+1%
Drug Acquisition Cost: Bendamustine	367 DKK	-20 %		1 878 993		+0%
		20 %		1 881 743		-0%
Drug Acquisition Cost: Rituximab	6.687 DKK	-20 %		1 859 469		+0%
		20 %		1 901 267		-0%
Administration Cost	3.203 DKK	-20 %		1 870 485		+0%
		20 %		1 890 250		-0%
Disease Management Costs	9.434 DKK	-20 %		1 679 291		-2%
		20 %		2 081 444		+2%
Monitoring Costs for IV Treatments	115 DKK	-20 %		1 880 082		+0%
		20 %		1 880 654		-0%
Total AE Costs*	12.125 DKK for Acala + Obin and 10.204 DKK for B + R	-20 %		1 878 327		-0%
		20 %		1 882 409		+0%
Patient Time & Transport Cost	361 DKK	-20 %		1 872 668		-0%
		20 %		1 888 068		+0%
Extrapolation Acala + Obin	TTP: Weibull	Gompertz		1 938 806		-32%
	TTD: Exponential	Gompertz		2 052 091		-3%
Extrapolation BR	HR via MAIC	HR via NMA		1 746 939		+3%
PPS Source	8. ELEVATE-RR OS	<b>Acala + Obin:</b> 4. ELEVATE PPS (Pooled Acalabrutinib arms) + ASCEND OS (IR/BR arm)		1 923 855		-2%
		<b>BR:</b> 2. ELEVATE PPS (O+C arm) + ASCEND OS (Acalabrutinib arm)				
PPS Distribution for Acala + Obin and B + R	Exponential	Weibull		1 900 852		-0%
		Gen gamma		1 799 521		+1%
Subsequent Treatment Distribution after Acala + Obin	Ven + R 100%	- 20% for Ven + R, + 20% for lbru		1 880 368		+1%

<b>Subsequent Treatment Distribution after BR</b>	Acala 40%, Ibru 5%, Ven + R 55%	- 20 percentage points for Acala, + 20 percentage points for Ibru	██████████	1 879 986	██████████	+0%
		- 20 percentage points for Acala, + 20 percentage points for Ven + R	██████████	1 812 721	██████████	+1%
		+ 20 percentage points for Acala, - 5 percentage points for Ibru and - 15 percentage points for Ven + R	██████████	1 931 198	██████████	-1%
		+ 20 percentage points for Acala, - 20 percentage points for Ven + R	██████████	1 948 014	██████████	-1%
<b>Mean Duration of Subsequent Treatments</b>	██████████ cycles (ELEVATE-RR PFS IRC)	82,73 cycles	██████████	2 348 547	██████████	-10%

\*Total AEs costs over 30 years

### 15.1.3 Scenario Analyses (Patients with 17p deletion/TP53 mutation)

Scenario analyses for acalabrutinib monotherapy versus ibrutinib and venetoclax + obinutuzumab were performed for the discount rate, time horizon, medication wastage, drug acquisition costs, and patient distribution in subsequent (2L) treatment (Table 38 and Table 39). Based on the assumption of comparable efficacy between acalabrutinib, ibrutinib and venetoclax + obinutuzumab, there is no need to provide scenario analyses for different extrapolation methods. The results were most sensitive to drug acquisition costs, changes in discount rate, time horizon and patient distribution in subsequent treatment.

**Table 38.** Scenario analyses for acalabrutinib monotherapy versus ibrutinib

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acala	Ibru		
<b>Base Case</b>		-	██████████	██████████	██████████	-
<b>Discount Rate</b>	3,5 %	0 %	██████████	██████████	██████████	+96%
		2 %	██████████	██████████	██████████	+39%
		5 %	██████████	██████████	██████████	-36%
<b>Time Horizon</b>	30 years	1 years	██████████	██████████	██████████	-750%
		2 years	██████████	██████████	██████████	-562%
		5 years	██████████	██████████	██████████	-190%
<b>Medication Wastage</b>	Excluded	Included	██████████	██████████	██████████	+0%
<b>Drug Acquisition Cost: Acalabrutinib</b>	45.224 DKK	-20 %	██████████	██████████	██████████	-90960%
		20 %	██████████	██████████	██████████	90960%
<b>Drug Acquisition Cost: Ibrutinib</b>	45.125 DKK	-20 %	██████████	██████████	██████████	90760%
		20 %	██████████	██████████	██████████	-90760%
<b>Subsequent Treatment Distribution after Ibru*</b>	Ven + R 100%	- 20% for Ven + R, + 20% for Acala	██████████	██████████	██████████	-13570%

\* It is possible that patients who progress after ibrutinib due to adverse events would receive acalabrutinib in 2L.

**Table 39.** Scenario analyses for acalabrutinib monotherapy versus venetoclax + obinutuzumab

Parameter	Base case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acala	Ven + Obin		
Base Case		-		2 900 390		-
Discount Rate	3,5 %	0 %		3 477 644		+12%
		2 %		3 117 961		+5%
		5 %		2 716 888		-5%
Time Horizon	30 years	1 years		918 148		-112%
		2 years		1 032 165		-78%
		5 years		1 378 449		-9%
Medication Wastage	Excluded	Included		2 900 797		+0%
Drug Acquisition Cost: Acalabrutinib	45.224 DKK	-20 %		2 769 516		-27%
		20 %		3 031 263		+27%
Drug Acquisition Cost: Venetoclax	40.010 DKK	-20 %		2 788 912		+1%
		20 %		3 011 868		-1%
Drug Acquisition Cost: Obinutuzumab	25.627 DKK	-20 %		2 859 943		+3%
		20 %		2 940 837		-3%
Subsequent Treatment Distribution after Acala Monotherapy	Ven + R 100%	- 20% for Ven + R, + 20% for Ibru		2 900 390		+5%
Subsequent Treatment Distribution after Ven + Obin	Acala 70%, Ibru 20% and Ven + R 10%	- 20 percentage points for Acala, + 20 percentage points for Ven + R		2 827 656		+5%
		- 20 percentage points for Acala, + 20 percentage points for Ibru		2 899 979		+0%
		+ 20 percentage points for Acala, - 10 percentage points for Ven + R and - 10 percentage points for Ibru		2 936 962		-3%
		+ 20 percentage points for Acala, - 20 percentage points for Ibru		2 900 801		-0%
PPS Source	8. ELEVATE-RR OS	5. ASCEND OS (Acalabrutinib arm)		2 973 917		+0%
Mean Duration of Subsequent Treatments	█ cycles (ELEVATE-RR PFS IRC)	82,73 cycles (ASCEND PFS IRC)		3 892 051		-73%

Scenario analyses for acalabrutinib + obinutuzumab combination therapy versus ibrutinib and venetoclax + obinutuzumab were performed for the discount rate, time horizon, medication wastage, drug acquisition costs, administration costs and patient distribution in subsequent (2L) treatment (Table 40 and Table 41). Based on the assumption of comparable efficacy between acalabrutinib, ibrutinib and venetoclax +

obinutuzumab, there is no need to provide scenario analyses for different extrapolation methods. The results were most sensitive to drug acquisition costs, changes in discount rate, time horizon, duration of subsequent treatments, and subsequent treatment for ibrutinib arm.

**Table 40.** Scenario analyses for acalabrutinib + obinutuzumab versus ibrutinib

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acala + Obin	Ibru		
<b>Base Case</b>		-				-
<b>Discount Rate</b>	3,5 %	0 %				+0%
		2 %				+0%
		5 %				0%
<b>Time Horizon</b>	30 years	1 years				-2%
		2 years				-1%
		5 years				-0%
<b>Medication Wastage</b>	Excluded	Included				-0%
<b>Drug acquisition Cost: Acalabrutinib</b>	45.224 DKK	-20 %				-195%
		20 %				+195%
<b>Drug Acquisition Cost: Obinutuzumab</b>	25.627 DKK	-20 %				-16%
		20 %				+16%
<b>Drug Acquisition Cost: Ibrutinib</b>	45.125 DKK	-20 %				+195%
		20 %				-195%
<b>Administration Cost</b>	3.203 DKK	-20 %				-3%
		20 %				+3%
<b>Subsequent Treatment Distribution after Ibru*</b>	Ven + R 100%	- 20% for Ven + R, + 20% for Acala				-29%

\* It is possible that patients who progress after ibrutinib due to adverse events would receive acalabrutinib in 2L.

**Table 41. Scenario analyses for acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab**

Parameter	Base Case	Scenario	Total Costs (DKK)		Difference (DKK)	% Change
			Acala + Obin	Ven + Obin		
Base Case		-		2 900 390		-
Discount Rate	3,5 %	0 %		3 477 644		+10%
		2 %		3 117 961		+4%
		5 %		2 716 888		-4%
Time Horizon	30 years	1 years		918 148		-94%
		2 years		1 032 165		-65%
		5 years		1 378 449		-7%
Medication Wastage	Excluded	Included		2 900 797		+0%
Drug Acquisition Cost: Acalabrutinib	45.224 DKK	-20 %		2 769 516		-22%
		20 %		3 031 263		+22%
Drug Acquisition Cost: Obinutuzumab	25.627 DKK	-20 %		2 859 943		+0%
		20 %		2 940 837		+0%
Drug Acquisition Cost: Venetoclax	40.010 DKK	-20 %		2 788 912		+1%
		20 %		3 011 868		-1%
Administration Cost	3.203 DKK	-20 %		2 893 432		-0%
		20 %		2 907 348		+0%
Subsequent Treatment Distribution after Acala + Obin	Ven + R 100%	- 20% for Ven + R, + 20% for Ibru		2 900 390		+5%
Subsequent Treatment Distribution after Ven + Obin	Acala 70%, Ibru 20% and Ven + R 10%	- 20 percentage points for Acala, + 20 percentage points for Ven + R		2 827 656		+5%
		- 20 percentage points for Acala, + 20 percentage points for Ibru		2 899 979		+0%
		+ 20 percentage points for Acala, - 10 percentage points for Ven + R and - 10 percentage points for Ibru		2 936 962		-2%
		+ 20 percentage points for Acala, - 20 percentage points for Ibru		2 900 801		-0%
PPS Source	8. ELEVATE-RR OS	5. ASCEND OS (Acalabrutinib Arm)		2 973 917		+0%
Mean Duration of Subsequent Treatments	█ cycles (ELEVATE-RR PFS IRC)	82,73 cycles (ASCEND PFS IRC)		3 892 051		-61%

### 15.1.3.1 Scenario Analysis by IGHV Status

The following scenario analyses were performed for the patient subpopulations with IGHV mutation and without IGHV mutation (Table 42 and Table 43, respectively). Patients without IGHV mutation accrue slightly lower incremental costs per patient for both acalabrutinib monotherapy and combination therapy compared to the overall patient group without 17p deletion/TP53 mutation. Whereas patients with IGHV mutation accrue considerably higher incremental costs per patient for both acalabrutinib monotherapy and combination compared to overall patients without 17p deletion/TP53 mutation. The rationale for these differences stems from the prognosis of these patients. Recent evidence from a Danish registry analysis shows that patients with unmutated IGHV have a poorer prognosis (Curovic Rotbain et al, 2020). Given the poorer prognosis, lifetime costs are reduced in these patients which reduces the incremental costs due to the greater decline in PFS, and therefore drug acquisition costs, observed.

The total costs per patient without the IGHV mutation over 30 years show that acalabrutinib monotherapy is associated with DKK [REDACTED] higher costs per patient than chlorambucil + obinutuzumab, and DKK [REDACTED] higher costs per patient than bendamustine + rituximab. The total costs per patient with IGHV mutation over 30 years show that acalabrutinib + obinutuzumab combination therapy is associated with DKK [REDACTED] higher costs per patient than chlorambucil + obinutuzumab, and DKK [REDACTED] higher costs per patient than bendamustine + rituximab.

The total costs per patient with mutated IGHV over 30 years show that acalabrutinib monotherapy is associated with DKK [REDACTED] higher costs per patient than chlorambucil + obinutuzumab, and DKK [REDACTED] higher costs per patient than bendamustine + rituximab. The total costs per patient with mutated IGHV over 30 years show that acalabrutinib + obinutuzumab combination therapy is associated with DKK [REDACTED] higher costs per patient than chlorambucil + obinutuzumab, and DKK [REDACTED] higher costs per patient than bendamustine + rituximab.

**Table 42.** Scenario analysis for the patient population without IGHV mutation

Cost Category	Total Costs per Treatment (DKK)				Incremental Costs (DKK): Acala vs.		Incremental Costs (DKK): Acala + Obin vs.	
	Acala	Acala + Obin	Chlor + Obin	BR	Chlor + Obin	BR	Chlor + Obin	BR
Disease Management	1 297 396	1 432 105	1 115 710	1 200 138	181 686	97 257	316 395	231 966
Drug Acquisition	[REDACTED]	[REDACTED]	209 099	91 190	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Drug Administration	-	33 962	33 882	44 322	-33 882	-44 322	80	-10 359
Treatment Monitoring	-	914	911	1 311	-911	-1 311	2	-398
Adverse Events	6 886	12 125	11 249	10 204	-4 363	-3 317	877	1 922
Subsequent Treatments	629 802	575 816	1 000 280	791 064	-370 478	-161 262	-424 463	-215 247
Patient Costs	49 680	63 363	51 230	53 674	-1 550	-3 994	12 133	9 689
<b>Total Costs</b>	[REDACTED]	[REDACTED]	<b>2 422 360</b>	<b>2 191 902</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**Table 43.** Scenario analysis for the patient population with IGHV mutation

Cost Category	Total Costs per Treatment (DKK)				Incremental Costs (DKK): Acala vs.		Incremental Costs (DKK): Acala + Obin vs.	
	Acala	Acala + Obin	Chlor + Obin	BR	Chlor + Obin	BR	Chlor + Obin	BR
Disease Management	1 521 936	1 540 266	1 178 525	1 180 989	343 412	340 948	361 742	359 277
Drug Acquisition	████████	████████	208 317	91 148	████████	████████	████████	████████
Drug Administration	-	33 972	33 755	44 301	-33 755	-44 301	217	-10 329
Treatment Monitoring	-	914	908	1 311	-908	-1 311	6	-397
Adverse Events	6 886	12 125	11 249	10 204	-4 363	-3 317	877	1 922
Subsequent Treatments	304 968	277 275	712 607	434 820	-407 639	-129 852	-435 332	-157 545
Patient Costs	58 278	67 506	53 602	52 937	4 676	5 341	13 903	14 569
<b>Total Costs</b>	████████	████████	<b>2 198 963</b>	<b>1 815 709</b>	████████	████████	████████	████████

#### 15.1.4 Deterministic Sensitivity Analyses

Univariate sensitivity analysis was undertaken by varying each key parameter to its reasonable limits. All the numeric variables (costs and other model parameters) were varied  $\pm 20\%$ . The parameters are listed in the cost per patient model (“DSA” sheet) and summarised with top 15 parameters in tornado diagrams.

For acalabrutinib monotherapy in comparison with chlorambucil + obinutuzumab (Figure 5) discount rate and disease management costs were the most sensitive inputs. Varying the discount rate from 2% to 5% resulted in variation of incremental costs per patient from DKK 2.366.636 to DKK 2.722.853. For acalabrutinib + obinutuzumab combination therapy in comparison with chlorambucil + obinutuzumab (Figure 6) discount rate, patient starting age and disease management costs were the most sensitive inputs. Variation in the patient starting age by  $\pm 5$  years resulted in variation of incremental costs per patient from DKK 3.845.619 to DKK 4.185.111.

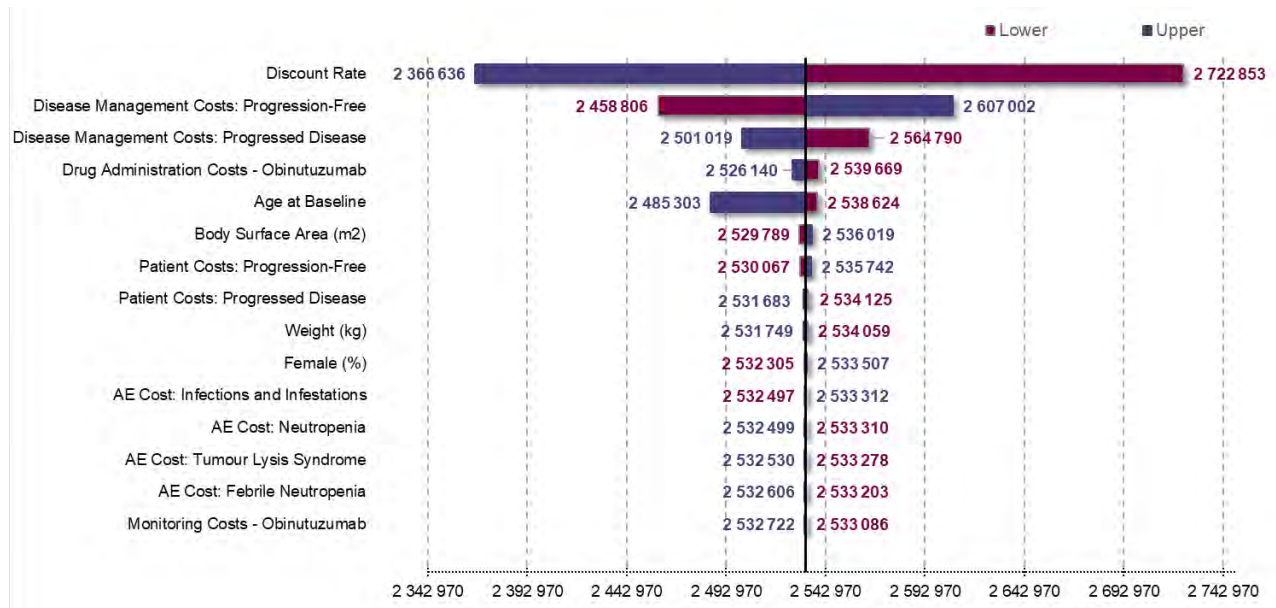
For acalabrutinib monotherapy and combination therapy in comparison with bendamustine + rituximab, Figure 7 and Figure 8 respectively, discount rate, progression free disease management costs and patient starting age were the most sensitive inputs. Variations in the discount rate between 2% and 5% resulted in variation of incremental costs per patient from DKK 2.859.944 to DKK 3.240.724 for acalabrutinib monotherapy and DKK 4.253.577 to DKK 5.067.363 for acalabrutinib combination therapy.

For acalabrutinib monotherapy in comparison with ibrutinib in the population with 17p deletion/TP53 mutation, Figure 9 shows that the costs of managing adverse events were the most sensitive parameters, with variation in the cost of infections by  $\pm 20\%$  changing the incremental costs between DKK -1.323 and DKK 251. The results for acalabrutinib combination therapy compared with ibrutinib are shown in Figure 10. These show that the cost of intravenous administration of obinutuzumab was the most sensitive parameter. Variation of  $\pm 20\%$  in the administration cost resulted in variation of incremental costs per patient from DKK 243.268 to DKK 256.749.

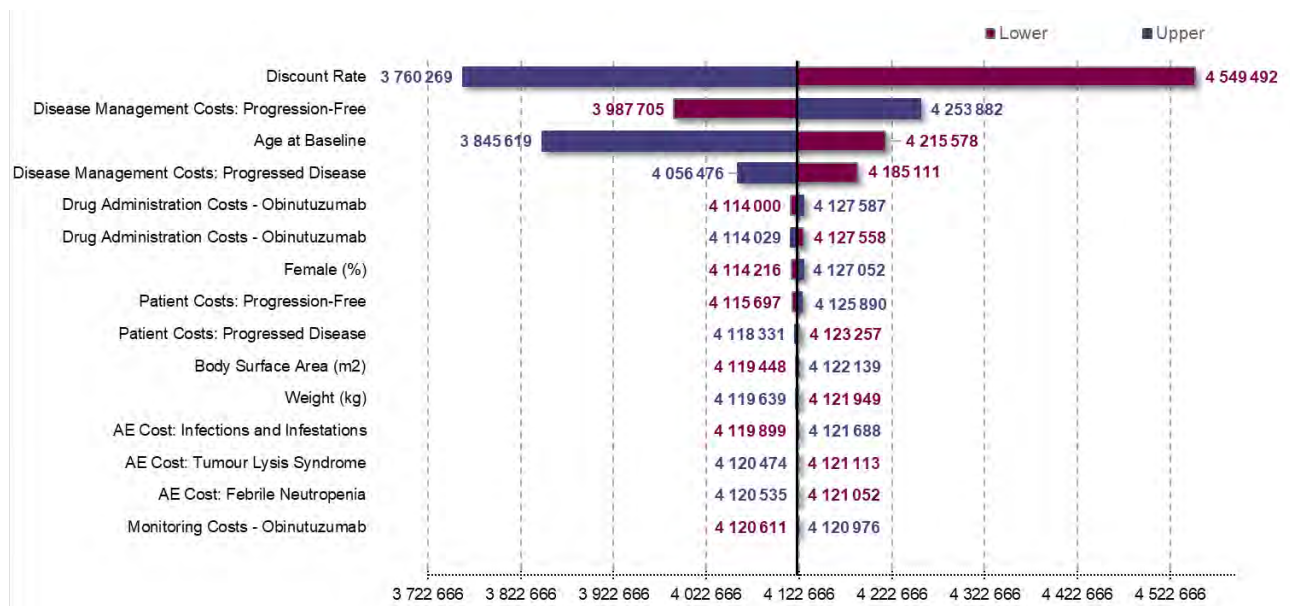
Results for acalabrutinib monotherapy and combination therapy in comparison with venetoclax + obinutuzumab in population with high-risk disease are shown in Figure 11 and Figure 12, respectively. The discount rate was again one of the key drivers of uncertainty in the incremental costs in both comparisons, with a change in the discount rate from 2% to 5% resulting in an increase in the incremental cost of DKK 128.740 for both treatments.



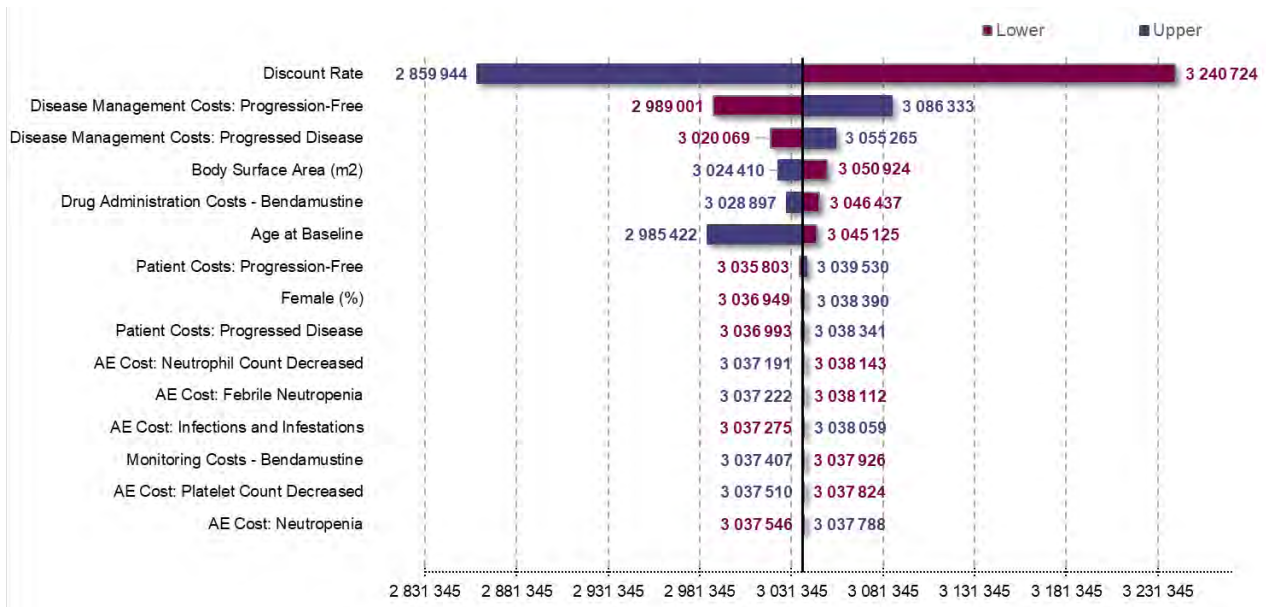
**Figure 5. Tornado diagram of acalabrutinib versus chlorambucil + obinutuzumab**



**Figure 6. Tornado diagram of acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab**



**Figure 7. Tornado diagram of acalabrutinib versus bendamustine + rituximab**



**Figure 8. Tornado diagram of acalabrutinib + obinutuzumab versus bendamustine + rituximab**

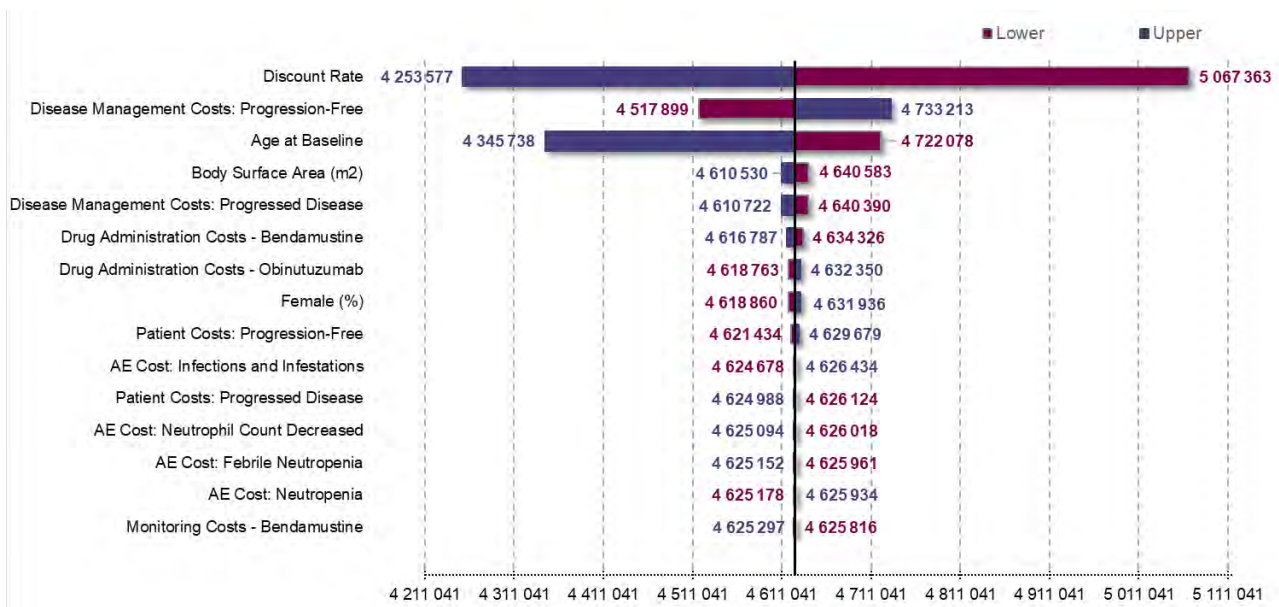


Figure 9. Tornado diagram of acalabrutinib versus ibrutinib

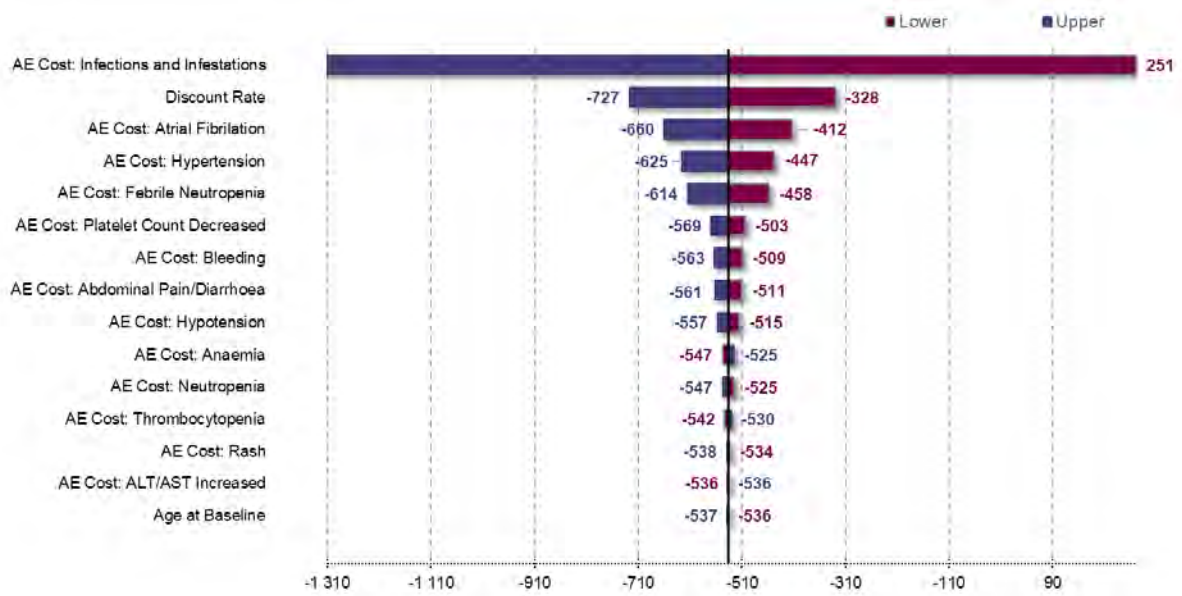


Figure 10. Tornado diagram of acalabrutinib + obinutuzumab versus ibrutinib

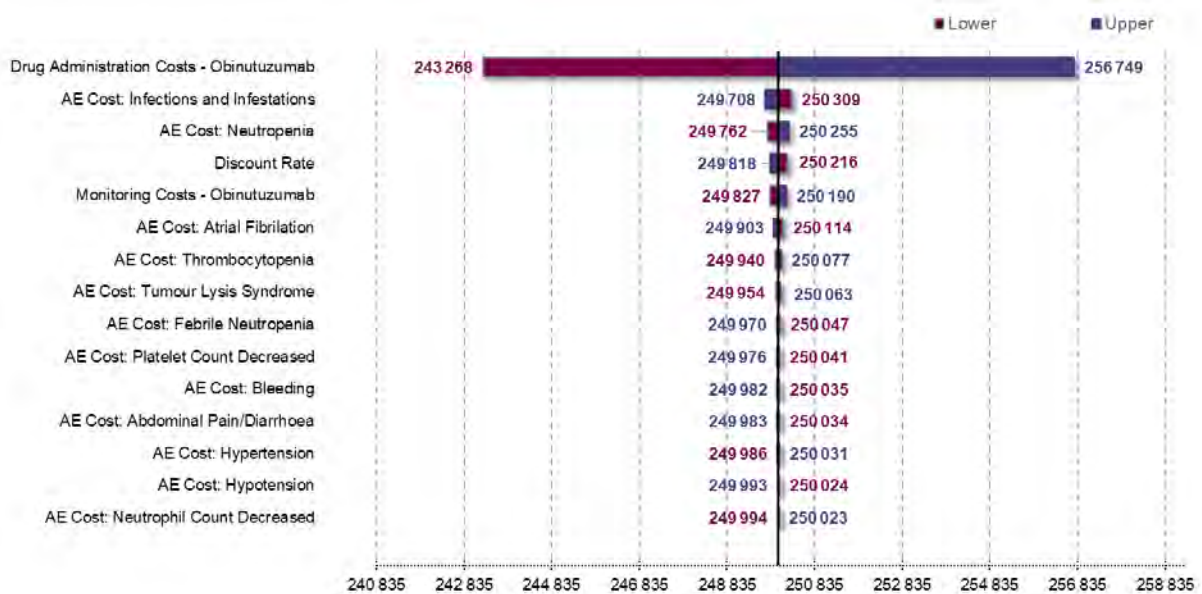


Figure 11. Tornado diagram of acalabrutinib versus venetoclax + obinutuzumab

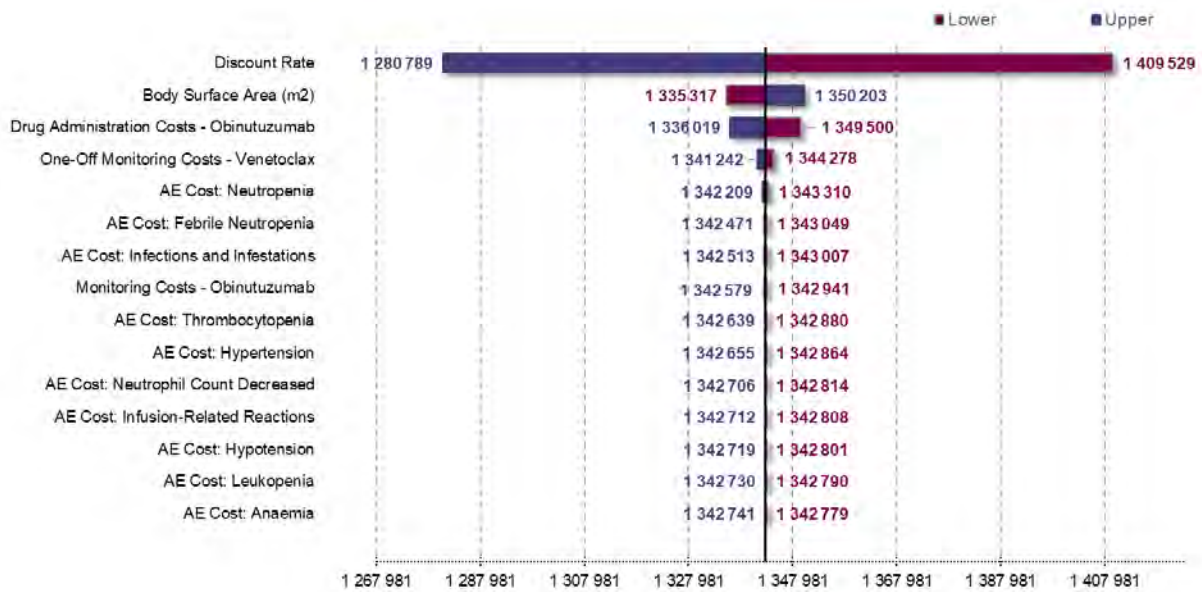
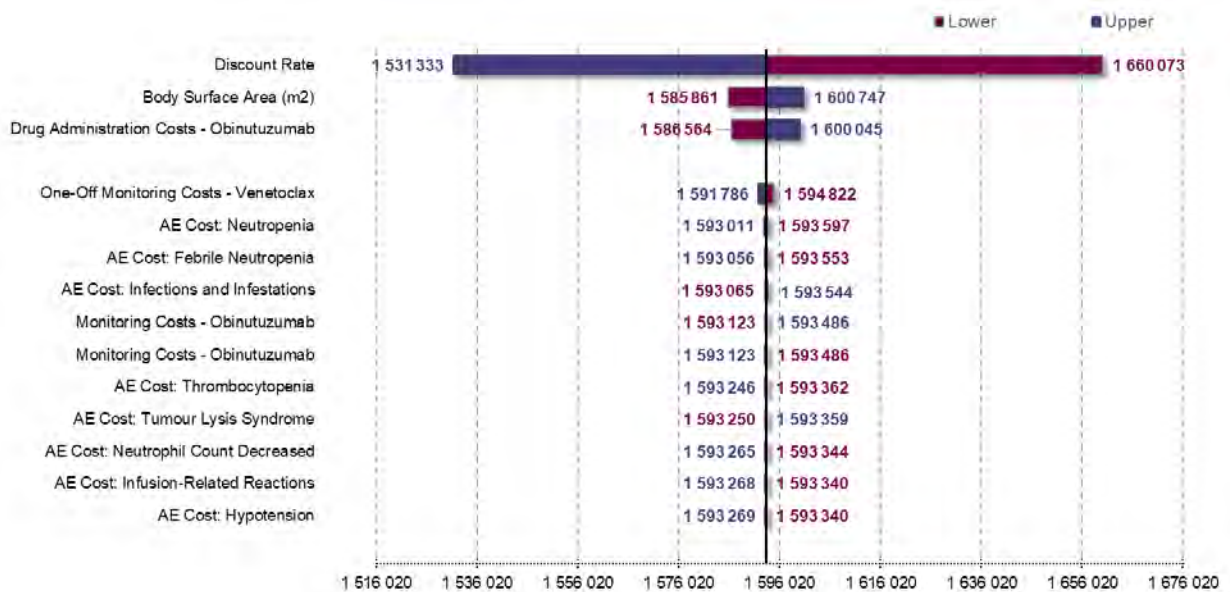


Figure 12. Tornado diagram of acalabrutinib + obinutuzumab versus venetoclax + obinutuzumab



## 15.2 Budget Impact Analysis

For the base case results the model compared two scenarios to assess the budget impact and cost implications of introducing acalabrutinib +/- obinutuzumab in patients without 17p deletion/TP53 mutation:

- Scenario without acalabrutinib: based on the current and forecasted market shares when acalabrutinib +/-obinutuzumab is not reimbursed in 1L.
- Scenario with acalabrutinib: based on the current and forecasted market shares when acalabrutinib +/-obinutuzumab is reimbursed in 1L.

The total number of patients initiating 1L treatment was estimated to be between 108 and 110 each year during 2022 and 2026 for patients without 17p deletion/TP53 mutation. For patients with 17p deletion/TP53 mutation, the number of eligible patients was estimated to be 15 each (Table 44). Using market share estimates and the number of patients eligible, the number of patients starting acalabrutinib monotherapy, acalabrutinib + obinutuzumab, and acalabrutinib with or without obinutuzumab during 2022-2026 were estimated (Table 44).

**Table 44.** Number of patients starting acalabrutinib therapy in three scenarios based on acalabrutinib availability for patients without and with 17p deletion/TP53 mutation

	2022	2023	2024	2025	2026
<b>Only Acalabrutinib Monotherapy Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Number of Eligible Patients	109	109	110	110	111
Patients Starting Acalabrutinib Monotherapy	█	█	█	█	█
<b>With 17p deletion/TP53 mutation</b>					
Number of Eligible Patients	15	15	15	15	15
Patients Starting Acalabrutinib Monotherapy	█	█	█	█	█
<b>Only Acalabrutinib + Obinutuzumab Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Number of Eligible Patients	109	109	110	110	111
Patients Starting Acalabrutinib + Obinutuzumab	█	█	█	█	█
<b>With 17p deletion/TP53 mutation</b>					
Number of Eligible Patients	15	15	15	15	15
Patients Starting Acalabrutinib + Obinutuzumab	█	█	█	█	█
<b>Both Acalabrutinib Monotherapy and Combination Therapy Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Number of Eligible Patients	109	109	110	110	111
Patients Starting Acalabrutinib Monotherapy	█	█	█	█	█
Patients Starting Acalabrutinib + Obinutuzumab	█	█	█	█	█
<b>With 17p deletion/TP53 mutation</b>					
Number of Eligible Patients	15	15	15	15	15
Patients Starting Acalabrutinib Monotherapy	█	█	█	█	█
Patients Starting Acalabrutinib + Obinutuzumab	█	█	█	█	█

The budget impact calculations include cost implications of introducing acalabrutinib +/- obinutuzumab in 1L along with cost implications of subsequent treatment. Costs for drug acquisition, administration, monitoring, disease management, and AEs were included.

Budget impact results in the three scenarios (introducing acalabrutinib monotherapy, introducing acalabrutinib + obinutuzumab, and introducing acalabrutinib both with or without obinutuzumab) are presented for patients with and without 17p deletion/TP53 mutation in Table 45. In both scenarios where either acalabrutinib monotherapy or combination therapy is introduced, the incremental budget impact showed an increasing trend in the initial years, and then stabilise in the longer term.

The incremental budget impact for patients with 17p deletion/TP53 mutation has a more gradual and limited increase over time, with the potential be cost saving in the initial year should only acalabrutinib monotherapy be available for these patients, with the budget impact increasing by 10-15% in the longer term.

**Table 45.** Budget impact (DKK) for introducing acalabrutinib therapy in three scenarios based on acalabrutinib availability for patients without and with 17p deletion/TP53 mutation

	2022	2023	2024	2025	2026
<b>Only Acalabrutinib Monotherapy Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Current Scenario	34 570 353	53 824 498	91 122 475	123 959 394	149 142 315
Scenario with Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Incremental Cost of Introducing Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Budget Impact (%)	███%	███%	███%	███%	███%
<b>With 17p deletion/TP53 mutation</b>					
Current Scenario	11 742 943	18 671 829	24 226 132	28 092 156	30 991 899
Scenario with Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Incremental Cost of Introducing Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Budget Impact (%)	███%	███%	███%	███%	███%
<b>Only Acalabrutinib + Obinutuzumab Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Current Scenario	34 570 353	53 824 498	91 122 475	123 959 394	149 142 315
Scenario with Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Incremental Cost of Introducing Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Budget Impact (%)	███%	███%	███%	███%	███%
<b>With 17p deletion/TP53 mutation</b>					
Current Scenario	11 742 943	18 671 829	24 226 132	28 092 156	30 991 899
Scenario with Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Incremental Cost of Introducing Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Budget Impact (%)	███%	███%	███%	███%	███%
<b>Both Acalabrutinib Monotherapy and Combination Therapy Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Current Scenario	34 570 353	53 824 498	91 122 475	123 959 394	149 142 315
Scenario with Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Incremental Cost of Introducing Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Budget Impact (%)	███%	███%	███%	███%	███%
<b>With 17p deletion/TP53 mutation</b>					
Current Scenario	11 742 943	18 671 829	24 226 132	28 092 156	30 991 899
Scenario with Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Incremental Cost of Introducing Acalabrutinib	██████████	██████████	██████████	██████████	██████████
Budget Impact (%)	███%	███%	███%	███%	███%

### 15.2.1 Budget Impact Scenario Analyses: Decreased Market Share

The scenario analyses assume that for each of the analyses reported above (by the presence of 17p deletion/TP53 mutation and whether acalabrutinib is reimbursed as monotherapy, combination therapy, or both), the market share for acalabrutinib decreased by 40% in comparison to base case analysis. The market shares were instead evenly distributed to comparator treatments. For patients without 17p deletion/TP53 mutation, the market shares were increased for chlorambucil + obinutuzumab and bendamustine + rituximab, and for patients with 17p deletion/TP53 mutation the market shares were increased for venetoclax + obinutuzumab. Tables 46 to 48 summarises market shares.

**Table 46.** Market shares for acalabrutinib monotherapy, with a 40% decrease for acalabrutinib

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>Without 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Bendamustine + Rituximab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Chlorambucil + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>With 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Venetoclax + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Ibrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%

**Table 47.** Market shares for acalabrutinib + obinutuzumab, with a 40% decrease for acalabrutinib

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>Without 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Bendamustine + Rituximab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Chlorambucil + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>With 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Venetoclax + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Ibrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%

**Table 48.** Market shares for acalabrutinib ± obinutuzumab, with a 40% decrease for acalabrutinib

	Current Scenario (without acalabrutinib)					New Scenario (with acalabrutinib)				
	2022	2023	2024	2025	2026	2022	2023	2024	2025	2026
<b>Without 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Bendamustine + Rituximab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Chlorambucil + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
<b>With 17p deletion / TP53 mutation</b>										
Acalabrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Acalabrutinib + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Venetoclax + Obinutuzumab	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%
Ibrutinib	■%	■%	■%	■%	■%	■%	■%	■%	■%	■%

The results are presented in Table 49 below. Decreasing the market share by 40% serves to decrease the year-on-year budget impact by approximately 37% compared to the base case for patients without 17p deletion/TP53 mutation. Decreasing the market share by 40% in patients with 17p deletion/TP53 mutation decreases the budget impact by 40-50% during the first two years, and by approximately 30% by 2026, compared to the base case.

**Table 49.** Budget impact (DKK) for introducing acalabrutinib therapy in three scenarios based on acalabrutinib availability for patients without and with 17p deletion/TP53 mutation with a reduced market share

	2022	2023	2024	2025	2026
<b>Only Acalabrutinib Monotherapy Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Current Scenario	34 570 353	53 824 498	91 122 475	123 959 394	149 142 315
Scenario with Acalabrutinib	■	■	■	■	■
Incremental Cost of Introducing Acalabrutinib	■	■	■	■	■
Budget Impact (%)	■%	■%	■%	■%	■%
<b>With 17p deletion/TP53 mutation</b>					
Current Scenario	11 742 943	18 671 829	24 226 132	28 092 156	30 991 899
Scenario with Acalabrutinib	■	■	■	■	■
Incremental Cost of Introducing Acalabrutinib	■	■	■	■	■
Budget Impact (%)	■%	■%	■%	■%	■%
<b>Only Acalabrutinib + Obinutuzumab Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
Current Scenario	34 570 353	53 824 498	91 122 475	123 959 394	149 142 315
Scenario with Acalabrutinib	■	■	■	■	■
Incremental Cost of Introducing Acalabrutinib	■	■	■	■	■



	2022	2023	2024	2025	2026
<b>Budget Impact (%)</b>	█%	█%	█%	█%	█%
<b>With 17p deletion/TP53 mutation</b>					
<b>Current Scenario</b>	11 742 943	18 671 829	24 226 132	28 092 156	30 991 899
<b>Scenario with Acalabrutinib</b>	█	█	█	█	█
<b>Incremental Cost of Introducing Acalabrutinib</b>	█	█	█	█	█
<b>Budget Impact (%)</b>	█%	█%	█%	█%	█%
<b>Both Acalabrutinib Monotherapy and Combination Therapy Available</b>					
<b>Without 17p deletion/TP53 mutation</b>					
<b>Current Scenario</b>	34 570 353	53 824 498	91 122 475	123 959 394	149 142 315
<b>Scenario with Acalabrutinib</b>	█	█	█	█	█
<b>Incremental Cost of Introducing Acalabrutinib</b>	█	█	█	█	█
<b>Budget Impact (%)</b>	█%	█%	█%	█%	█%
<b>With 17p deletion/TP53 mutation</b>					
<b>Current Scenario</b>	11 742 943	18 671 829	24 226 132	28 092 156	30 991 899
<b>Scenario with Acalabrutinib</b>	█	█	█	█	█
<b>Incremental Cost of Introducing Acalabrutinib</b>	█	█	█	█	█
<b>Budget Impact (%)</b>	█%	█%	█%	█%	█%

## 16 Conclusive Discussion

The cost analyses were presented for acalabrutinib and acalabrutinib + obinutuzumab versus comparator treatments identified by the Danish Medicine Council. The analyses considered both PU CLL patients without and with 17p deletion/TP53 mutation. In addition, the subgroups with IGHV mutation and without IGHV mutation were included as scenario populations in the cost per patient analysis.

### 16.1 Interpretation of the Economic Evidence

In the patients without 17p deletion/TP53 mutation, the average cost per patient over 30 years is DKK █ for acalabrutinib monotherapy and DKK █ for acalabrutinib + obinutuzumab, compared to DKK 2.385.130 for chlorambucil + obinutuzumab, and DKK 1.880.368 for bendamustine + rituximab. The drug acquisition costs constitute a major part of the total costs for acalabrutinib based therapies. Whilst acalabrutinib, in either regimen, is associated with an increased acquisition cost per patient in this patient group, this can be attributed to the prolonged progression-free survival, and therefore the time on first line treatment, demonstrated with acalabrutinib in the indirect treatment comparisons. Consequently, the longer duration of first line treatment is partially offset by the considerable reductions in the costs of subsequent therapies.

In the patients with 17p deletion/TP53 mutation, the average cost per patient over 30 years is DKK █ for acalabrutinib monotherapy and DKK █ for acalabrutinib + obinutuzumab, compared to DKK █ for ibrutinib and DKK 2.900.390 for venetoclax + obinutuzumab. Drug acquisition costs formed a major component of all included regimens. The drug acquisition costs for venetoclax + obinutuzumab are lower due to the fixed-period treatment duration (12 cycles) in the Summary of Product Characteristics, however evidence is still lacking regarding how the treatment regimen will be used in practice with regards to discontinuation at 12 cycles or retreatment. A scenario analysis showed that patients without IGHV mutation accrue lower incremental costs per patient for both acalabrutinib monotherapy and combination therapy compared to the ITT population. Whereas patients with IGHV mutation accrue considerably higher incremental costs per patient for both acalabrutinib monotherapy and combination compared to the ITT population.

In the short-term, acalabrutinib offers some cost savings aspects when compared to all other regimens, both in the patient groups with and without 17p deletion/TP53 mutations. The improved safety profile of acalabrutinib demonstrated in the indirect treatment comparison provides an opportunity to avoid these costs of care. In addition, acalabrutinib also has a reduced burden of drug administration and treatment monitoring when compared to IV therapies, such as venetoclax + obinutuzumab and bendamustine + rituximab. These can offer key cost savings in the short-term, and avoiding these in-hospital aspects of care may also be particularly pertinent to patients in the near future given the ongoing COVID-19 pandemic (Fürstenau et al, 2020).

The selected cost savings aspects of acalabrutinib treatment are somewhat reflected in the results of the budget impact model, showing cost savings or only marginal changes in budget impact in the initial years for patients with 17p deletion/TP53 mutation. The cost savings due to subsequent treatments are also evident. Whilst the budget impact analysis showed that implementing acalabrutinib will increasingly impact the expenditure until 2023, as the costs related to subsequent treatments are included in the analysis, the healthcare expenditure decreases again and stabilise from 2023 till 2025. This is due to patients treated with either chlorambucil + obinutuzumab or bendamustine + rituximab progressing to 2L treatment.

Three scenario analyses were performed to address the uncertainties associated with the estimations of market shares. The scenarios explored the budget consequences when market shares for acalabrutinib monotherapy, combination therapy, and acalabrutinib +/- obinutuzumab were decreased with 40% compared to the base case. As expected, the budget impact decreased.

## 16.2 Modelling Uncertainties

The outputs from the cost per patient analysis represent a plausible estimation costs per patient for acalabrutinib based therapy versus comparators. While the model relies on long-term survival extrapolations and immature data, conservative assumptions have been made whenever possible and sensitivity analyses were performed to assess uncertainty in the analysis.

The immature clinical data from ELEVATE-TN imposes uncertainty for the subsequent treatment modelling and extrapolation of trial data. Survival in the model was informed by several data sources. Whilst TTP and TTDeath data from ELEVATE-TN were used to model pre-progression transitions, the trial was not used to inform PPS. Given the low number of post-progression deaths in the ELEVATE-TN trial, the base case estimates used external data sources studying on treatments in the relapsed and/or refractory CLL patients to inform PPS.

An additional limitation of the cost per patient analysis was that due to the complex nature of treatment sequencing models the assumptions surrounding subsequent treatments could be considered simplistic. In order to provide the most clinically relevant estimates, the subsequent treatment distribution was chosen to align with the PPS data source used and aligned with anticipated second-line treatment for the primary treatment option as estimated by Danish clinicians. Furthermore, the model contains functionality to model only one subsequent treatment option. Thus only the second line treatment is considered and both survival and costs related to lines of therapy beyond this are not considered.

Also, the indirect comparison between acalabrutinib and bendamustine was based on MAIC in the base case analysis and the NMA was presented as a scenario. MAIC was considered as the most plausible ITC methodology and the NMA scenario analysis showed that the results were not sensitive for the ITC method. However, PFS endpoints for bendamustine + rituximab were not assessed by IRC. Therefore, the HRs were based on INV assessed PFS and were utilized in the analysis. Meanwhile, the IRC assessed PFS which was the primary endpoint in the ELEVATE-TN, was utilized for acalabrutinib. This causes uncertainty in the indirect

comparisons but was considered as the most plausible approach given the reliability of the PFS data of acalabrutinib and its congruence throughout all comparisons in the analysis.

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## 18 Appendices

### MAIC report PU CLL

The document was attached to the dossier as a separate document.

### NMA report

The document was attached to the dossier as a separate document

### Overview of the scenario analysis settings for survival curve extrapolation in patient population with/without IGHV mutation

**Table 50.** Overview of the scenario analysis settings for survival curve extrapolation in patient population with IGHV mutation

<b>Acalabrutinib Monotherapy</b>	
TTP Distribution	Weibull
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR OS
<b>Acalabrutinib + Obinutuzumab</b>	
TTP Distribution	Weibull
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR OS
<b>Chlorambucil + Obinutuzumab</b>	
TTP Distribution	Lognormal
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR OS
<b>Bendamustine + Rituximab (ITC)</b>	
TTP/TTDeath Source	NMA HR applied to both TTP/TTDeath using acalabrutinib combination therapy as the base-line treatment
PPS Source	ELEVATE-RR OS

**Table 51.** Overview of the scenario analysis settings for survival curve extrapolation in patient population without IGHV mutation

<b>Acalabrutinib Monotherapy</b>	
TTP Distribution	Weibull
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR OS
<b>Acalabrutinib + Obinutuzumab</b>	
TTP Distribution	Weibull
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR OS
<b>Chlorambucil + Obinutuzumab</b>	
TTP Distribution	Lognormal
TTDeath Distribution	Exponential
PPS Source	ELEVATE-RR OS
<b>Bendamustine + Rituximab (ITC)</b>	

TTP/TTDeath Source	NMA HR applied to both TTP/TTDeath using acalabrutinib combination therapy as the base-line treatment
PPS Source	ELEVATE-RR OS

### Estimation of Survival Curves

The document was attached to the dossier as a separate document (*Estimation of survival curves 1L*)



# Medicinrådets protokol for vurdering af acalabrutinib som monoterapi og acalabrutinib i kombination med obinutuzumab til behandling af kronisk lymfatisk leukæmi



## Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

## Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

*Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil den ansøgende virksomhed få besked.*

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# 1. Begreber og forkortelser

<b>BTK:</b>	Brutons tyrosinkinase
<b>CI:</b>	Konfidensinterval
<b>CIRS:</b>	Cumulative illness scale
<b>CLL:</b>	Kronisk lymfatisk leukæmi
<b>CLL-IPI:</b>	<i>International Prognostic Index for Chronic Lymphocytic Leukemia</i>
<b>DLG:</b>	Dansk Lymfom Gruppe
<b>EMA:</b>	Det Europæiske Lægemiddelagentur ( <i>European Medicines Agency</i> )
<b>EPAR:</b>	<i>European Public Assessment Report</i>
<b>FISH:</b>	<i>Fluorescent in-situ hybridization</i>
<b>GRADE:</b>	System til at vurdere evidens ( <i>Grading of Recommendations, Assessment, Development and Evaluation</i> )
<b>HR:</b>	<i>Hazard ratio</i>
<b>IGHV:</b>	<i>Immunoglobulin heavy-chain variable region</i>
<b>iwCLL:</b>	<i>Intention to treat</i>
<b>OR:</b>	<i>Odds ratio</i>
<b>PICO:</b>	Population, intervention, komparator og effektmål ( <i>Population, Intervention, Comparison and Outcome</i> )
<b>PP:</b>	<i>Per Protocol</i>
<b>RCT:</b>	Randomiseret kontrolleret studie ( <i>Randomised Controlled Trial</i> )
<b>RR:</b>	Relativ risiko
<b>SMD:</b>	<i>Standardized Mean Difference</i>



## 2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra AstraZeneca, som ønsker, at Medicinrådet vurderer acalabrutinib som: a) monoterapi til patienter med kronisk lymfatisk leukæmi (1. linje), b) kombinationsbehandling med obinutuzumab til behandling af patienter med tidligere ubehandlet kronisk lymfatisk leukæmi (1. linje) og c) monoterapi til behandling af patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én tidligere behandling (2. linje eller mere). Vi modtog den foreløbige ansøgning den 4. september 2020.

### 2.1 Kronisk lymfatisk leukæmi

Kronisk lymfatisk leukæmi (CLL) er en kræftsygdom i blodet, som opstår i kroppens B-celler og påvirker deres regulering af celledeling og celledød. Det fører til en ophobning af B-celler bl.a. i knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket. Det hyppigste symptom på CLL er træthed, og oftest opdages sygdommen tilfældigt. Øvrige diskrete symptomer omfatter typisk hævede lymfeknuder, forstørret milt, blodmangel, uforklarlig feber, vægttab og øget infektionstendens.

Kronisk lymfatisk leukæmi er den meste almindelig blodkræft i de vestlige lande og udgør ca. 30 % af samtlige leukæmier [1]. Incidensen er i Danmark ca. 6-7 pr. 100.000 indbyggere pr. år, og der registreres ca. 450-500 nye tilfælde om året [2]. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark [3]. Medianalderen er ved diagnosetidspunktet 70 år, og dobbelt så mange mænd som kvinder får diagnosen [1,2]. Da CLL ofte er asymptomatisk på diagnosetidspunktet, opdages det typisk ved en tilfældighed efter en blodprøve. Diagnosen stilles ved konstatering af vedvarende unormale niveauer af B-celler (lymfocytose), defineret som > 5 mia. monoclonale B-celler pr. liter blod i tre måneder eller derover. På diagnosetidspunktet foretages en vurdering af sygdomsstadie (baseret på sygdomsudbredelse, stadietopdeling jf. Binet-systemet) og sygdommens aggressivitet (risikoprofil på baggrund af kromosomforandringer (cytogenetiske abnormaliteter) og eventuel mutation i et gen, der koder for en specifik immunreceptor (immunoglobulin heavy-chain variable region (IGHV))).

Kronisk lymfatisk leukæmi har ofte et mildt (indolent) forløb, hvor patienterne med tidlige stadier og langsomt progredierende sygdom følges ved årlige kontroller eller afsluttes til egen læge. Medianoverlevelse fra diagnosetidspunktet varierer fra ca. 4 år til mere end 12 år afhængigt af sygdomsstadie og risikoprofil. Både sygdomsstadie, patientens symptomer og risikoprofil har indflydelse på igangsættelse og valg af behandling, ligesom de har betydning for patienternes prognose, hvilket er afspejlet i den internationale prognostiske indeks for CLL (*CLL-International Prognostic Index (IPI)*) [4].

Del17p/TP53-mutation er forbundet med en væsentligt dårligere prognose og har betydning for den behandling, der tilbydes, idet patienter med del17p/TP53-mutation ikke behandles med kemoimmunoterapi. Af andre kromosomforandringer med betydning for prognosen er del11q og trisomi 12, som er forbundet med en dårligere prognose



samt del13q, som er forbundet med bedre prognose. Umutteret IGHV-status er associeret med forringet prognose og signifikant kortere overlevelse sammenlignet med muteret IGHV-status uanset stadiet af sygdommen [5,6].

## 2.2 Acalabrutinib som monoterapi og i kombination med obinutuzumab

Acalabrutinib hæmmer enzymet Brutons tyrosinkinase (BTK), som er vigtig for deling og vækst af de abnorme B-celler i CLL [9,10].

Lægemidlerne administreres som følger i serier a 28 dage:

- Acalabrutinib som monoterapi:  
p.o. 100 mg 2 x dagligt (hver 12. time) indtil sygdomsprogression eller uacceptabel toksicitet.
- Acalabrutinib i kombination med obinutuzumab:  
acalabrutinib p.o. 100 mg 2 x dagligt (hver 12. time) indtil sygdomsprogression eller uacceptabel toksicitet; og  
obinutuzumab i.v. 100 mg på dag 1 og 900 mg på dag 2 og 1000 mg på dag 8 og 15 i 2. serie, herefter i.v. 1000 mg på dag 1 i serie 3-7.

Acalabrutinib som monoterapi har markedsføringstilladelse til 1. og 2. linje, mens acalabrutinib i kombination med obinutuzumab har markedsføringstilladelse til 1. linje. Markedsføringstilladelsen blev givet 5. november 2020.

## 2.3 Nuværende behandling

Behandlingen af CLL varetages af de hæmatologiske afdelinger. På diagnosetidspunktet skelnes mellem behandlingskrævende og ikkebehandlingskrævende sygdom. Ikke-behandlingskrævende sygdom følges med *watch and wait*, indtil sygdommen bliver behandlingskrævende ifølge kriterier defineret af *International Workshop on Chronic Lymphocytic Leukemia* (iwCLL).

Ved behandlingskrævende sygdom afhænger behandlingsstrategien af patientspecifikke faktorer (performancestatus, komorbiditet (cumulative illness rating scale (CIRS)), alder, præferencer), sygdomskaraktistika (tumorbyrde, stadie, risikoprofil (karakteriseret ved fluorescent in-situ hybridization [FISH]), IGHV-mutationsstatus) og behandlingsmuligheder.

I behandlingsøjemed opdeles patientpopulationen efter, hvorvidt de har deletion17p/p53-mutation eller ej og efter performancestatus, alder og komorbiditeter. Hvorvidt patienterne har deletion17p/p53-mutation eller ej er afgørende for, hvilken behandling de skal have i 1. linje. Patienter *uden* deletion17p/p53-mutation bliver behandlet med cytostatika i form af enten chlorambucil, fludarabin og cyclofosamid eller bendamustin i kombination med et anti-CD20-antistof. Patienter *med* deletion17p/p53-mutation er ikke



følsomme for behandling med cytostatika og behandles i stedet med proteinkinase-hæmmeren ibrutinib eller venetoclax i kombination med obinutuzumab. Hvis de to behandlinger ikke tolereres, kan i stedet anvendes idelalisib i kombination med rituximab. Idelalisib anvendes sjældent i Danmark.

For patienter *uden* deletion17p/p53-mutation afgøres valget af cytostatika og anti-CD20-antistof af patientens alder, performancestatus og mængden af komorbiditet [11]. Fludarabin og cyclofosfamid i kombination med rituximab anvendes typisk til de yngre patienter med god performancestatus, bendamustin og rituximab til den ældre patientpopulation med god performancestatus (eller de yngre patienter med dårlig performancestatus), og chlorambucil plus et CD20-antistof til patienter med dårlig performancestatus. Traditionelt har man anvendt cytostatika i første linje, når det var muligt, fordi de medicinske behandlingsmuligheder har været få, og fordi højere alder og deletion17p/p53-mutation senere i sygdomsforløbet kan udelukke behandling med cytostatika. Dog har nye targeterede behandlinger vist sig at være mere effektive og med en bedre bivirkningsprofil, hvorfor brugen af kemoimmunterapi er faldende.

Patienter med umuteret sygdom har en dårligere prognose end patienter med muteret IGHV-status, men i nuværende dansk klinisk praksis skelnes der i behandlingsøjemed ikke imellem, hvorvidt patienterne har IGHV-mutation eller ej, selvom det er af betydning for patienternes prognose. Studier viser, at en opdeling af patienterne i forhold til IGHV-status er relevant for effekten af nogle behandlinger, og fagudvalget forventer, at den praksis på sigt vil blive aktuel i dansk sammenhæng [12–14]. Denne ændring i behandlingspraksis er reflekteret i den seneste retningslinje for CLL fra DLG, hvor tidligere ubehandlede patienter uden IGHV-mutation og uden deletion17p/p53-mutation anbefales behandlet med enten ibrutinib eller venetoclax i kombination med et CD20-antistof (enten rituximab eller obinutuzumab). Aktuelt er det dog ikke muligt at behandle efter denne retningslinje, da Medicinrådet ikke har anbefalet venetoclax til patienter uden del17p/TP53-mutation.

Ved tilbagefald efter behandling med cytostatika behandles patienterne uanset deletion17p/ p53-mutation med enten venetoclax i kombination med rituximab, som er et anti-CD20-antistof, eller ibrutinib [11].

Der er ca. 150 patienter om året med behandlingsbehov i 1. linje [11], hvoraf ca. 90 % (ca. 135 patienter) ikke har deletion17p/p53-mutation og derfor behandles med cytostatika i kombination med et anti-CD20-antistof [15]. I denne patientgruppe forventer fagudvalget, at 40 % (ca. 55 patienter) har muteret IGHV, og 60 % (ca. 80 patienter) er umuteret. De resterende 10 % (ca. 15 patienter) med deletion17p/p53-mutation behandles med ibrutinib eller venetoclax i kombination med obinutuzumab.

Fagudvalget vurderer, at ca. 65-70 patienter om året behandles i 2. linje. Fagudvalgets estimering af patientantal i de forskellige grupper er baseret på informationer fra den landsdækkende LYFO-database, viden om tid til første tilbagefald og forekomsten af deletion17p/p53-mutation på forskellige tidspunkter i behandlingsforløbet [16–19].



## 3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene. Fagudvalget har stillet fire spørgsmål til 1. linje, idet ansøger har søgt om vurdering af både acalabrutinib monoterapi og acalabrutinib i kombination med obinutuzumab, og begge vurderinger foretages til tidligere ubehandlede patienter med og uden del17p/TP53-mutation. Derudover har fagudvalget stillet et klinisk spørgsmål til 2. linje vedrørende acalabrutinib til patienter med relaps.

### 3.1 Klinisk spørgsmål 1

*Hvilken værdi har acalabrutinib som monoterapi sammenlignet med kemoimmunterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion17p/p53-mutation?*

#### *Population*

Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion17p/p53-mutation.

#### *Intervention*

Acalabrutinib som monoterapi doseret som følger i serier a 28 dage:

- p.o. 100 mg 2 x dagligt (hver 12. time) indtil sygdomsprogression eller uacceptabel toksicitet.

#### *Komparatorer*

Chlorambucil i kombination med obinutuzumab doseret som følger i 6 serier a 28 dage:

- Chlorambucil p.o. 0,5 mg/kg på dag 1 og 15
- Obinutuzumab i.v. 100 mg på dag 1, 900 mg på dag 2 og 1.000 mg på dag 8 og 15 i 1. serie, herefter 1.000 mg på dag 1 i serie 2-6.

Bendamustin i kombination med rituximab doseret som følger i op til 6 serier a 28 dage:

- Bendamustin i.v. 70-90 mg/m<sup>2</sup> på dag 1 og 2
- Rituximab i.v. 375 mg/m<sup>2</sup> på dag 1 i første serie, herefter i.v. 500 mg/m<sup>2</sup> på dag 1 i efterfølgende serier.

Fludarabin, cyclofosfamid i kombination med rituximab (R-FC) doseret som følger i 6 serier a 28 dage:

- Fludarabin 25 mg/m<sup>2</sup> i.v. dag 1-3 eller 40 mg/m<sup>2</sup> p.o. dag 1-3
- Cyclofosfamid 250 mg/m<sup>2</sup> i.v. eller p.o. dag 1-3
- Rituximab 375 mg/m<sup>2</sup> i.v. dag 1, 1. serie, serie 2-6: 500 mg/m<sup>2</sup>





Anvendelsen af de forskellige komparatorer afhænger i dansk klinisk praksis af patienternes alder og komorbiditet. Ansøger bedes belyse sammenligninger med alle komparatorer og gøre tydeligt rede for studiepopulationerne, hvad angår baselinekarakteristika, prognostiske faktorer (herunder IGHV-mutationsstatus) og sammenlignelighed med den danske patientpopulation.

#### *Effektmål*

De valgte effektmål står i tabel 1.

## 3.2 Klinisk spørgsmål 2

*Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med kemoimmunterapi for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion17p/p53-mutation?*

#### *Population*

Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion17p/p53-mutation.

#### *Intervention*

Acalabrutinib i kombination med obinutuzumab doseret som følger i serier a 28 dage:

- acalabrutinib p.o. 100 mg 2 x dagligt (hver 12. time) indtil sygdomsprogression eller uacceptabel toksicitet; og
- obinutuzumab i.v. 100 mg på dag 1 og 900 mg på dag 2 og 1000 mg på dag 8 og 15 i 2. serie, herefter i.v. 1.000 mg på dag 1 i serie 3-7.

#### *Komparatorer*

Chlorambucil i kombination med obinutuzumab (CD20-antistof) doseret som følger i 6 serier a 28 dage:

- Chlorambucil p.o. 0,5 mg/kg på dag 1 og 15
- Obinutuzumab i.v. 100 mg på dag 1, 900 mg på dag 2 og 1.000 mg på dag 8 og 15 i 1. serie, herefter 1.000 mg på dag 1 i serie 2-6.

Bendamustin i kombination med rituximab doseret som følger i op til 6 serier a 28 dage:

- Bendamustin i.v. 70-90 mg/m<sup>2</sup> på dag 1 og 2
- Rituximab i.v. 375 mg/m<sup>2</sup> på dag 1 i første serie, herefter i.v. 500 mg/m<sup>2</sup> på dag 1 i efterfølgende serier.

Fludarabin, cyclofosfamid i kombination med rituximab (R-FC) doseret som følger i 6 serier a 28 dage:

- Fludarabin 25 mg/m<sup>2</sup> i.v. dag 1-3 eller 40 mg/m<sup>2</sup> p.o. dag 1-3
- Cyclofosfamid 250 mg/m<sup>2</sup> i.v. eller p.o. dag 1-3



- Rituximab 375 mg/m<sup>2</sup> i.v. dag 1, 1. serie, serie 2-6: 500 mg/m<sup>2</sup>.

Anvendelsen af de forskellige komparatorer afhænger i dansk klinisk praksis af patienternes alder og komorbiditet. Ansøger bedes belyse sammenligninger med alle komparatorer og gøre tydeligt rede for studiepopulationerne, hvad angår baselinekarakteristika, prognostiske faktorer og sammenlignelighed med den danske patientpopulation.

#### *Effektmål*

De valgte effektmål står i tabel 1.

### 3.3 Klinisk spørgsmål 3

*Hvilken værdi har acalabrutinib som monoterapi sammenlignet med dansk standardbehandling hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation?*

#### *Population*

Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation.

#### *Intervention*

Acalabrutinib som monoterapi doseret som beskrevet i afsnit 3.1.

#### *Komparator*

- Ibrutinib p.o. 420 mg dagligt indtil progression.
- Venetoclax i kombination med obinutuzumab

Obinutuzumab i.v., serie 1: 100 mg på dag 1, 900 mg på dag 2 og 1.000 mg på dag 8 og 15, serie 2-6: 1.000 mg på dag 1.

Venetoclax p.o., serie 1: 20 mg på dag 22-28, serie 2: 50 mg på dag 1-7, 100 mg på dag 8-14, 200 mg på dag 15-21 og 400 mg på dag 22-28. Serie 3-12: 400 mg på dag 1-28 (kontinuerligt til afslutning af cyklus 12).

Fagudvalget ønsker at se sammenligningen foretaget med den af komparatorerne, der giver det bedste sammenligningsgrundlag. Begge komparatorer bør kunne vælges i den sundhedsøkonomiske model.

#### *Effektmål*

De valgte effektmål står i tabel 1.



### 3.4 Klinisk spørgsmål 4

*Hvilken værdi har acalabrutinib i kombination med obinutuzumab sammenlignet med dansk standardbehandling hos patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation?*

#### *Population*

Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation.

#### *Intervention*

Acalabrutinib i kombination med obinutuzumab doseret som beskrevet i afsnit 3.2.

#### *Komparator*

- Ibrutinib p.o. 420 mg dagligt indtil progression.
- Venetoclax i kombination med obinutuzumab, som angivet i afsnit 3.3.

Fagudvalget ønsker at se sammenligningen foretaget med den af komparatorerne, der giver det bedste sammenligningsgrundlag. Begge komparatorer bør kunne vælges i den sundhedsøkonomiske model.

#### *Effektmål*

De valgte effektmål står i tabel 1.

### 3.5 Klinisk spørgsmål 5

*Hvilken værdi har acalabrutinib som monoterapi sammenlignet med dansk standardbehandling til 2.-linjebehandling af patienter med kronisk lymfatisk leukæmi?*

#### *Population*

Patienter med kronisk lymfatisk leukæmi, der oplever behandlingskrævende relaps eller behandlingssvigt efter mindst en tidligere behandling.

#### *Intervention*

Acalabrutinib som monoterapi doseret som beskrevet i afsnit 3.1.

#### *Komparator*

- Venetoclax i kombination med rituximab doseret som følger:  
Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og 24 måneder frem.  
Fra uge 6, i 6 serier a 28 dage rituximab 375 mg/m<sup>2</sup> i.v. på dag 1 i serie 1, 500 mg/m<sup>2</sup> på dag 1 i serie 2-6.
- Ibrutinib p.o. 420 mg dagligt indtil progression



Fagudvalget ønsker at se sammenligningen foretaget med den af komparatorerne, der giver det bedste sammenligningsgrundlag. Begge komparatorer bør kunne vælges i den sundhedsøkonomiske model.

### Effektmål

De valgte effektmål står i tabel 1.

## 3.6 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel. I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og de mindste klinisk relevante forskelle.

**Tabel 1** Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Overlevelse (OS)	<i>Kritisk</i>	<i>Dødelighed</i>	Forskel i overlevelseshastighed ved 3 år eller ved længst mulig opfølgningstid	5 %-point
Progressionsfri overlevelse (PFS)	<i>Vigtigt</i>	<i>Livskvalitet, alvorlige symptomer og bivirkninger***</i>	Forskel i andel der opnår PFS efter 3 år eller længst muligt opfølgningstid	10 %-point
Bivirkninger	<i>Vigtigt</i>	<i>Livskvalitet, alvorlige symptomer og bivirkninger</i>	Andel der oplever grad 3-4 uønskede hændelser (+ kvalitativ gennemgang)	10 %-point
Livskvalitet	<i>Vigtigt</i>	<i>Livskvalitet, alvorlige symptomer og bivirkninger</i>	EORTC QLQ-C30	10 point

\*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.

\*\* Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

\*\*\* Eftersom PFS er et sammensat effektmål, der indeholder både progression og død, anvendes væsentlighedskriterierne for alvorlige symptomer og bivirkninger.



### 3.6.1 Kritiske effektmål

#### *Overlevelse*

Det primære mål for behandling af CLL er at forbedre patientens overlevelse (overall survival, OS). Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død, uanset årsag. Overlevelse opgøres typisk som en medianoverlevelse eller som en andel af patienter, der er i live ved en given opfølgningstid. Den mediane overlevelse er oftest ikke tilgængelig ved godkendelsen af nye lægemidler til behandling af CLL, fordi overlevelsen med nuværende behandlingsmuligheder er mellem 4 og 12 år. Overlevelseshraten ved 3 år er i omegnen af 90 % for patienter, der behandles i førstelinje [20]. Overlevelsen ønskes derfor opgjort som andelen af patienter, der er i live efter 3 år eller efter længst mulig opfølgningstid. For 3-årsoverlevelseshrate vurderer fagudvalget, at 5 %-point er en klinisk relevant forskel mellem grupperne.

I tilfælde hvor de ønskede overlevelseshdata ikke er tilgængelige, ønsker fagudvalget at ansøge supplerer med information om surrogateffektmålet PFS-rate. Hvis de ønskede overlevelseshdata er tilgængelige, vil data for PFS ikke anvendes i kategoriseringen. Hvis den endelige ansøgning beror på PFS, bedes ansøger redegøre for sammenhængen mellem surrogateffektmålet og det kliniske effektmål overlevelse.

### 3.6.2 Vigtige effektmål

#### *Progressionsfri overlevelse*

Progressionsfri overlevelse (progression-free survival, PFS) er defineret som tiden fra randomisering til sygdomsprogression, jf. iwCLL guidelines [21]. PFS anses desuden af EMA for at være et passende primært effektmål for vurdering af nye lægemidler til CLL, men den nødvendige opfølgningstid for modne PFS-data (median) er over fem år. Fagudvalget ønsker derfor PFS opgjort som PFS-rate ved 3 år eller med længst mulig opfølgningstid. PFS vurderes at være et vigtigt effektmål. Da hændelsesraterne for progression ved 3-årsopfølgning vil være højere end hændelsesraterne for død, forventes der en større forskel i PFS-rate sammenlignet med OS-rate mellem grupperne ved 3-årsopfølgning. Derfor vurderer fagudvalget, at den mindste klinisk relevante forskel for 3-års PFS-rate er 10 %-point.

#### *Livskvalitet*

EORTC-QLQ-C30 er et generisk spørgeskema, som anvendes til kræftpatienter. Redskabet måler livskvalitet, symptomer og overordnet helbredsstatus. Spørgeskemaet består af 30 spørgsmål og er udviklet til brug i klinisk forskning. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer. Den mindste klinisk relevante forskel baserer sig på Osoba et al., hvor en lille ændring i livskvalitet er defineret som 10 point [22]. Fagudvalget vælger at anvende den mindste klinisk relevante forskel på 10 point mellem grupperne. Fagudvalget bemærker, at det kan være vanskeligt at foretage en meningsfuld sammenligning af patienternes livskvalitet på tværs af de forskellige behandlinger og studier, da behandlingsregimerne har



forskellig varighed. Fagudvalget ønsker, at ansøger undersøger, hvorvidt der for intervention og komparator findes fælles opfølgningstider for ændringen i livskvalitet og opgør disse i den endelige ansøgning.

#### *Bivirkninger*

##### **Andel patienter med mindst én uønsket hændelse af grad 3-4**

Fagudvalget ønsker alvorlige uønskede hændelser opgjort som andel af patienter, der oplever mindst en grad 3-4 bivirkning, og en forskel mellem grupperne på 10 procentpoint anses som klinisk relevant. Fagudvalget vurderer, at størstedelen af patienterne (ca. 70 %) vil opleve en grad 3-4 uønskede hændelser i løbet af 2 år. Da fagudvalget ikke har kendskab til kliniske studier, der direkte sammenligner effekten af acalabrutinib med alle komparatorer, bør ansøger vurdere, om sammenligning af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, median opfølgningstid, dataindsamling og hvordan bivirkninger/hændelser er opgjort og rapporteret. Overvejelser omkring dette skal fremgå i den endelige ansøgning.

##### **Kvalitativ gennemgang af uønskede hændelser og bivirkninger**

Fagudvalget vil desuden foretage en kvalitativ gennemgang af bivirkningstyperne med udgangspunkt i SAE-lister fra studier med henblik på at vurdere, om der er forskel i bivirkningsprofilerne mht. alvorlighed, håndterbarhed og hyppighed af bivirkningerne. Den kvalitative gennemgang af bivirkningslisterne vil ligeledes belyse, hvorvidt en eventuel forskel mellem behandlingerne i andel af patienter, der oplever alvorlige bivirkninger, skyldes klinisk betydende bivirkninger. Fagudvalget vil inddrage produktresuméerne i det omfang, det er nødvendigt. Ansøger bedes derfor vedlægge disse.

## 4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data<sup>1</sup>. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie (ELEVATE-TN), hvor acalabrutinib med og uden obinutuzumab er sammenlignet direkte

<sup>1</sup> For yderligere detaljer se [Medicinrådets kriteriepapir om anvendelse af upublicerede data](#)



med chlorambucil i kombination med obinutuzumab. Studiet er rapporteret i følgende publikation:

- Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial. *Lancet*. 2020;395(10232):1278–91.

Derudover findes studiet ASCEND, der sammenligner acalabrutinib med bendamustin + rituximab eller idelalisib til patienter i 2. linje.

- Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M, et al. ASCEND: Phase III, Randomized Trial of Acabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2020;38(25):2849–61.

Det er ikke tilstrækkeligt datagrundlag til at besvare alle de kliniske spørgsmål. Ansøger skal derfor undersøge, om der findes andre studier, som besvarer de effektmål, der ikke er rapporteret i ovennævnte studier og belyser de komparatorer, der ikke indgår i ovennævnte studier. Ansøger skal på baggrund af studierne foretage en indirekte sammenligning for at besvare de kliniske spørgsmål, som de direkte sammenligninger ikke kan besvare. Ansøger skal derudover konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

#### **Kriterier for litteratursøgning**

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmbillede eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

#### **Kriterier for udvælgelse af litteratur**

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i [PRISMA-Statement](#).

Ved usikkerheder om hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.



## 5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

### Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimerterne.

### Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.





### Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvisse situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

### Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetiser data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurder, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studierne validitet og relevans, uanset valg af analysemetode.

### Særligt for denne protokol

Ansøger bedes undersøge muligheden for at besvare de kliniske spørgsmål ved en netværksmetaanalyse og bedes gøre det, såfremt det er metodemæssigt forsvarligt. Ved brug af netværksmetaanalyser anbefaler Medicinrådet, at det analyserede netværk bliver begrænset til de behandlingsalternativer (aktive såvel som eventuelt placebo, 'best supportive care' eller 'standard of care'), som er nødvendige for at belyse sammenligningen mellem det nye lægemiddel og de(n) valgte komparator(er).

### Sundhedsøkonomiske analyser

En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være



gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, f.eks. behandlingstid eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

## 6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

## 7. Andre overvejelser

### 7.1 IGHV-mutationsstatus

Ansøger bedes med henblik på evt. differentiering af effekt at bidrage med separate effektopgørelser for patienter hhv. umuteret og hypermuteret IGHV-status for alle



effektmål i sammenligningen med kemoimmunterapi. Opdeling af populationen ift. IGHV-mutationsstatus bør også kunne tilgodeses i den sundhedsøkonomiske model.

## 7.2 Kombination med obinutuzumab

Fagudvalget ønsker at undersøge værdien af at kombinere acalabrutinib med obinutuzumab til patienter i 1. linje, og dette ønske bedes afspejlet i den sundhedsøkonomiske model.

## 7.3 Behandling med acalabrutinib før eller efter ibrutinib

Tidligere behandling med en B-celle-receptorhæmmer er et eksklusionskriterium i ASCEND-studiet. Da acalabrutinib og ibrutinib begge tilhører denne gruppe og har samme target (BTK), ønsker fagudvalget, at ansøger redegør for evidensen for at anvende de to behandlinger efter hinanden. Fagudvalget ønsker, at ansøger inddrager viden om mutation af C481-sitet i forbindelse med behandlingssvigt på ibrutinib, og hvorvidt det har betydning for evt. efterfølgende effekt af acalabrutinib.

## 7.4 Samtidige vurderinger i fagudvalget

Fagudvalget gør opmærksom på, at ibrutinib + rituximab også er under vurdering i Medicinrådet til tidligere ubehandlede patienter uden del17p/TP53-mutation.

# 8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.



## 9. Referencer

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# 10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

## Medicinrådets fagudvalg vedrørende kronisk lymfatisk leukæmi (CLL)

Sammensætning af fagudvalg	
Formand	Indstillet af
Robert Schou Pedersen <i>Overlæge</i>	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
Medlemmer	Udpeget af
Thor Høyer <i>Afdelingslæge</i>	Region Nordjylland
Annika Rewes <i>Afdelingslæge</i>	Region Syddanmark
Rasmus Bo Dahl-Sørensen <i>Afdelingslæge</i>	Region Sjælland
Jindrich Mourek <i>Overlæge</i>	Region Hovedstaden
Stine Trolle Poulsen <i>Farmaceut</i>	Dansk Selskab for Sygehusapoteksledelse
Samuel Azuz <i>Reservelæge</i>	Dansk Selskab for Klinisk Farmakologi
To patienter/patientrepræsentanter	Danske Patienter

### Medicinrådets sekretariat

Medicinrådet  
Dampfærgevej 27-29, 3.th.  
2100 København Ø  
+45 70 10 36 00  
[medicinraadet@medicinraadet.dk](mailto:medicinraadet@medicinraadet.dk)



# 11. Versionslog

## Versionslog

Version	Dato	Ændring
1.0	8. december 2020	Godkendt af Medicinrådet



# 12. Bilag

## Bilag 1: Søgestreng

Søgestreng for identifikation af relevant litteratur i PubMed.

<https://www.ncbi.nlm.nih.gov/pubmed/advanced>

#	Søgetermer	Kommentar
1	Leukemia, Lymphocytic, Chronic, B-Cell[mh]	Søgetermer for indikationen
2	CLL[tiab]	
3	chronic lymphocytic leukemia[tiab] OR chronic lymphocytic leukaemia[tiab]	
4	chronic lymphatic leukemia[tiab] OR chronic lymphatic leukaemia[tiab]	
5	chronic lymphoblastic leukemia[tiab] OR chronic lymphoblastic leukaemia[tiab]	
6	chronic b-cell leukemia[tiab] OR chronic b-cell leukaemia[tiab]	
7	SLL[tiab] OR small lymphocytic lymphoma[tiab] OR small cell lymphoma[tiab]	
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	
9	newly diagnosed[tiab] OR treatment-naive[tiab] OR treatment-naïve[tiab]	Søgetermer for tidligere ubehandlede patienter
10	1L[tiab] OR firstline[tiab] OR first-line[tiab] OR frontline[tiab] OR front-line[tiab] OR primary treatment[tiab] OR primary therapy[tiab] OR untreated[tiab] OR initial therapy[tiab]	
11	Recurrence[mh] OR Neoplasm Recurrence, Local[mh] OR 2L[ti] OR secondline[ti] OR second-line[ti] OR relapse*[ti] OR refractory[ti] OR recurren*[ti] OR previously treated[ti]	Søgetermer for 2.-linjebehandling til eksklusion i spg 1-4
12	Recurrence[mh] OR Neoplasm Recurrence, Local[mh] OR 2L[tiab] OR secondline[tiab] OR second-line[tiab] OR relapse*[tiab] OR refractory[tiab] OR recurren*[tiab] OR previously treated[tiab]	Søgetermer 2.-linjebehandling til anvendelse i spg 5
13	(#8 AND (#9 OR #10)) NOT #11	Population klinisk spg 1-4
14	(#8 AND #12)	Population klinisk spg 5





#	Søgetermer	Kommentar
15	acalabrutinib[nm] OR acalabrutinib[tiab] OR ACP-196[tiab] OR Calquence*[tiab]	Søgetermer for intervention og komparatorer
16	venetoclax[nm] OR venetoclax[tiab] OR Venclyxto*[tiab] OR Venclexta*[tiab]	
17	obinutuzumab[nm] OR obinutuzumab[tiab] OR Gazyva*[tiab] or afutuzumab[tiab]	
18	Chlorambucil[mh] OR chlorambucil[tiab] OR amboclorin*[tiab] OR chloraminophene[tiab] OR chlorbutin*[tiab] OR Leukeran*[tiab]	
19	Bendamustine Hydrochloride[mh] OR bendamustin*[tiab] OR Levact*[tiab] OR Treanda*[tiab]	
20	Rituximab[mh] OR rituximab[tiab] OR Rituxan*[tiab] OR Mabthera*[tiab]	
21	fludarabine[nm] OR fludarabine[tiab] OR Fludara*[tiab]	
22	Cyclophosphamide[mh] OR cyclophosphamide[tiab] OR cyclophosphan*[tiab] OR cytophosphan*[tiab] OR Cytoxan*[tiab] OR Endoxan*[tiab] OR Neosar*[tiab]	
23	R-FC[tiab] OR RFC[tiab]	
24	PCI 32765[nm] OR ibrutinib[tiab] OR Imbruvica*[tiab] OR PCI-32765[tiab] OR PCI32765[tiab]	
25	#15 OR (#17 AND #18) OR (#19 AND #20) OR (#23 OR (#20 AND #21 AND #22)) OR #24	Intervention og komparatorer spg 1-4
26	#15 OR #24 OR (#20 AND #16)	Intervention og komparator spg 5
27	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	Søgetermer for ikke relevante publikationstyper og dyrestudier (der ekskluderes)
28	animals[mh] NOT humans[mh]	
29	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	
30	#27 OR #28 OR #29	
31	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]	Filter til identifikation af RCT'er



#	Søgetermer	Kommentar
32	(#13 AND #25 AND #31)	Kombination af population, intervention og komparatorer til spg 1-4.
33	(#14 AND #26 AND #31)	Kombination af population, intervention og komparatorer til spg 5.
34	(#32 OR #33) NOT #30	Endelig søgning

Feltkoder: mh = MeSH Term nm = Supplementary Concept/Substance tiab = title/abstract, inkl. forfatterkeywords pt = publication type

#### Søgestreng for identifikation af relevant litteratur i CENTRAL (Cochrane Library).

<https://www.cochranelibrary.com/advanced-search/search-manager>

#	Søgetermer	Kommentar
#1	[mh "Leukemia, Lymphocytic, Chronic, B-Cell"]	Søgetermer for indikationen
#2	(CLL or SLL):ti,ab	
#3	(chronic next (lymphocytic or lymphatic or lymphoblastic or b-cell or small) next leuk*emia):ti,ab,kw	
#4	#1 or #2 or #3	
#5	(acalabrutinib or ACP-196 or Calquence*):ti,ab,kw	Søgetermer for intervention og komparatorer
#6	(venetoclax or Venclyxto* or Venclexta* or "ABT 199" or ABT199 or "GDC 0199" or GDC0199 or "RG 7601" or RG7601):ti,ab,kw	
#7	(obinutuzumab or Gazyva* or afutuzumab or "GA 101" or GA101 or "RO 5072759" or RO5072759):ti,ab,kw	
#8	(chlorambucil or chlorambucil or amboclorin or chloraminophene or chlorbutin or Leukeran*):ti,ab,kw	
#9	(bendamustin* or Levact* or Treanda*):ti,ab,kw	
#10	(rituximab or Rituxan* or Mabthera*):ti,ab,kw	
#11	(fludarabine or Fludara*):ti,ab,kw	



#	Søgetermer	Kommentar
#12	(cyclophosphamide or cyclophosphan* or cytophosphan* or Cytoxan* or Endoxan* or Neosar*):ti,ab,kw	
#13	(R-FC or RFC):ti,ab	
#14	(ibrutinib or Imbruvica* or "PCI 32765" or PCI32765):ti,ab,kw	
#15	#5 or (#7 and #8) or (#9 and #10) or (#13 or (#10 and #11 and #12)) or #14 or (#6 and #10)	Kombination af Intervention og komparatorer
#16	("conference abstract" or review):pt	Søgetermer for ikke relevante
#17	(clinicaltrials.gov or trialsearch):so	publikationstyper (der ekskluderes)
#18	NCT*:au	
#19	#16 or #17 or #18	
#20	(#4 and #15) not #19	
#21	#20 not pubmed:an	Endelig søgning

Feltkoder: ti: title ab: abstract kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type