Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi

Anb

Version 1.0

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 baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne. I nogle tilfælde spiller sygdommens alvorlighed en særlig rolle i vurderingen.

Anbefalingen er et klinisk og økonomisk baseret råd til regionerne til brug for deres beslutning om at anvende et givet lægemiddel.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

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Indholdsfortegnelse

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1. Anbefaling vedrørende venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi

PATIENTER MED DEL17P/TP53-MUTATION
MEDICINRÅDET ANBEFALER
venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi med del17p/TP53. Medicinrådet anbefaler venetoclax i kombination med obinutuzumab, fordi behandlingen samlet set ser ud til at være lige så god som den nuværende standardbehandling med ibrutinib. Omkostningerne til kombinationsbehandlingen er samtidig lavere end omkostningerne til ibrutinib.

PATIENTER UDEN DEL17P/TP53-MUTATION
MEDICINRÅDET ANBEFALER IKKE
venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi uden del17p/TP53. Medicinrådet anbefaler ikke venetoclax i kombination med obinutuzumab, fordi behandlingen er forbundet med højere omkostninger end kemoimmunterapi. Derfor vurderer Medicinrådet, at der ikke er et rimeligt forhold mellem lægemidlets dokumenterede effekt og omkostningerne forbundet med behandlingen.

2. Medicinrådets konklusion vedrørende lægemidlets værdi

Medicinrådet finder, at værdien af venetoclax + obinutuzumab sammenlignet med kemoimmunterapi **ikke kan kategoriseres** i henhold til Medicinrådets metoder hos patientpopulationen uden del17p/TP53-mutation. Evidensens kvalitet er **meget lav**. Mængden og typen af bivirkninger for venetoclax + obinutuzumab er sammenlignelig med chlorambucil + obinutuzumab, mens bivirkningsprofilen for venetoclax + obinutuzumab er at foretrække i sammenligning med både bendamustin + rituximab og fludarabin + cyclofosfamid + rituximab.
Baseret på data for PFS, vurderer Medicinrådet, at der med venetoclax + obinutuzumab er en behandlingsgevinst i subpopulationen af patienter, der er IGHV-umuterede sammenlignet med kemoimmunoterapi.

Medicinrådet finder, at værdien af venetoclax + obinutuzumab sammenlignet med ibrutinib **ikke kan kategoriseres** i henhold til Medicinrådets metoder hos patientpopulationen med del17p/TP53-mutation. Evidensens kvalitet er **meget lav**. Mængden og typen af bivirkninger er sammenlignelig for de to behandlinger, og data for effekt giver ikke anledning til at skelne mellem de to behandlinger, som Medicinrådet derfor betragter som klinisk ligestillede behandlingsalternativer.

Læs mere i Medicinrådets vurdering af lægemidlets værdi og den bagvedliggende protokol (se bilag). Ansøgers høringssvar har ikke givet anledning til ændringer i vurderingen af lægemidlet.

3. Resultater af sundhedsøkonomiske analyser

I Medicinrådets hovedanalyse bliver den inkrementelle omkostning pr. patient ca. 135.000 kr. ved sammenligning med chlorambucil + obinutuzumab, 257.000 kr. ved sammenligning med fludarabin + cyclofosfamid + rituximab og 209.000 kr. ved sammenligning med bendamustin + rituximab sammenlignet med standardbehandlingen igennem et helt behandlingsforløb. Budgetkonsekvenserne ved en anbefaling bliver i det femte år efter en anbefaling 61 mio. kr.

Lægemiddelvirksomheden har dog givet en fortrolig rabat, og derfor er de reelle inkrementelle omkostninger og budgetkonsekvenser lavere.

Opgjort i listepriser vil det koste ca. 1,6 mio. kr. mindre at behandle en patient med venetoclax + obinutuzumab end med ibrutinib i 1. linje baseret på den sundhedsøkonomiske analyse af et helt behandlingsforløb. I det femte år efter en anbefaling vil det koste 10 mio. kr. mindre for sundhedsvæsenet at ibrugtage lægemidlet. Lægemiddelfirmaerne bag både venetoclax og ibrutinib har dog givet en fortrolig rabat, og derfor er den reelle besparelse mindre.

Læs mere i den sundhedsøkonomiske afrapportering (se bilag).

4. Alvorlighed

Sygdommens alvorlighed er altid medtaget i Medicinrådets vurdering af et lægemiddels værdi. Det sker i forbindelse med valg af effektmål, og den vægt effektestimaterne tillægges, hvilket vil være forskelligt alt efter typen af effektmål. Derudover har Medicinrådet et alvorlighedsprincip, som Medicinrådet kan inddrage i helt særlige situationer. Dette har ikke været nødvendigt at inddrage i denne sag.

5. Anbefalingen betyder

PATIENTER MED DEL17P/TP53-MUTATION
Anbefalingen betyder, at Medicinrådet råder regionerne til at bruge venetoclax + obinutuzumab til patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med del17p/TP53-mutation, men ikke nødvendigvis som førstevalg til alle patienter. Lægemidlet vil indgå i en kommende Medicinrådets behandlingsvejledning og lægemiddelrekommandation inden for terapiområdet. Indtil da anbefaler Medicinrådet, at regionerne bruger det lægemiddel, der er forbundet med de laveste omkostninger.

PATIENTER UDEN DEL17P/TP53-MUTATION
Anbefalingen betyder, at Medicinrådet råder regionerne til ikke at bruge venetoclax + obinutuzumab til patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden del17p/TP53-mutation.

6. Sagsbehandlingstid

Medicinrådet har brugt 14 uger på arbejdet med venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi.

7. Kontaktinformation til Medicinrådet

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8. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	18. november 2020	Godkendt af Medicinrådet

9. Bilag

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. venetoclax, version 1.0
2. Forhandlingsnotat fra Amgros vedr. venetoclax
3. Høringssvar fra ansøger, inkl. efterfølgende dialog vedr. den sundhedsøkonomiske afrapportering
4. Høringssvar fra ansøger, inkl. efterfølgende dialog vedr. lægemidlets værdi
5. Medicinrådets vurdering vedr. venetoclax til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi, version 1.1
6. Ansøgers endelige ansøgning
7. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
8. Medicinrådets protokol for vurdering vedr. venetoclax til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi, version 1.0

Medicinrådet

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Medicinrådet

Sundhedsøkonomisk afrapportering

Venetoclax

Kronisk lymfatisk leukæmi

Version 1.0

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Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for venetoclax + obinutuzumab til behandling af patienter med tidligere ubehandlet kronisk lymfatisk leukæmi, samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under afsnittene "*Sekretariatets vurdering*". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.

Afsnit 2.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

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Opsummering

Baggrund

Venetoclax + obinutuzumab er indiceret til behandling af patienter med tidligere ubehandlet kronisk lymfatisk leukæmi.
Omkring 150 nye patienter pr. år kandiderer årligt til behandling af den ansøgte indikation i Danmark. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af AbbVie.

Analyse

Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med venetoclax + obinutuzumab. Analysen har en tidshorisont på 30 år. Venetoclax + obinutuzumab sammenlignes med chlorambucil + obinutuzumab, bendamustin + rituximab, fludarabin + cyclofosfamid + rituximab og ibrutinib.

Inkrementelle omkostninger og budgetkonsekvenser

De inkrementelle omkostninger for venetoclax + obinutuzumab til patienter uden deletion 17p/p53-mutation bliver ca. [redacted] DKK ved sammenligning med chlorambucil + obinutuzumab, [redacted] DKK ved sammenligning med fludarabin + cyclofosfamid + rituximab og [redacted] DKK ved sammenligning med bendamustin + rituximab. Hvis analysen udføres med AIP, bliver den inkrementelle omkostning pr. patient ca. 135.000 DKK ved sammenligning med chlorambucil + obinutuzumab, 257.000 DKK ved sammenligning med fludarabin + cyclofosfamid + rituximab og 209.000 ved sammenligning med bendamustin + rituximab.
For patienter med deletion 17p/p53-mutation bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK ved sammenligning med ibrutinib i sekretariatets hovedanalyse. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. -1,6 mio. DKK.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af venetoclax + obinutuzumab som standardbehandling vil være ca. [redacted] DKK i år 5 for patienter uden deletion 17p/p53-mutation og [redacted] DKK for patienter med deletion 17p/p53-mutation. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 61 mio. DKK for patienter uden deletion 17p/p53-mutatio i år 5, mens de er ca. -10 mio. DKK for patienter med deletion 17p/p53-mutation.

Konklusion

Resultatet af hovedanalysen viser, at der er omkostninger forbundet med en anbefaling af venetoclax + obinutuzumab i 1. linje. Omkostningerne i analysen er i høj grad drevet af de høje lægemiddelpriser. Analysen inkluderer behandling i 2. linje. Ændringer af, hvilke behandlinger der vælges i de efterfølgende linjer, har stor indflydelse på analysens resultat.

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Liste over forkortelser

AIP	Apotekernes indkøbspris
BSC	Best supportive care
CLL	Kronisk lymfatisk leukæmi
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
OS	Samlet overlevelse
SAIP	Sygehusapotekernes indkøbspris

1. Baggrund for den sundhedsøkonomiske analyse

AbbVie (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af venetoclax og har den 12. august 2020 indsendt en ansøgning til Medicinrådet om anbefaling af venetoclax + obinutuzumab som standardbehandling på danske hospitaler til behandling af patienter med tidligere ubehandlet kronisk lymfatisk leukæmi. Som et led i denne ansøgning vurderer Medicinrådets sekretariat på vegne af Medicinrådet den sundhedsøkonomiske analyse, ansøger har indsendt. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

1.1 Patientpopulation

Kronisk lymfatisk leukæmi (CLL) er den almindeligste leukæmi i de vestlige lande og udgør ca. 30 % af alle 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 i Danmark [2]. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark [3]. Medianalderen er ved diagnose 70 år, og dobbelt så mange mænd som kvinder får diagnosen [1,2].
Denne analyse omhandler voksne patienter med tidligere ubehandlet kronisk lymfatisk leukæmi.

1.1.1 Subpopulationer

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 cyclofosfamid 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 proteinkinasehæmmeren ibrutinib. Hvis ibrutinib ikke tolereres kan i stedet anvendes idelalisib i kombination med rituximab.
For patienter uden deletion 17p/p53-mutation afgøres valget af cytostatika og anti-CD20-antistof af patientens alder, performancestatus og mængden af komorbiditet. Fludarabin + cyclofosfamid + rituximab anvendes typisk til de yngre patienter med god performance status, bendamustin + rituximab til den ældre patientpopulation med god performacestatus og chlorambucil + et CD20 antistof til patienter med dårlig performance status.

1.1.2 Komparator

Medicinrådet har som komparator til venetoclax + obinutuzumab for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion 17p/p53-mutation defineret chlorambucil + obinutuzumab, bendamustin + rituximab og fludarabin + cyclofosfamid + rituximab.

For patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion 17p/p53-mutation er ibrutinib eneste definerede komparator, se Tabel 1.

Tabel 1: Definerede populationer og komparatorer

Population	Komparator
Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion 17p/p53-mutation.	Chlorambucil + obinutuzumab Bendamustin + rituximab Fludarabin + cyclofosfamid + rituximab
Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion 17p/p53-mutation.	Ibrutinib

1.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af venetoclax + obinutuzumab som mulig standardbehandling på danske hospitaler til patienter med tidligere ubehandlet kronisk lymfatisk leukæmi.
Medicinrådet har vurderet den kliniske merværdi af venetoclax + obinutuzumab som vedligeholdelsesbehandling og specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1*:*

Hvilken værdi har venetoclax + obinutuzumab sammenlignet med cytostatika i kombination med et anti-CD20-antistof for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion 17p/p53-mutation?

Klinisk spørgsmål 2:

Hvilken værdi har venetoclax + obinutuzumab sammenlignet med ibrutinib for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion 17p/p53-mutation?

2. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for venetoclax + obinutuzumab sammenlignet med følgende behandlingsalternativer:

- Chlorambucil + obinutuzumab
- Bendamustin + rituximab
- Fludarabin + cyclofosfamid + rituximab
- Ibrutinib

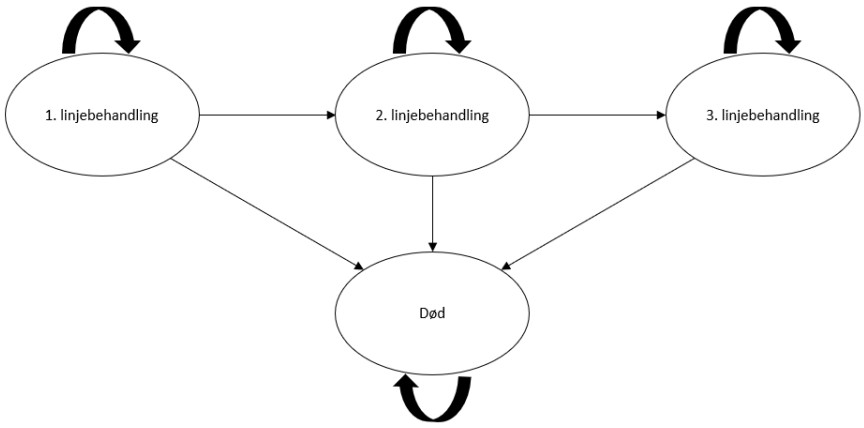
I det nedenstående vil den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

2.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere omkostningerne forbundet med behandling af CLL fra 1. til 3. behandlingslinje.
Analysen baserer sig på fase III-studiet CLL14, hvor venetoclax + obinutuzumab sammenlignes med behandling med chlorambucil + obinutuzumab[1].

2.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival model* til at estimere omkostningerne forbundet med behandling med venetoclax for de to subgrupper af CLL-patienter med og uden deletion 17p/p53-mutation. Modellen består af 60 halvårlige cyklusser. I modellen estimeres omkostninger forbundet med behandlingsalternativerne fra 1. linjebehandling til 3. linje, hvor 2. linje antages at bestå af ibrutinib for patienter uden deletion 17p/p53-mutation, hvor patienterne har fået kemoimmunterapi i 1. linje. For patienter med deletion 17p/p53-mutation antages behandling efter ibrutinib i 1. linje at være venetoclax + rituximab, mens 2. linjebehandling for venetoclax + obinutuzumab antages at være ibrutinib. 3. linjebehandling antages at bestå af best supportive care (BSC) for alle patienter. Figur 1 viser modellens struktur.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen

Patienternes vej gennem modellens forskellige stadier bestemmes af sandsynligheder for at progrediere eller dø i hvert stadie. Sandsynligheden bestemmes i 1. linje af OS- og PFS-kurver for 1. linjebehandling af CLL-patienter, med og uden deletion 17p/p53-mutation, med venetoclax + obinutuzumab. Disse kurver er estimeret ved hjælp af Hazard Ratio (HR) baseret på indirekte sammenligninger af de forskellige behandlingsalternativer i de forskellige behandlingslinjer. De indirekte sammenligninger er foretaget ved en netværks-metaanalyse på baggrund af de samme studier, der indgår i den kliniske vurdering. Ansøger har også inkluderet baggrundsmortalitet fra den generelle danske befolkning, som er baseret på to års data (2018-2019) fra statistikbanken [3].
De patienter, der overlever en behandlingslinje, vil fortsætte til næste behandlingslinje indtil 3. linje, som består af best supportive care (BSC), hvor patienten bliver indtil død.
Til at estimere 2. linjebehandlingsforløb benytter ansøger PFS- og OS-kurver, der baseres på kurverne for venetoclax + rituximab fra en publiceret netværksmetaanalyse. Ansøger benytter HR på [redacted] for patienter uden deletion 17p/p53-mutation, mens der for patienter med deletion 17p/p53-mutation anvendes en HR på [redacted]. HR anvendt til at estimere PFS og OS stammer fra samme netværksmetaanalyse. [2]
Ansøger har inkluderet omkostninger til 3. linjebehandling, som estimeres ud fra samme overlevelseskurver som 2. linje, men ansøger antager, at HR er [redacted] for 3. linjebehandling. En HR på [redacted] vil give en gennemsnitlig overlevelse for en patient, der modtager kemoimmunterapi, på mellem 8 og 8,7 år, alt efter hvilken kemoimmunterapi der vælges. Ansøgers estimerede HR er vist i Tabel 2.

Tabel 2: Ansøgers estimeret HR

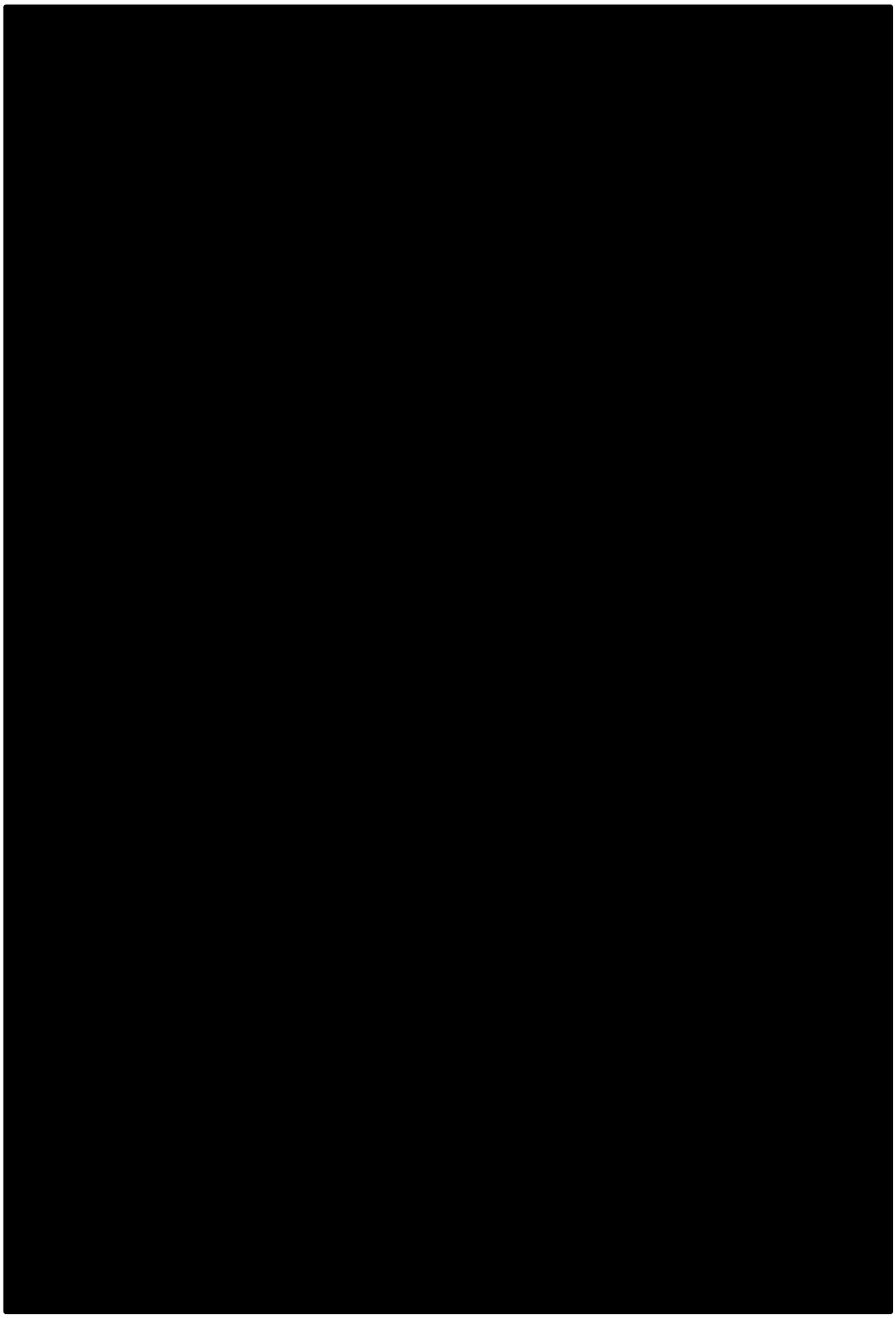
	1. linje		2. linje	
	PFS	OS	PFS	OS
Fludarabin + cyclofosfamid + rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustin + rituximab	[redacted]	[redacted]	[redacted]	[redacted]

Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	-	-	[redacted]	[redacted]
1 linje vs. 2. linje (uden deletion)	-	-	[redacted]	[redacted]
1 linje vs. 2. linje (med deletion)	-	-	[redacted]	[redacted]

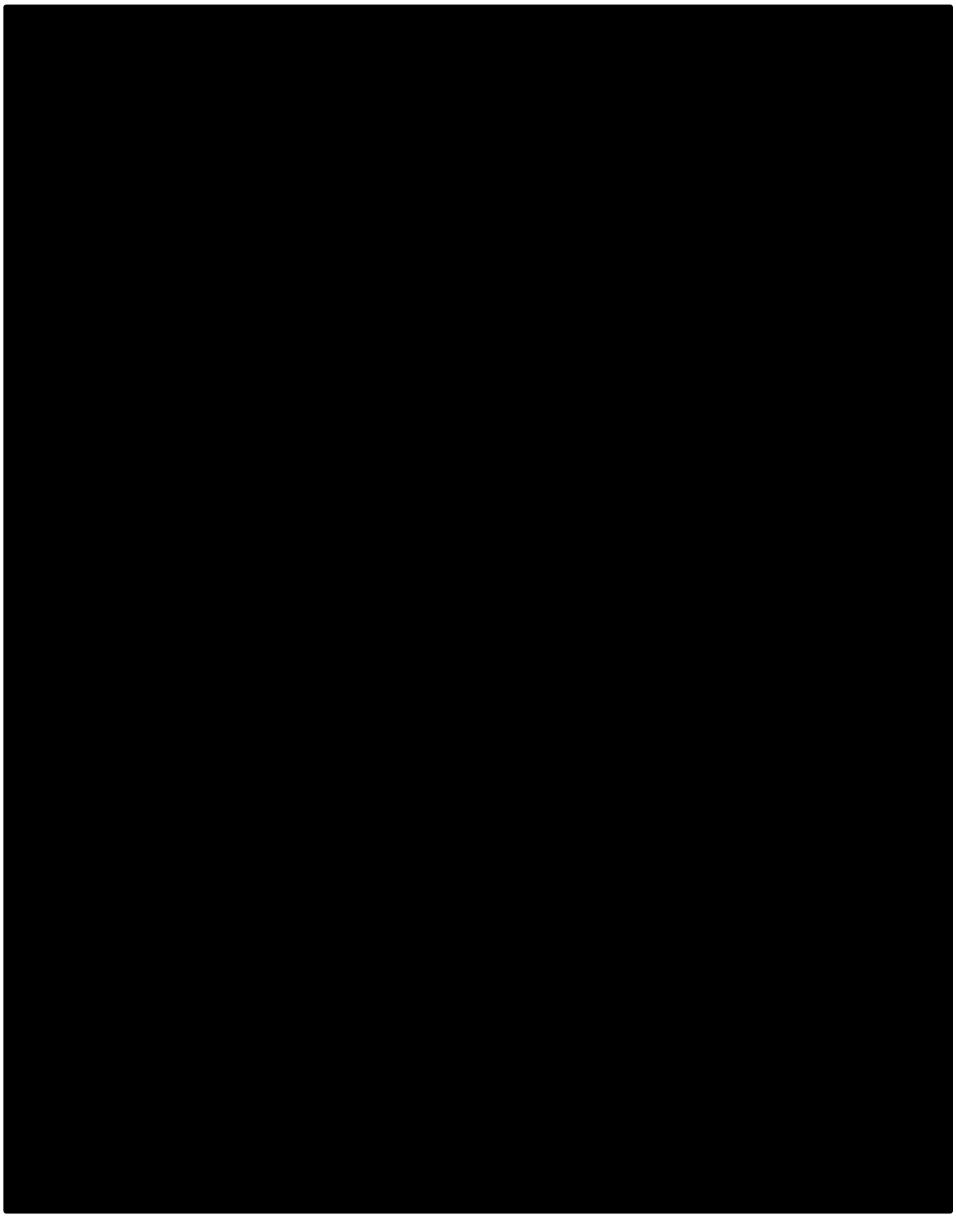
Modellen indeholder fire behandlingsarme for patienterne uden deletion 17p/p53-mutation, så det er muligt at sammenligne venetoclax + obinutuzumab med hver af komparatorerne angivet i Medicinrådets protokol. For patienterne med deletion 17p/p53-mutation er der i overensstemmelse med Medicinrådets protokol kun valgt én komparator.

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan Meier (KM)-data for PFS og OS fra CLL14-studiet. Ansøger har anvendt en [redacted] til at ekstrapolere PFS for venetoclax + obinutuzumab. For chlorambucil + obinutuzumab har ansøger anvendt en [redacted] funktion til at ekstrapolere PFS-data, se Figur 2.

For OS har ansøger valgt en [redacted] til at ekstrapolere OS for både venetoclax + obinutuzumab og chlorambucil + obinutuzumab, se Figur 3.



Figur 2: Ekstrapolering af PFS-data. VENG: venetoclax + obinutuzumab, GClb: chlorambucil + obinut-uzumab



Figur 3: Ekstrapolering af OS-data. VENG: venetoclax + obinutuzumab, GClb: chlorambucil + obinutuzumab

Sekretariatets vurdering

Sekretariatet har konsulteret fagudvalget i forhold til antagelserne for 2. linjebehandling, og på baggrund af fagudvalgets tilbagemelding ændres 2. linjebehandling fra at bestå af ibrutinib for alle patienter behandlet med kemoimmunterapi i 1. linje til at bestå af ibrutinib i 50 % af tilfældene og venetoclax + rituximab i 50 % af tilfældene. Ansøgers tilgang til estimering af omkostninger i 3. linje findes ikke acceptabel. Der mangler argumentation for valg og underbygning med referencer eller ekspertudsagn. Sekretariatet har konsulteret fagudvalget, som ikke er enig i ansøgers antagelse omkring 3. linjebehandling.

Sekretariatet accepterer ansøgers modelantagelser, men 2. linjebehandling ændres, så det svarer til dansk klinisk praksis, og 3. linjebehandling ekskluderes fra sekretariatets hoved-analyse.

2.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på 30 år for at opfange hele CLL-patientens levetid, som har en gennemsnits-alder på 70 år ved modellens start.
Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Sekretariatets vurdering

Sekretariatet accepterer ansøgers valg vedr. analyseperspektiv.

2.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøko-nomiske analyse af venetoclax + obinutuzumab. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger. Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP i den endelige afrapportering.

2.2.1 Lægemiddelomkostninger

Ansøger har baseret de anvendte lægemiddeldoser på Medicinrådets protokol for vurde-ring af venetoclax, se Tabel 3. Da rituximab doseres i forhold til patientens kropsoverflade, antager ansøger, at en gennemsnitlig patient har en kropsoverflade på 1,89 m^2. Chloram-bucil gives som en vægtbaseret dosis, og ansøger antager, at den gennemsnitlige patient vejer 65 kg.

Tabel 3: Anvendte lægemiddelpriser, SAIP, (september 2020)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Venetoclax	100 mg	112 stk.	[redacted]	Amgros
Obinutuzumab	1.000 mg	1 stk.	[redacted]	Amgros
Chlorambucil	2 mg	25 stk.	[redacted]	Amgros
Bendamustin	2,5 mg/ml	5 x 40 ml	[redacted]	Amgros
Rituximab	500 mg	1 stk.	[redacted]	Amgros

Fludarabin	25 mg/ml	5 x 2 ml	[redacted]	Amgros
Cyclophosphamid	500 mg	1 stk.	[redacted]	Amgros
Ibrutinib	420 mg	28 stk.	[redacted]	Amgros

Sekretariatets vurdering

Ansøger har antaget, at en gennemsnitlig patient vejer 65 kg. Denne antagelse er ikke underbygget med nogen form for argumentation og findes derfor usikker. Sekretariatet vælger at udføre en følsomhedsanalyse, hvor effekten af variation af patienternes vægt undersøges.
Sekretariatet har konsulteret fagudvalget i forhold til valgte lægemidler. De giver udtryk for, at dansk klinisk praksis er at give fludarabin og cyclofosfamid peroralt. Derfor ændres de to lægemidler til at blive givet peroralt i sekretariatets hovedanalyse.

Sekretariatet accepterer ansøgers lægemiddelomkostninger, men ændrer administrationsformen for fludarabin og cyclofosfamid. Desuden udfører sekretariatet en følsomhedsanalyse, der undersøger effekten af at variere den gennemsnitlig patientvægt.

2.2.2 Hospitalsomkostninger

I forbindelse med opstart af de forskellige behandlingsalternativer forventer ansøger at der vil være varierende antal indlæggelsesdage forbundet med lægemiddelbehandlingen. Ansøger antager, at der vil være to indlæggelsesdage forbundet med opstart af behandling med venetoclax + obinutuzumab, chlorambucil + obinutuzumab, fludarabin + cyclofosfamid + rituximab og bendamustin + rituximab. Ved opstart med venetoclax + rituximab antager ansøger, at der vil være fem indlæggelsesdage forbundet med dette. Behandlingen med ibrutinib antager ansøger vil være forbundet med én indlæggelsesdag, mens behandling med BSC, som ligger i den sidste del af sygdommen, vil indebære 30 indlæggelsesdage.
Ansøger har estimeret, at der vil være fire ambulante kontrolbesøg årligt i forbindelse med alle behandlingsalternativerne. Estimerede antal indlæggelsesdage og ambulante besøg for alle behandlinger er vist i Tabel 4.

Tabel 4: Estimerede indlæggelsesdage og ambulante besøg i forbindelse med behandlingsalternativerne

Behandling	Behandlingsstart	Kontrolbesøg
Venetoclax + obinutuzumab	2	4
Chlorambucil + obinutuzumab	2	4

fludarabin + cyclo-fosfamid + rituxi-mab	2	4
venetoclax + rituxi-mab	5	4
Ibrutinib	1	4
bendamustin + ri-tuximab	2	4
BSC	30	4

Ansøger estimerer de forskellige ressourcer i forbindelse med hospitalsbesøgene ved anvendelse af DRG-takster fra 2020. De anvendte takster er vist i Tabel 5.

Tabel 5: Omkostninger til lægemiddeladministration

	Takst [DKK]	DRG 2020
Indlæggelsesdage	3.235	17MA98
Ambulante besøg	3.235	17MA98

Ansøgers analyse for 3. linjebehandling bygger på en antagelse om, at alle patienter vil modtage BSC. Derudover vælger ansøger yderligere at antage, at BSC i alle tilfælde vil koste 50.000 DKK. Ansøger argumenterer med, at det i nogle tilfælde vil være dyrere, da nogle få patienter vil modtage en allogen stamcelletransplantation, og har derfor valgt at inkludere en sensitivitetsanalyse, der undersøger, hvilken indflydelse det vil have på omkostningerne, hvis halvdelen af patienterne, der modtager BSC, også vil modtage en allogen stamcelletransplantation.

Sekretariatets vurdering

Ansøgers antagelse om, at alle patienter vil modtage BSC som 3. linjebehandling, og at dette i alle tilfælde vil koste 50.000 DKK, findes ikke tilstrækkeligt redegjort for eller på anden måde dokumenteret. Derfor vælger sekretariatet at ekskludere 3. linjebehandling fra egen hovedanalyse.

Sekretariatet har konsulteret fagudvalget for at få valideret hospitalsomkostningerne. Fagudvalget mener, at behandlingsopstart i hovedparten af tilfældene ikke vil medføre indlæggelse. Derfor bliver indlæggelsesdage udskiftet med en takst for ambulant kontakt i sekretariatets hovedanalyse. Ansøgers antagelse om, at alle behandlinger kræver fire kontrolbesøg årligt, findes heller ikke i overensstemmelse med dansk klinisk praksis.

For venetoclax + obinutuzumab og chlorambucil + obinutuzumab forventes patienterne at have 4 kontrolbesøg i første serie og 9 gange i serie 2-6. For bendamustin + rituximab forventes 12 besøg, for fludarabin + cyclofosfamid + rituximab forventes 6 besøg, og for ibrutinib forventes 6 besøg første år og fire besøg efterfølgende år.

Sekretariatet ekskluderer 3. linjebehandling fra sekretariatets hovedanalyse. Derudover ændres indlæggelsesdage i forbindelse med behandlingsopstart til at være en ambulant kontakt, og antal kontrolbesøg ændres til fagudvalgets estimater.

2.2.3 Bivirkningsomkostninger

Ansøger har inkluderet bivirkningsomkostninger. I modellen falder omkostninger til bivirkninger i første cyklus ved behandlingsstart. Denne simplificerede tilgang er valgt, da ansøger argumenterer for, at bivirkninger er en engangsomkostning. De inkluderede bivirkningsfrekvenser er vist i Tabel 6.
I ansøgers model benyttes risici for bivirkning af grad 3 eller mere med en forskel på mindst 2 % mellem behandlingsarmene. Frekvenserne for bivirkninger ved behandling med venetoclax + obinutuzumab og chlorambucil + obinutuzumab stammer fra CLL14-studiet. Disse frekvenser antages af ansøger også at være repræsentative for behandlingen med venetoclax + rituximab og benyttes til at værdisætte omkostningerne forbundet med disse behandlinger. Til at værdisætte omkostningerne ved fludarabin + cyclofosfamid + rituximab, bendamustin + rituximab og ibrutinib-behandling er sandsynligheder for hændelserne baseret på tre forskellige kliniske studier [4–6].

Tabel 6: Rapporterede bivirkningsfrekvenser ved behandlingsalternativerne

	Venetoclax + obinutuzumab [%]	chlorambucil + obinutuzumab [%]	fludarabin + cyclofosfamid + rituximab [%]	bendamustin + rituximab [%]	Ibrutinib [%]
Asteni	2,8	0,5	0	0	0
Diarré	3,8	0,5	0	7,0	4,0
Dyspnø	2,4	0,5	0	0	0
Febril neutropeni	5,2	3,7	0	0	1,0
Infusionsrelateret reaktion	9,0	10,3	0	0	0
Leukopeni	2,4	4,7	24,0	48,0	0
Neutropeni	52,8	47,7	34,0	59,0	12,0

Penumoni	5,7	4,2	0	9,0	0
Sepsis	4,2	1,4	0	1,0	0
Trombocytopeni	13,7	15,0	7,0	14,0	0

Til at estimere, hvilke omkostninger der er forbundet med bivirkningerne, anvender ansøger DRG 2020-takster. I Tabel 7 er de anvendte DRG-takster vist.

Tabel 7: Anvendte DRG-takster til prissætning af bivirkninger i analysen

Bivirkning	Takst [DKK]	DRG 2020
Asteni	4.082	23MA03
Diarré	5.297	06MA11
Dyspnø	17.830	04MA23
Febril neutropeni	37.603	16MA03
Infusionsrelateret reaktion	36.312	18MA08
Leukopeni	22.589	16MA10
Neutropeni	37.603	16MA03
Penumoni	37.050	04MA13
Sepsis	43.180	18MA01
Trombocytopeni	25.365	16MA09

For 3. linjebehandling, som antages altid at bestå af BSC, har ansøger yderligere antaget, at behandlingen i alle tilfælde vil bestå af omkostninger på 20.000 DKK i forbindelse med behandling af bivirkninger.

Sekretariatets vurdering

Ansøges antagelse om at inkludere omkostninger på 20.000 DKK til behandling af bivirkninger ved BSC ekskluderes fra sekretariatets hovedanalyse, da den ikke er argumenteret eller underbygget.

Sekretariatet ekskluderer omkostninger til bivirkninger ved 3. linjebehandling med BSC.

2.2.4 Patientomkostninger

Patientomkostninger estimeres ud fra en antagelse om, at en patient tilbringer 24 timer ved en dags hospitalisering, mens et ambulant besøg estimeres at tage tre timer pr. besøg. Til at beregne tidsomkostningen anvender ansøger den gennemsnitlige timeløn for en lønmodtager i Danmark efter skat, som af ansøger angives at være 179 DKK, jf. Medicinrådets værdisætning af enhedsomkostninger. Transport til og fra hospitalet i forbindelse med både indlæggelse og ambulante besøg estimeres at koste 100 DKK, jf. Medicinrådets værdisætning af enhedsomkostninger.

Sekretariatets vurdering

Sekretariatet har ændret i ansøgers estimat for hospitalsomkostninger i forbindelse med behandlingsopstart og kontrolbesøg. Dette medfører også ændringer i patientomkostningerne, da antallet af hospitalsbesøg er ændret. Dette vil blive ændret i sekretariatets hovedanalyse.

Sekretariatet accepterer ansøgers antagelser for patienttid, men ændrer antallet af hospitalsbesøg, så det er i overensstemmelse med dansk klinisk praksis.

2.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen.
Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

- Variation i valg af 2. linjebehandling
- Variation i omkostningen forbundet med BSC
- Ændring af prognose for PFS og OS fra den indirekte sammenligning
- Ændring af prognose for 2. linjebehandling

Sekretariatets vurdering

Ansøgers følsomhedsanalyser findes ikke relevante, idet sekretariatet havde flere kritikpunkter til ansøgers hovedanalyse og som følge heraf har ændret i antagelserne i sekretariatets hovedanalyse. De følsomhedsanalyser, ansøger har indsendt, er baseret på antagelser fra hovedanalysen, og vil derfor ikke blive præsenteret.

Sekretariatet vælger ikke at præsentere ansøgers følsomhedsanalyser, men tilføjer en følsomhedsanalyse, der undersøger variation af den gennemsnitlige patientvægt.

2.4 Opsummering af basisantagelser

I Tabel 8 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 8: Basisantagelser for ansøgers og sekretariatets hovedanalyse

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	30 år (livstid)	30 år (livstid)
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patientomkostninger
Behandlingslinje	1. linje behandling 2. linje behandling 3. linjebehandling	1. linjebehandling 2. linjebehandling
2. linjebehandling: • Efter kemoimmunterapi: • Efter Venetoclax + obinutuzumab • Efter ibrutinib	 Ibrutinib Ibrutinib Venetoclax + rituximab	 50 % ibrutinib, 50 % venetoclax + rituximab Ibrutinib Venetoclax + rituximab
Parametriske funktioner for PFS Venetoclax + obinutuzumab: Chlorambucil + obinutuzumab:	[redacted] [redacted] [redacted]	[redacted] [redacted] [redacted]
Parametriske funktioner for OS Venetoclax + obinutuzumab: Chlorambucil + obinutuzumab:	[redacted] [redacted] [redacted]	[redacted] [redacted] [redacted]
HR 1. linje for komparatorer:	(PFS; OS)	(PFS/OS)

Fludarabin + cyclofosfamid + rituximab	[redacted]	[redacted]
Bendamustin + rituximab	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
HR 2. linje for komparatorer:	(PFS; OS)	(PFS; OS)
Fludarabin + cyclofosfamid + rituximab	[redacted]	[redacted]
Bendamustin + rituximab	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
Inkludering af spild	Nej	Nej

3. Resultater

3.1 Resultatet af sekretariatets hovedanalyse

Sekretariatets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, men med følgende justeringer:

- Ændring i valg af 2. linjebehandling
- Ekskludering af 3. linjebehandling
- Ændring i hospitalskontakt i forbindelse med behandlingsopstart
- Ændring af antal kontrolbesøg
- Administrationsform for fludarabin ændres til p.o.
- Administrationsform for cyclofosfamid ændres til p.o.

For patienter uden deletion 17p/p53-mutation bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK ved sammenligning med chlorambucil + obinutuzumab, [redacted] DKK ved sammenligning med fludarabin, cyclofosfamid + rituximab og [redacted] DKK ved sammenligning med bendamustin + rituximab i sekretariatets hovedanalyse. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. 135.000 DKK ved sammenligning med chlorambucil + obinutuzumab, 257.000 DKK ved sammenligning med fludarabin + cyclofosfamid + rituximab og 209.000 ved sammenligning med bendamustin + rituximab.
Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 9, Tabel 10 og Tabel 11.

Tabel 9: Resultatet af sekretariatets hovedanalyse ved sammenligning med chlorambucil + obinutuzumab, DKK, diskonterede tal

	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	384.987	193.407	191.579
Patientomkostninger	72.876	35.790	37.086
2. linjebehandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 10: Resultatet af sekretariatets hovedanalyse ved sammenligning med fludarabin + cyclo-fosfamid + rituxi-mab, DKK, diskonterede tal

	Venetoclax + obinutuzumab	Fludarabin + cyclofosfamid + rituximab	Inkrementelle omkostninger [DKK]

Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	384.987	91.282	293.705
Patientomkostninger	72.876	17.643	55.234
2. linjebehandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 11: Resultatet af sekretariatets hovedanalyse ved sammenligning med bendamustin + rituximab, DKK, diskonterede tal

	Venetoclax + obinutuzumab	Bendamustin + rituximab	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	384.987	78.391	306.595
Patientomkostninger	72.876	10.954	61.922
2. linjebehandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

For patienter med deletion 17p/p53-mutation bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK i sekretariatets hovedanalyse, se Tabel 12. Udføres analysen med AIP, bliver den inkrementelle omkostning pr. patient ca. -1,6 mio. DKK.

Tabel 12: Resultatet af sekretariatets hovedanalyse for patienter ved sammenligning med ibrutinib, DKK, diskonterede tal

	Venetoclax + obinutuzumab	Ibrutinib	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	236.952	100.621	136.331
Patientomkostninger	43.615	22.414	21.201

2. linjebehandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse for meromkostninger udfører sekretariatet en følsomhedsanalyse for gennemsnitlig patientvægt, se Tabel 13.

Tabel 13: Resultatet af sekretariatets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Forøgelse af gennemsnitlig patientvægt til 85 kg	[redacted]

4. Budgetkonsekvenser

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

- Venetoclax + obinutuzumab bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Venetoclax + obinutuzumab bliver ikke anbefalet som standardbehandling.

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimat af patientantal og markedsandel

Budgetkonsekvensanalysen er baseret på de samme input og antagelser som ansøgers hovedanalyse, bortset fra at patient- og transportomkostninger er blevet ekskluderet fra analysen.

Ansøger estimerer behandlingsvalg i 1. linje ud fra patienternes alder og tilstand. Ansøger antager på baggrund af den landsdækkende LYFO-database, at 25 % af patienterne er under 65 år.
Det antages af ansøger, at andelen af patienter uden deletion 17p/p53-mutation, der har god almen tilstand, ligger på 50 %. Det antages at andelen af patienter, der er under 65 år og som har god almen tilstand, udgør 25 % af den samlede population og vil blive behandlet med fludarabin, cyclofosfamid + rituximab, mens patienter med god almen tilstand over 65 år behandles med bendamustin + rituximab. De resterende 50 % af patienterne med deletion 17p/p53-mutation antages at blive behandlet med chlorambucil + obinutuzumab.
For patienter med deletion 17p/p53-mutation antager ansøger, at 100 % af patienterne vil blive behandlet med ibrutinib i 1 linje.
På baggrund af Medicinrådets protokol, antager ansøger, at 150 patienter årligt er kandidater til 1. linjebehandling. Ud af disse patienter vil 135 være uden deletion 17p/p53-mutation, mens de resterende 15 har mutationen. Ansøgers estimat af markedsoptag er vist i Tabel 14 og Tabel 15.

Tabel 14: Ansøgers estimat af patientantal for patienter uden deletion 17p/p53-mutation

	År 1	År 2	År 3	År 4	År 5
Uden deletion17p/p53-mutation med anbefaling					
Venetoclax + obinutuzumab	81	81	81	81	81
Chlorambucil + obinutuzumab	7	7	7	7	7

Bendamustin + rituximab	14	14	14	14	14
Fludarabin + cyclofosfamid + rituximab	34	34	34	34	34
Uden deletion17p/p53-mutation uden anbefaling					
Venetoclax + obinutuzumab	0	0	0	0	0
Chlorambucil + obinutuzumab	68	68	68	68	68
Bendamustin + rituximab	34	34	34	34	34
Fludarabin + cyclofosfamid + rituximab	34	34	34	34	34

Tabel 15: Ansøgers estimat af patientantal for patienter med deletion 17p/p53-mutation

	År 1	År 2	År 3	År 4	År 5
Med deletion17p/p53-mutation med anbefaling					
Venetoclax + obinutuzumab	12	12	12	12	12
Ibrutinib	3	3	3	3	3
Med deletion17p/p53-mutation uden anbefaling					
Venetoclax + obinutuzumab	0	0	0	0	0
Ibrutinib	15	15	15	15	15

Sekretariatets vurdering

Sekretariatet har konsulteret fagudvalget i forhold til ansøgers estimater omkring markedsoptag og ændrer disse estimater så de svarer til dansk klinisk praksis, se Tabel 16 og Tabel 17.
I Medicinrådets vurderingsrapport for venetoclax + obinutuzumab fremhæves patienter der er IGHV-umuterede som dem de patienter der har bedst gavn af behandlingen. Patienterne vurderes ikke at have bedre gavn af behandlingen end de der er IGHV-muterede,

men kemoimmunterapi vurderes at være en mindre effektiv behandling til denne gruppe. I vurderingsrapporten estimerer fagudvalget at ca. 60 % af patienterne uden deletion 17p/p53-mutation er IGHV-umuterede, hvilket svare til ca. 80 patienter. Sekretariatet udfører en følsomhedsanalyse af budgetkonsekvensanalysen, hvor patientantallet vil være svarende til antallet af patienter der er IGHV-umuterede.

Tabel 16: Sekretariatets estimat af patientantal for patienter uden deletion 17p/p53-mutation

	År 1	År 2	År 3	År 4	År 5
Uden deletion17p/p53-mutation med anbefaling					
Venetoclax + obinutuzumab	81	81	81	81	81
Chlorambucil + obinutuzumab	14	14	14	14	14
Bendamustin + rituximab	34	34	34	34	34
Fludarabin + cyclofosfamid + rituximab	7	7	7	7	7
Uden deletion17p/p53-mutation uden anbefaling					
Venetoclax + obinutuzumab	0	0	0	0	0
Chlorambucil + obinutuzumab	34	34	34	34	34
Bendamustin + rituximab	88	88	88	88	88
Fludarabin + cyclofosfamid + rituximab	14	14	14	14	14

Tabel 17: Sekretariatets estimat af patientantal for patienter med deletion 17p/p53-mutation.

	År 1	År 2	År 3	År 4	År 5
Med deletion17p/p53-mutation med anbefaling					
Venetoclax + obinutuzumab	11	11	11	11	11
Ibrutininb	4	4	4	4	4

	Med deletion17p/p53-mutation uden anbefaling				
Venetoclax + obinutuzumab	0	0	0	0	0
Ibrutinib	15	15	15	15	15

4.2 Sekretariatets budgetkonsekvensanalyse

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

- Baseres på sekretariatets hovedanalyse
- Ændret markedsandele for patienter uden deletion 17p/p53-mutation

Sekretariatet estimerer, at anvendelse af venetoclax + obinutuzumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter uden deletion 17p/p53-mutation. Resultatet er præsenteret i Tabel 18.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 61 mio. DKK i år 5.

Tabel 18: Sekretariatets analyse af totale budgetkonsekvenser for patienter uden deletion 17p/p53-mutation, 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]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sekretariatet estimerer, at anvendelse af venetoclax + obinutuzumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med deletion 17p/p53-mutation.

Resultatet er præsenteret i Tabel 19.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. -10 mio. DKK i år 5.

Tabel 19: Sekretariatets analyse af totale budgetkonsekvenser for patienter med deletion 17p/p53-mutation, 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]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.2.1 Resultatet af følsomhedsanalyse af budgetkonsekvensanalysen

Sekretariatet estimerer, at anvendelse af venetoclax + obinutuzumab til patienter, der er IGHV-umuterede og er uden deletion 17p/p53-mutation, vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 20.

Tabel 20: Sekretariatets følsomhedsanalyse af totale budgetkonsekvenser for patienter uden deletion 17p/p53-mutation, der er IGHV-umuterede, 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]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5. Diskussion

Resultatet af hovedanalysen viser, at der er omkostninger forbundet med en anbefaling af venetoclax + obinutuzumab i 1. linje. Omkostningerne i analysen er i høj grad drevet af de højere lægemiddelpriser. Analysen tager højde for, at behandlingen i 2. linje ændres, hvis venetoclax + obinutuzumab gives i 1. linje. Ændringer af, hvilke behandlinger der vælges i de efterfølgende linjer, har stor indflydelse på analysens resultat.

6. Referencer

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7. Bilag

7.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK ved sammenligning med GCbl6, [redacted] DKK ved sammenligning med fludarabin, cyclofosfamid + rituximab og [redacted] DKK ved sammenligning med bendamustin + rituximab over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 21.

Tabel 21: Resultatet af ansøgers hovedanalyse for patienter uden deletion 17p/p53-mutation, DKK

	Omkostning [DKK]	Inkrementelle omkostninger [DKK]
Venetoclax + rituximab	[redacted]	-
Chlorambucil + obinutuzumab	[redacted]	[redacted]
Fludarabin + cyclofosfamid + rituximab	[redacted]	[redacted]
Bendamustin + rituximab	[redacted]	[redacted]

For patienter med deletion 17p/p53-mutation bliver de inkrementelle omkostninger [redacted] DKK.

Tabel 22: Resultatet af ansøgers hovedanalyse for patienter med deletion 17p/p53-mutation, DKK.

	Omkostning [DKK]	Inkrementelle omkostninger [DKK]
Venetoclax + rituximab	[redacted]	-
Ibrutinib	[redacted]	[redacted]

7.2 Ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen.
Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af venetoclax vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter uden deletion 17p/p53-mutation, mens de bliver ca. [redacted] DKK for

patienter med deletion 17p/p53-mutation. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 23 og Tabel 24.

Tabel 23: Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter uden deletion 17p/p53-mutation, mio. DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 24: Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter med deletion 17p/p53-mutation, mio. DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	18.11.2020
Leverandør	Abbvie
Lægemiddel	Venetoclax (venclyxto)
Ansøgt indikation	Venclyxto i kombination med obinutuzumab er indiceret til behandling af tidligere ubehandlet kronisk lymfatisk leukæmi (CLL) hos voksne patienter.

Forhandlingsresultat

Amgros har opnået følgende pris på venetoclax:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Venetoclax	100 mg	112 stk.	40.010,34	[redacted]	[redacted]

Venetoclax er dækket af en kontrakt, der løber indtil d. 31.3.2021. Der er netop blevet publiceret et udbud med kontraktstart d. 1.4.2021 og et år frem.

Leverandøren vurderer, at prisen, der er gældende i dag, er rimelig ift. den ansøgte indikation og derfor tilbyder de ikke en ny pris.

[redacted]

Vurdering af forhandlingsresultatet

Klinisk spørgsmål 1:

Det er Amgros' vurdering, at vi **ikke** har opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

[redacted]

Klinisk spørgsmål 2:

Det er Amgros' vurdering, at vi på nuværende tidspunkt har opnået den bedste pris i relation til sammenligningen med ibrutinib. Denne vurdering baserer vi på følgende punkter:

[redacted]

Leverandøren giver udtryk for, at de vil byde ind med en bedre pris i udbuddet.

Konklusion

Amgros vurderer, at vi ikke har opnået den bedst mulige pris på venetoclax, til det ene kliniske spørgsmål.

[redacted]

Relation til markedet

Nedenstående tabel viser lægemiddelpriserne for de forskellige behandlingskombinationer til CLL over 48 uger. Doseringerne er baseret på lægemidlernes SPC.

Venetoclax alene	[redacted]
Pris venetoclax + obinutuzumab	[redacted]
Ibrutinib	[redacted]
Chlorambucil + obinutuzumab	[redacted]
Bendamustin + rituximab	[redacted]
Fludarabin + cyclofosfamid + rituximab	[redacted]

Status fra andre lande

Sverige (TLV) har godkendt denne kombination (august 2020) til udvalgte patienter populationer.

https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2020-08-28-venclyxto-i-kombination-med-obinutuzumab-ingar-i-hogkostnadsskyddet-med-begransning.html

Fra: Pernille Winther Johansen
Til: Eskildsen, Lars
Cc: Karen Kleberg Hansen
Emne: SV: Venetoclax ansøgning
Dato: 10. november 2020 08:38:39
Vedhæftede filer: image001.png

Kære Lars,

Tak for dine kommentarer til vurderingsrapport og sundhedsøkonomisk vurdering. Vi er enige i punkterne med undtagelse af din kommentar til budgetkonsekvensanalysen. Det estimat du skriver I kommer frem til, er for en 5 årig periode, mens den sundhedsøkonomiske afrapportering angiver budgetkonsekvenserne i år 5. Dog har vi rettet, så det angives at venetoclax medfører en besparelse på 10 mio. i år 5 og ikke en omkostning.

Som nævnt i en tidligere mail, så bedes du indsende det tekniske dokumentet med markeringer af fortrolig information, da det vil blive offentliggjort. Der er deadline for dette i dag.

Med venlig hilsen

Pernille Winther Johansen
Sundhedsøkonom
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Fra: Eskildsen, Lars <lars.eskildsen@abbvie.com>
Sendt: 28. oktober 2020 13:08
Til: Pernille Winther Johansen <pwj@medicinraadet.dk>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>
Emne: RE: Venetoclax ansøgning

Hej Pernille,

Mange tak for din besked – jeg kigger på det og vender tilbage så hurtigt som muligt.

Mvh. Lars

From: Pernille Winther Johansen <pwj@medicinraadet.dk>
Sent: 23. oktober 2020 15:11
To: Eskildsen, Lars <lars.eskildsen@abbvie.com>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>
Subject: [EXTERNAL] Venetoclax ansøgning

Kære Lars,

Jeg skriver til dig for at gøre opmærksom på, at det tekniske dokument der er en del af den sundhedsøkonomiske ansøgning til Medicinrådet, vil blive offentliggjort når der er truffet beslutning for venetoclax.
På nuværende tidspunkt er der ikke lavet nogle markeringer i det tekniske dokument, der indikerer at der er tale om fortrolig information. Hvis der er dele af det tekniske dokument i mener er fortrolig information som I ikke ønsker bliver offentliggjort, skal I sende en version af den tekniske rapport, hvor I tydeligt markerer (gerne med gul overstregning) hvad i anser for fortroligt, og så vil vi sørge for at censurere disse dele inden offentliggørelse.

Med venlig hilsen

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Fra:	Eskildsen, Lars
Til:	Karen Kleberg Hansen
Cc:	Pernille Winther Johansen; Tarang Sharma
Emne:	RE: Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for venetoclax i kombination med obinutuzumab
Dato:	27. oktober 2020 09:22:29
Vedhæftede filer:	image002.png image004.jpg image005.jpg

Kære Karen,

Jeg vil gerne benytte lejligheden til at takke for et godt samarbejde vedr vores ansøgning.

Vi har et par enkelte kommentarer, men ikke nogen jeg mener vil få indflydelse på den kliniske vurdering.

Medicinrådets vurdering:

- Side 18 – afsnit 5.1.5 ”Det vil i dag enten være venetoclax + obinutuzumab eller ibrutinib, som er henholdsvis en to-årig eller kontinuert behandling", der burde nok stå venetoclax + rituximab?

Sundhedsøkonomiske vurdering:

- Side 4 - Abbvie har forsøgt at genskabe resultaterne af de sundhedsøkonomiske beregninger, og kommer frem til lignede resultater for omkostningerne over 30 år per patient. For subpopulationen med 17p/TP53, estimerer Medicinrådet en besparelse per patient på -1,6 mio. kr., men estimere en positiv budget konsekvens på 10 mio. kr. over 5 år. Abbvie estimerer med samme antagelser som Medicinrådet, en besparelse på -23,5 mio. kr. over 5 år.
- Side 25 – tabel 14: behandlingen står som venetoclax+rituximab og ikke venetoclax + obinutuzumab, vi antager det er en fejl
- Side 26 – tabel 15: behandlingen står som venetoclax+rituximab og ikke venetoclax + obinutuzumab, vi antager det er en fejl

Mvh. Lars

Hilsen/Best Regards

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signatur

From: Karen Kleberg Hansen <kkh@medicinraadet.dk>
Sent: 9. oktober 2020 15:36
To: Eskildsen, Lars <lars.eskildsen@abbvie.com>
Cc: Pernille Winther Johansen <pwj@medicinraadet.dk>; Tarang Sharma <TSH@medicinraadet.dk>
Subject: [EXTERNAL] Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for venetoclax i kombination med obinutuzumab

Kære Lars

Vedhæftet er udkast til Medicinrådets vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for venetoclax i kombination med obinutuzumab.

Medicinrådet drøfter vurderingen af lægemidlets værdi og modelantagelserne for den sundhedsøkonomiske afrapportering den 21. oktober. I får besked fra sekretariat, hvis Rådet har ændringer til vurderingen.

I har i alt 20 dage til at sende eventuelle bemærkninger til kategoriseringen af lægemidlets værdi og den sundhedsøkonomiske afrapportering. **Jeres frist for at indgive høringssvar er derfor den 28. oktober.** I er selvfølgelig velkomne til at sende eventuelle bemærkninger inden denne dato. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen.

Vurderer sekretariatet og fagudvalget, at jeres høringssvar giver anledning til at revurdere kategoriseringen af lægemidlets værdi, skal Rådet drøfte vurderingen igen. Det vil med overvejende sandsynlighed udskyde tidspunktet for Rådets drøftelse af anbefalingen.

Jeres eventuelle høringssvar indgår i det materiale, som bliver fremlagt for Medicinrådet i forbindelse med behandlingen af anbefalingen. Jeres eventuelle høringssvar bliver offentliggjort sammen med anbefalingen.

Mvh
Karen

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Medicinrådets behandling af personoplysninger

Når du har kontakt med Medicinrådet (f.eks. når du sender en e-mail til os), indsamler og behandler vi dine personoplysninger (f.eks. kontaktoplysninger i form af navn, e-mailadresse, titel/stilling mv.) I Medicinrådets persondatapolitik finder du mere information om Medicinrådets behandling af personoplysninger, dine rettigheder og oplysninger om, hvordan du kan kontakte os.

Medicinrådet

Medicinrådets vurdering af venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi

Versionsnr.: 1.1

Medicinrådet

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 sammenfatter vi 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.

Godkendt af Medicinrådet den 21. oktober 2020
Dokumentnummer 97916
Versionsnummer 1.1

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf

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1 Medicinrådets konklusion

Medicinrådet finder, at værdien af venetoclax + obinutuzumab sammenlignet med kemoimmunterapi **ikke kan kategoriseres** i henhold til Medicinrådets metoder hos patientpopulationen uden del17p/TP53-mutation. Evidensens kvalitet er **meget lav**.

Mængden og typen af bivirkninger for venetoclax + obinutuzumab er sammenlignelig med chlorambucil + obinutuzumab, mens bivirkningsprofilen for venetoclax + obinutuzumab er at foretrække i sammenligning med både bendamustin + rituximab og fludarabin + cyclofosfamid + rituximab.

Baseret på data for PFS, vurderer Medicinrådet, at der med venetoclax + obinutuzumab er en behandlingsgevinst i subpopulationen af patienter, der er IGHV-umuterede sammenlignet med kemoimmunoterapi.

Medicinrådet finder, at værdien af venetoclax + obinutuzumab sammenlignet med ibrutinib **ikke kan kategoriseres** i henhold til Medicinrådets metoder hos patientpopulationen med del17p/TP53-mutation. Evidensens kvalitet er **meget lav**.

Mængden og typen af bivirkninger er sammenlignelig for de to behandlinger, og data for effekt giver ikke anledning til at skelne mellem de to behandlinger, som Medicinrådet derfor betragter som klinisk ligestillede behandlingsalternativer.

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.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforhold er det ikke muligt at kategorisere lægemidlets samlede værdi.

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

CI	Konfidensinterval
CIRS	*Cumulative Illness Rating Scale*
CLL	Kronisk lymfatisk leukæmi
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
FISH	Fluorescens in situ hybridisering
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
ITT	*Intention to treat*
iwCLL	*International Workshop on Chronic Lymphocytic Leukemia*
OR	*Odds ratio*
PFS	Progressionsfri overlevelse
PP	*Per-protocol*
R-FC	Fludarabin, cyclofosfamid i kombination med rituximab
RR	Relativ risiko
SMD	*Standardized Mean Difference*
VEN-O	Venetoclax i kombination med obinutuzumab

3 Introduktion

Formålet med Medicinrådets vurdering af venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi (CLL) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Abbvie. Vi modtog ansøgningen den 12. august 2020.

De kliniske spørgsmål er:

Klinisk spørgsmål 1:

Hvilken værdi har venetoclax i kombination med obinutuzumab sammenlignet med cytostatika i kombination med et anti-CD20-antistof for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi uden deletion17p/p53-mutation?

Klinisk spørgsmål 2:

Hvilken værdi har venetoclax i kombination med obinutuzumab sammenlignet med ibrutinib for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation?

3.1 Kronisk lymfatisk leukæmi

Kronisk lymfatisk leukæmi (CLL) er en hæmatologisk kræftsygdom, som opstår i kroppens B-lymfocytter og påvirker deres regulering af celledeling og celledød. Det fører til en ophobning af B-lymfocytter bl.a. i knoglemarv, lymfeknuder, milt og blod. B-lymfocytternes normale funktioner bliver herved svækket, ligesom funktionen af knoglemarvens andre celler kan blive påvirket. Symptomerne hos patienter med kronisk lymfatisk leukæmi er relaterede hertil og omfatter typisk hævede lymfeknuder, forstørret milt, blodmangel, træthed, uforklarlig feber, vægttab og øget infektionstendens.

CLL er den almindeligste leukæmi 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 i Danmark [2]. Ifølge Kræftens Bekæmpelses database lever ca. 4.000 patienter med sygdommen i Danmark [3]. Medianalderen er ved diagnose 70 år, og dobbelt så mange mænd som kvinder får diagnosen [1,2].

CLL er ofte asymptomatisk på diagnosetidspunktet og kan blive opdaget tilfældigt efter en blodprøve. Diagnosen stilles ved konstatering af persisterende (vedvarende) lymfocytose, defineret som > 5 mia. monoklonale B-lymfocytter pr. liter blod i tre måneder eller derover. På diagnosetidspunktet foretages en vurdering af sygdomsstadie (baseret på sygdomsudbredelse, Binet-stadieinddeling) og sygdommens aggressivitet (risikoprofil på baggrund af cytogenetiske forandringer og *immunoglobulin heavy-chain variable region* (IGHV)-mutationsstatus). Både sygdomsstadiet, patientens symptomer og risikoprofilen har indflydelse på igangsættelse og valg af behandling, ligesom de har betydning for patientens prognose. CLL har ofte et 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 til mere end 12 år afhængig af sygdomsstadie og risikoprofil.

3.2 Venetoclax i kombination med obinutuzumab

Venetoclax hæmmer funktionen af Bcl-2, som er et protein, der modvirker programmeret celledød. Bcl-2 er overudtrykt i B-lymfocytter, når man har CLL. Når funktionen af Bcl-2 hæmmes, er B-lymfocytterne ikke længere beskyttet mod programmeret celledød, og de vil derfor dø. Derved vil antallet af B-lymfocytter falde, og patientens tilstand vil blive forbedret.

Obinutuzumab er et monoklonalt humant antistof rettet mod CD-20, som er udtrykt på overfladen af B-lymfocytter. Når antistoffet binder til B-lymfocytterne, vil kroppens immunforsvar blive aktiveret og nedbryde cellerne.

Venetoclax og obinutuzumab administreres som følger i serier a 28 dage:

- 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).

Venetoclax har allerede markedsføringstilladelse i kombination med rituximab til behandling af patienter med CLL, der tidligere har modtaget mindst én behandling. Den behandling blev anbefalet som mulig standardbehandling af Medicinrådet i december 2019.

Denne vurdering vedrører markedsføringstilladelsen til følgende indikation: *Venetoclax i kombination med obinutuzumab er indiceret til behandling af tidligere ubehandlet kronisk lymfatisk leukæmi (CLL) hos voksne patienter.*

3.3 Nuværende behandling

Behandlingen af CLL varetages af de hæmatologiske afdelinger. På diagnosetidspunktet skelnes mellem behandlingskrævende og ikkebehandlingskrævende sygdom. Ikkebehandlingskrævende 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 illnes rating scale (CIRS)), alder, præferencer), sygdomskarakteristika (tumorbyrde, stadie, risikoprofil (karakteriseret ved FISH), 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 cyclofosfamid 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 proteinkinasehæmmeren ibrutinib. Hvis ibrutinib ikke tolereres kan i stedet anvendes idelalisib i kombination med rituximab.

For patienter uden deletion17p/p53-mutation afgøres valget af cytostatika og anti-CD20-antistof af patientens alder, performancestatus og mængden af komorbiditet [4]. 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 performacestatus, 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. I takt med nye og mere målrettede behandlingsmuligheder er der dog påbegyndt en bevægelse væk fra anvendelse af cytostatika, blandt andet fordi cytostatika er forbundet med langvarig immundepletion.

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 [4].

I nuværende dansk klinisk praksis skelnes der i behandlingsøjemed ikke imellem, hvorvidt patienterne har muteret IGHV eller ej, selvom det er af betydning for patienternes prognose. Patienter med umuteret sygdom har en dårligere prognose end patienter med muteret IGHV-status. 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 [5–7]. Denne ændring i behandlingspraksis er reflekteret i den seneste retningslinje for CLL fra Dansk Lymfomgruppe, 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 det afventer anbefaling fra Medicinrådet.

Der er ca. 150 patienter om året med behandlingsbehov i 1. linje [4], hvoraf ca. 90 % (ca. 135 patienter) ikke har deletion17p/p53-mutation og derfor behandles med cytostatika i kombination med et anti-CD20-antistof [8]. 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.

Fagudvalgets angivelse af antallet af patienter i de forskellige grupper er baseret på estimater fra den landsdækkende LYFO-database, viden om tid til første tilbagefald og forekomsten af deletion17p/p53-mutation på forskellige tidspunkter i behandlingsforløbet [9–13].

4 Metode

Medicinrådets protokol for vurdering af venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

De kliniske spørgsmål er:

Klinisk spørgsmål 1:

Hvilken værdi har venetoclax i kombination med obinutuzumab sammenlignet med cytostatika i kombination med et anti-CD20-antistof 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
Venetoclax i kombination med obinutuzumab doseret som beskrevet i afsnit 2.2.

- 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 slut af cyklus 12).

Komparator
a) 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.

b) Bendamustin i kombination med rituximab doseret som følger i op til 6 serier a 28 dage:

- Bendamustin i.v. 70-90 mg/m^2 på dag 1 og 2.
- Rituximab i.v. 375 mg/m^2 på dag 1 i første serie, herefter i.v. 500 mg/m^2 på dag 1 i efterfølgende serier.

c) Fludarabin, cyclofosfamid i kombination med rituximab doseret som følger i 6 serier a 28 dage:

- Fludarabin 25 mg/m^2 i.v. eller 40 mg/m^2 p.o. dag 1-3.
- Cyclofosfamid 250 mg/m^2 i.v. eller 250 mg/m^2 p.o. dag 1-3.
- Rituximab 375 mg/m^2 i.v. dag 1, 1. serie, serie 2-6: 500 mg/m^2.

I klinisk praksis afhænger anvendelsen af de tre komparatorer af patienternes alder og komorbiditet. I protokollen blev ansøger bedt om at vælge den eller de komparatorer, hvor der findes det bedste evidensgrundlag.

Effektmål
De valgte effektmål står i tabel 1.

Klinisk spørgsmål 2:

Hvilken værdi har venetoclax i kombination med obinutuzumab sammenlignet med ibrutinib for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation?

Population
Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation.

Intervention
Venetoclax i kombination med obinutuzumab, dosering jf. klinisk spørgsmål 1.

Komparator

- Ibrutinib p.o. 420 mg dagligt indtil progression.

Effektmål
De valgte effektmål står i tabel 4.1.

Tabel 4.1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, den mindste klinisk relevante forskel (retningsgivende) samt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål	Vigtighed	Kategori	Måleenhed	Mindste klinisk relevante forskel
Overlevelse	*Kritisk*	*Dødelighed*	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid	5 %-point
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger**	Forskel i andel der opnår progressionsfri overlevelse (PFS) efter 3 år eller længst mulig opfølgningstid	10 %-point
Bivirkninger	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel der oplever grad 3-4 uønskede hændelser (+ kvalitativ gennemgang)	10 %-point
Livskvalitet	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	EORTC QLQ-C30	10 point

* Eftersom PFS er et sammensat effektmål, der indeholder både progression og død, anvendes væsentlighedskriterierne for alvorlige symptomer og bivirkninger.

Andre overvejelser

Fagudvalget har i protokollen ønsket informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

Fagudvalget vil i vurderingen af venetoclax i kombination med obinutuzumab overveje, hvorvidt anvendelse heraf i første linje udelukker anvendelse af kemoterapi i senere linjer, og hvorvidt dette er problematisk.

For klinisk spørgsmål 1 vil fagudvalget se på separate effektopgørelser baseret på IGHV-status for at belyse, hvorvidt der er en differentieret effekt af venetoclax i kombination med obinutuzumab overfor kemoimmunoterapi.

Fagudvalget har i protokollen ønsket information om, hvorfor venetoclax gives i kombination med rituximab i anden linje og med obinutuzumab i første linje, samt hvorvidt der forventes nogen forskel i den kliniske effekt ved tillæg af de to anti-CD20-antistoffer.

Fagudvalget har bedt ansøger om at redegøre for, hvorvidt der er evidens for, at patienter kan blive genbehandlet med venetoclax.

5 Resultater

5.1 Klinisk spørgsmål 1a – Patienter uden deletion17p/TP53-mutation, sammenligning med chlorambucil i kombination med obinutuzumab

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 1 fuldtekstartikel og 2 publicerede abstracts, der alle rapporterer resultater fra CLL-14-studiet, som sammenligner behandling med venetoclax og obinutuzumab med chlorambucil og obinutuzumab. Fischer et al. rapporterer resultater ved medianopfølgningstid på 28,1 måneder og Al-Sawaf et al. ved medianopfølgningstid på 39,6 måneder.

Reference (titel, forfatter, tidsskrift, årstal, indeksering)	Navn på klinisk forsøg	Intervention	Komparator	Opfølgningstid, median
Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019;380(23):2225–36. [14]	CLL-14 (NCT02242942)	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	28,1 mdr.
Al-Sawaf O, Gentile B, Devine J, Sail K, Tandon M, Fink A-M, et al. Rapid Improvement of Patient-Reported Outcomes with Venetoclax Plus Obinutuzumab in Patients with Previously Untreated CLL and Coexisting Conditions: A Prospective Analysis from the CLL14 Trial. Blood. 2019;134(Supplement_1):4305–4305 [15]				39,6 mdr.
Al-Sawaf O, Zhang C, Tandon M, et al. Fixed-Duration Venetoclax-Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia: Follow-Up of Efficacy and Safety Results from the Multicenter, Open-Label, Randomized, Phase 3 CLL14 Trial (EHA 2020 Abstract #S155). EHA libary. 2020. [16]				39,6 mdr.

Studiekarakteristika

CLL-14 er et fase III, open-label, multicenter, randomiseret studie udført hos voksne patienter med komorbiditet og tidligere ubehandlet CLL uanset mutationsstatus. Komorbiditet blev defineret ved *Cumulative Illness Rating Scale* (CIRS) score på > 6 eller kreatinin clerance < 70 ml/min.

Patienter blev randomiseret i et forhold på 1:1 til venetoclax+obinutuzumab (n = 216) eller chlorambucil + obinutuzumab (n = 216), og randomisering blev stratificeret for Binet-stadie og geografisk region.

Behandling med venetoclax + obinutuzumab blev doseret som beskrevet i afsnit 4.

Chlorambucil + obinutuzumab blev doseret som beskrevet i afsnit 4 for de første 6 cyklusser. Dog fortsattes behandling med chlorambucil i samme dosering i yderligere 6 cyklusser.

Det primære endepunkt var investigator-bedømt PFS. De sekundære endepunkter var: PFS (bedømt af uafhængig review komité), *minimal residual disease* negativitet (MRD), overlevelse, *duration of response*, *event-free survival*, tid til næste behandlingslinje.

Population

Baselinekarakteristika er velbalanceret mellem de to behandlingsarme. Populationen inkluderer ca. 90 % patienter uden deletion17p/TP53-mutation, og fagudvalget vurderer, at populationen stemmer overens med den population, man ser i dansk kliniske praksis.

Komparator

I Danmark anvendes der primært 6 cyklusser af chlorambucil i kombination med enten obinutuzumab eller rituximab. Der foretages dog også yderligere behandlingscyklusser, såfremt patienten tolererer det, og det vurderes at være forbundet med en forbedret respons. Komparator vurderes derfor at være sammenlignelig med dansk klinisk praksis.

5.1.2 Databehandling og analyse

Nedenfor beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål. Hvis ikke andet er anført er det angivne data fra ITT-populationen.

Overlevelse

Ansøger har indsendt 2- og 3-års overlevelse og 2- og 3-års PFS, som fagudvalget anser som en surrogat for overlevelse. For subgruppen med hhv. umuteret og muteret IGHV-status er der indsendt 2-års PFS. I protokollen var der efterspurgt 3-årsoverlevelse og 3-års PFS. Da der ikke foretages formel kategorisering for subgrupper baseret på IGHV-status, vil fagudvalget inkludere det indsendte 2-årsdata for subgrupperne med henblik på en vurdering af, hvorvidt der ser ud til at være forskel i effekt på tværs af subgrupperne. Jf. protokollen vil fagudvalget inddrage PFS-data i kategoriseringen, hvis overlevelsesdata ikke er tilgængeligt eller ikke er med tilstrækkelig opfølgning. Selvom der er leveret 3-årsoverlevelsesdata, vurderer fagudvalget, at det er relevant at supplere med PFS-data, da overlevelsesdata ikke har tilstrækkelig opfølgningstid til at udtale sig om en evt. overlevelsesgevinst ved behandlingen, og data for 3-årsraterne vurderes umodne. PFS-data er inkluderet i kategorisering og narrativt under diskussion af effektmålet overlevelse, men er ved den tidligste opfølgningstid også umodne[17]. PFS-data ved den senere opfølgningstid må formodes at være mere modne, men der er ikke indsendt en Kaplan Meier-kurve, og modenheden af PFS data er derfor usikker

Forskellen i overlevelsesrater og PFS-rater er angivet uden tilhørende 95 % konfidensintervaller (CI), hvilket skyldes, at der ikke findes en universel accepteret metode til at beregne 95 % CI for forskel i Kaplan Meier-estimater. Hazard ratio'en for Kaplan Meier for overlevelse og PFS bliver derfor bærende for kategoriseringen.

Bivirkninger

Ansøger har indsendt data vedrørende grad 3-4 hændelser samt produktresuméer til en narrativ gennemgang som angivet jf. protokollen. Det indsendte materiale er i overensstemmelse med protokollen.

Livskvalitet

Ansøger har indsendt data vedrørende ændring i livskvalitet over tid målt med instrumentet EORTC QLQ-C30, som angivet i protokollen. Graferne er aflæst visuelt, og der kan derfor ikke beregnes et konfidensinterval omkring forskellen.

5.1.3 Evidensens kvalitet

Fagudvalget har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen.

Risk of bias er vurderet ved brug af risk of bias tool 2.0. Da studiet er open-label, er der forbehold for risk of bias for effektmålene *uønskede hændelser* og *livskvalitet*, da begge effektmål indeholder et subjektivt element.

Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1). Evidensens kvalitet er for alle effektmål nedgraderet for inkonsistens, pga. at der kun foreligger et studie. Der er nedgraderet to niveauer for unøjagtighed for effektmålene overall survival, bivirkninger og livskvalitet, da konfidensintervallerne indeholder både positive og negative værdier eller ikke fremgår. Evidensens samlede kvalitet er **meget lav**, hvilket betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I tabel 5.1 herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1a.

Tabel 5.1. Resultater for klinisk spørgsmål 1a – venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

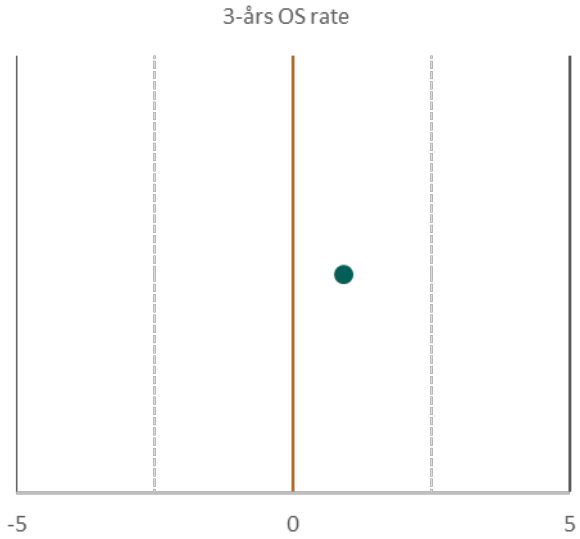
Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse	Andel patienter der er i live efter 3 år (MKRF: 5 %-point)	Kritisk	0,9 %-point*	Kan ikke kategoriseres	HR: 1,03 (0,602-1,753)	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel der opnår PFS efter 3 år (MKRF 10%-point)	Vigtig	32,4 %-point*	Kan ikke kategoriseres	HR: 0,31 (0,22-0,44)	Stor merværdi	
Bivirkninger	Andel patienter der oplever en eller flere grad 3-4 hændelser (MKRF: 10 %)	Vigtig	2 %-point [-5,7 % - 10 %]	Kan ikke kategoriseres	RR: 1,03 (0,93 – 1,14)	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	Gennemsnitlig ændring over tid EORTC-QLQ C-30	Vigtig	-0,7 point*	Kan ikke kategoriseres	-*	Kan ikke kategoriseres	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres. Fagudvalget vurderer, at venetoclax + obinutuzumab samlet set ikke har dårligere effekt eller sikkerhedsprofil end chlorambucil + obinutuzumab					
Kvalitet af den samlede evidens		Meget lav					

CI = konfidensinterval, HR = hazard ratio, MKRF = mindste klinisk relevante forskel, RR = relativ risiko. * CI kan ikke beregnes, og derfor kan effektmålet ikke kategoriseres.

Overlevelse

Som beskrevet i protokollen er effektmålet *overlevelse* kritisk for vurderingen af lægemidlet, fordi CLL er en kronisk uhelbredelig kræftsygdom. Medianoverlevelse ved diagnosetidspunktet er mellem 4-12 år, og mange af patienterne vil grundet høj alder og komorbiditet dø af andre årsager end CLL. Det kan derfor også være særdeles vanskeligt for nye lægemidler at eftervise en overlevelsesgevinst ved godkendelsestidspunktet, hvor overlevelsesdata med tilstrækkelig opfølgningstid ikke er tilgængelig eller forventelig. Fagudvalget inddrager data for 3-årsoverlevelsen og 3-års PFS i vurderingen af effekten på overlevelse. Fagudvalget inddrager PFS som et supplement til data for overlevelse og anser det som et surrogateffektmål herfor.

Baseret på den relative effektforskel (HR: 1,03 (0,602-1,753)) for samlet overlevelse kan lægemidlets værdi ikke kategoriseres jf. Medicinrådets metode, da konfidensintervallet overlapper 1 (ingen effekt) og indeholder både positiv og negativ værdi. Efter 3 år var overlevelsesraten 88,9 % i venetoclax + obinutuzumab-gruppen mod 88 % i chlorambucil + obinutuzumabgruppen. Punktestimatet for den absolutte effektforskel på 0,9 %-point afspejler ikke en klinisk relevant effektforskel. Der kan ikke beregnes konfidensintervaller, og derfor kan den foreløbige værdi ikke kategoriseres efter Medicinrådets metoder. Den absolutte forskel er afbildet i figur 1.



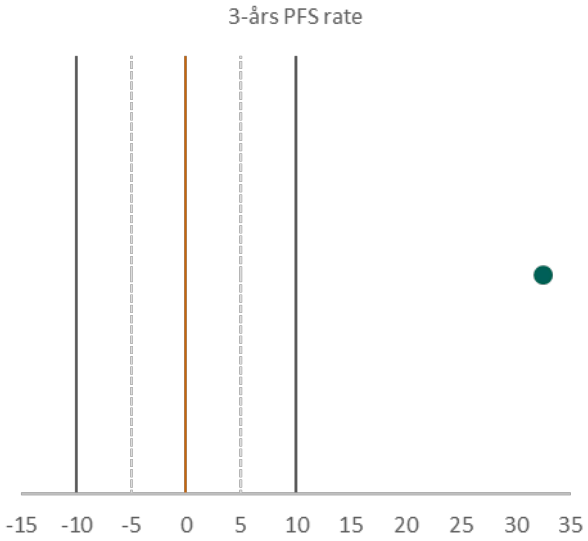
Figur 1. Punktestimat for den absolutte forskel for 3-årsoverlevelsesrate. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Progressionfri overlevelse (PFS)

Baseret på den relative effektforskel ved en opfølgningstid på 39,6 måneder er der foreløbigt en stor merværdi for PFS (HR: 0,31 (0,22-0,44).

3-års PFS er 81,9 % for patienter behandlet med venetoclax + obinutuzumab og 49,5 % for patienter behandlet med chlorambucil + obinutuzumab.

Den absolutte effektforskel på 3-års PFS-raterne er 32,4 %-point og afspejler en klinisk relevant forskel (figur 2). Da der ikke findes et konfidensinterval omkring den absolutte effektforskel, kan den foreløbige værdi ikke kategoriseres jf. Medicinrådets metode.



Figur 2. Punktestimat for den absolutte forskel for 3-års PFS-rate. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

IGHV-status

Fagudvalget har under andre overvejelser i protokollen efterspurgt data, der kan belyse effekten i subgrupper af patienter med henholdsvis umuteret og muteret IGHV-status. Ansøger har indsendt 2-års PFS-rater fra subgrupperne. For de umuterede patienter er raten 89,4 % i venetoclax + obinutuzumabarmen og 51 % i chlorambucilarmen (HR: 0,22 (0,12-0,38)). For de muterede patienter er raten 90,3 % i venetoclax + obinutuzumabarmen og 85,6 % i chlorambucilarmen (HR: 0,64 (0,28-1,46)). 2-årsrater for hele populationen (inkl. patienter, hvor mutationsstatus ikke er registreret) er 88,2 % og 64,1 % for henholdsvis venetoclax + obinutuzumab og chlorambucil + obinutuzumab. Dette indikerer, at effekten i ITT-analysen af PFS fortrinsvis er drevet af patienter med umuteret IGHV-status, der responderer dårligere på konventionel kemoimmunoterapi herunder chlorambucil + obinutuzumab.

Fagudvalget vurderer, at den aggregerede værdi for effektmålet overlevelse ikke kan kategoriseres. Fagudvalget lægger vægt på at effekten af chlorambucil + obinutuzumab på PFS er dårligere hos de umuterede patienter og at effektforskellen i PFS rater hos den samlede population ser ud til at være drevet af den forskel. Der vil derfor primært være en gevinst ved at behandle umuterede patienter med venetoclax + obinutuzumab fremfor chlorambucil + obinutuzumab.

Bivirkninger

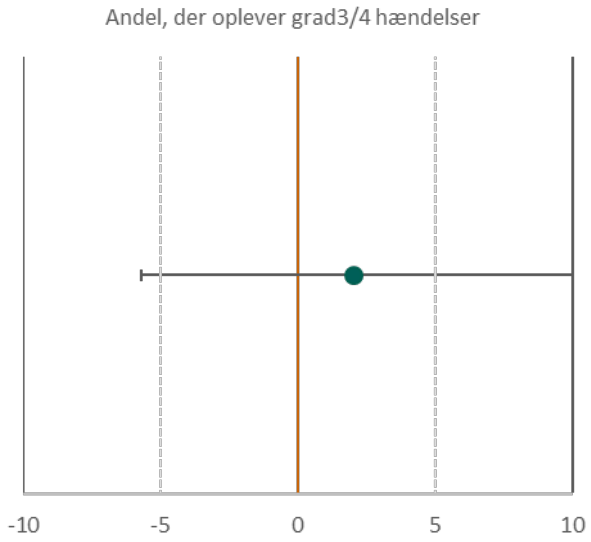
Effektmålet bivirkninger er vigtigt for vurderingen af lægemidlets værdi, fordi sygdommen har en lang medianoverlevelse, og bivirkninger har stor betydning for patienternes livskvalitet.

Fagudvalget specificerede i protokollen, at effektmålet skal belyses på to måder, 1) andel der oplever en eller flere grad 3/4 uønskede hændelser, 2) kvalitativ vurdering af bivirkningsprofilen, herunder alvorlighed, håndterbarhed og frekvens.

Andel der oplever en eller flere grad 3/4 uønskede hændelser

Grad 3-4 hændelser blev rapporteret for 79 % af patienter i venetoclax + obinutuzumabgruppen mod 77 % i chlorambucil + obinutuzumabgruppen. Punktestimatet for den absolutte effektforskel (2 %-point (-5,7 % -10 %)) afspejler ikke en klinisk relevant effektforskel. Konfidensintervallet overlapper 0 (ingen effekt). Derfor

kan den foreløbige værdi af venetoclax + obinutuzumab ikke kategoriseres efter Medicinrådets metoder. Den absolutte forskel er afbildet i figur 3.



Figur 3. Punktestimat og 95 % konfidensinterval for andelen af patienter der oplever grad 3/4 hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Da konfidensintervallet for den relative effektforskel (RR: 1,03 (0,96-1,1)) overlapper 1 (ingen effekt), bliver lægemidlets værdi foreløbigt 'kan ikke kategoriseres'.

Kvalitativ gennemgang af bivirkningsprofilen

Venetoclax + obinutuzumab og chlorambucil + obinutuzumab har overordnet set sammenlignelige sikkerhedsprofiler. Venetoclax + obinutuzumab er ikke mindre toksisk end chlorambucil + obinutuzumab, da der blev rapporteret alvorlige uønskede hændelser hos 49 % af patienterne behandlet med venetoclax + obinutuzumab mod 42 % behandlet med chlorambucil + obinutuzumab (SPC). Tilsvarende blev der rapporteret grad 3-4 hændelser hos 78,8 % af patienter behandlet med venetoclax + obinutuzumab mod 76,6 % behandlet med chlorambucil + obinutuzumab (studie). Bivirkningsprofilen for venetoclax + obinutuzumab og chlorambucil + obinutuzumab domineres af neutropenier med hhv. 52,8 % mod 48,1 % grad 3-4 hændelser (studie). Der er set en højere frekvens af fatale infektioner for venetoclax + obinutuzumab end for chlorambucil + obinutuzumab, hvilket har medført en fremhævning i produktresuméet om behov for øget monitorering for infektioner hos patienter med udbredt cytopeni. Fagudvalget vurderer ikke, at det vil påvirke den vanlige monitoreringspraksis, idet patienterne allerede monitoreres tilstrækkeligt. I CLL-14-studiet døde 1,9 % af patienterne af alvorlige infektioner under behandling med venetoclax + obinutuzumab og tilsvarende 1,9 % efter behandlingsophør (smpc).

Livskvalitet

Punktestimatet for den absolutte effektforskel (-0,7 point) afspejler ikke en klinisk relevant effektforskel. Der kan ikke beregnes konfidensintervaller, og der kan ikke beregnes en relativ effektforskel, og derfor kan den foreløbige værdi ikke kategoriseres efter Medicinrådets metoder. Både patienter behandlet med venetoclax + obinutuzumab og chlorambucil + obinutuzumab oplever en forbedring i deres livskvalitet over tid målt på instrumentet: EORTC QLQ-C30.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af venetoclax + obinutuzumab sammenlignet med chlorambucil + obinutuzumab til patienter med tidligere ubehandlede patienter med kronisk lymfatisk leukæmi uden deletion 17p-/TP53-mutation **ikke kan kategoriseres**. Fagudvalget vurderer, at venetoclax + obinutuzumab samlet set ikke har en dårligere sikkerhedsprofil end chlorambucil + obinutuzumab, baseret på typen og mængden af grad 3-4 hændelser.

Overordnet set kan der ikke dokumenteres en merværdi af lægemidlet på effektmålet *overlevelse*. Dette er forventeligt i en population med en gennemsnitsalder på 72 år og med høj komorbiditet og en god prognose for deres CLL-sygdom, og hvor der efter progression kan tilbydes flere effektive behandlingslinjer. Baseret på subgruppeanalyser vurderer fagudvalget dog, at venetoclax + obinutuzumab tilbyder et bedre behandlingsalternativ, hvad angår effekt i patientpopulationen med umuteret IGHV. Patienterne progredierer hurtigere efter endt behandling med chlorambucil + obinutuzumab og må derfor også opstarte ny behandling tidligere. Det vil i dag enten være venetoclax + rituximab eller ibrutinib, som er henholdsvis en to-årig eller kontinuert behandling. Venetoclax + obinutuzumab til tidligere ubehandlede patienter forventes derfor også at tilbyde en væsentlig længere behandlingsfri periode, hvilket fagudvalget vurderer er en stærk patientpræference.

5.2 Klinisk spørgsmål 1b – Patienter uden deletion17p/TP53-mutation, sammenligning med bendamustin i kombination med rituximab

5.2.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udover CLL-14-studiet beskrevet under klinisk spørgsmål 1, hvori den relevante intervention indgår, udvalgt yderligere 3 fuldtekstartikler, der rapporterer resultater fra 3 studier. De 3 studier er randomiserede studier, hvori den relevante komparator, bendamustin i kombination med rituximab indgår som én af behandlingsarmene. Det indsendte data udgør grundlaget for en narrativ sammenligning mellem venetoclax + obinutuzumab og bendamustin + rituximab og giver ikke mulighed for at foretage en formel kategorisering af venetoclax + obinutuzumab sammenlignet med bendamustin + rituximab.

Reference (titel, forfatter, tidsskrift, årstal, indeksering)	**Navn på klinisk forsøg (NCT)**	**Intervention**	**Komparator**	**Opfølgningstid, median**
Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. Woyach JA, et al. N Engl J Med. 2018;379(26):2517–28. [7]	Alliance (NCT01886872)	Ibrutinib + rituximab Ibrutinib	Bendamustin + rituximab	38 mdr.
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. Eichhorst B, et al. Lancet Oncol. 2016. [18]	CLL10 (NCT00769522)	Bendamustin + rituximab	Fludarabin + cyclofosfamid + rituximab	36 mdr.
Rituximab plus bendamustine or chlorambucil for chronic	MABLE (NCT01056510)	Bendamusitin + rituximab	Chlorambucil + rituximab	23,5 mdr.

lymphocytic leukemia: Primary analysis of the randomized, open-label mable study. Michallet AS, et al.. Haematologica. 2018;103(4):698–706.[19]				

Studiekarakteristika

Alliance

Alliance er et fase III, open-label, multicenter, randomiseret studie udført hos voksne patienter med tidligere ubehandlet CLL uanset mutationstype. Opfølgningstiden var 38 måneder.

Patienter blev randomiseret i et forhold på 1:1:1 til hhv. bendamustin + rituximab (n = 183), ibrutinib + rituximab (n = 182) og ibrutinib (n = 182).

Behandlinger blev doseret som beskrevet i afsnit 4, hvilket stemmer overens med dansk klinisk praksis.

Det primære endepunkt var PFS, og de sekundære endepunkter var *minimal residual disease* negativitet (MRD) og overlevelse.

CLL10

CLL10 er et fase III, open-label, multicenter, randomiseret studie udført hos voksne patienter med tidligere ubehandlet CLL uden deletion17p-mutation og uden væsentlig komorbiditet (CIRS ≤ 6). Opfølgningstiden var 36 måneder.

Patienter blev randomiseret i et forhold på 1:1 hhv. bendamustin + rituximab og fludarabin + cyclofosfamid + rituximab.

Behandlinger blev doseret som beskrevet i afsnit 4, hvilket stemmer overens med dansk klinisk praksis.

Det primære endepunkt var investigatorbedømt PFS, og de sekundære endepunkter var overlevelse, *minimal residual disease* negativitet (MRD).

CLL14

Se afsnit 5.1.1. for en gennemgang af studiet.

MABLE

MABLE er et fase III, open-label, multicenter, randomiseret studie udført hos voksne patienter med tidligere ubehandlet CLL, der ikke var kandidater til fludarabin + cyclofosfamid + rituximab. Opfølgningstiden var 23,5 måneder.

Patienter blev randomiseret i et forhold på 1:1 hhv. bendamustin + rituximab og chlorambucil + rituximab.

Behandlinger blev doseret som beskrevet i afsnit 4, hvilket stemmer overens med dansk klinisk praksis.

Det primære endepunkt var komplet repons rate, og de sekundære endepunkter var overlevelse, PFS og *minimal residual disease* negativitet (MRD).

Population

Alliance

Fagudvalget vurderer, at populationen i Alliance stemmer overens med den population, der får bendamustin + rituximab i dansk klinisk praksis. Populationen stemmer også tilstrækkeligt overens med studiepopulationen i CLL-14 til, at resultaterne kan sammenlignes. CLL-14-populationen inkluderede patienter med væsentlig komorbiditet CIRS > 6. Medianalder i studierne er ens og en stor andel af patienterne havde høj risiko sygdom målt ved hhv. Rai-stadie og Binet-stadie i Alliance og CLL-14. I både

CLL14 og Alliance er der en mindre gruppe af patienter, der i dansk klinisk praksis ikke ville være behandlet med kemoimmunterapi.

CLL10
Fagudvalget vurderer, at populationen *i CLL-10* afviger noget fra den population, der får bendamustin + rituximab i dansk klinisk praksis. Dette er overensstemmende med forsøgets formål, der var at udfordre, hvorvidt fludarabin + cyclofosfamid + rituximab bør være standardbehandling til fortrinsvis unge patienter i god almen tilstand uden alvorlig komorbiditet. Patientpopulationen stemmer derfor heller ikke overens med studiepopulationen i CLL-14 (ældre patienter med komorbiditet) med en medianalder på 72 mod 61 år i CLL-10. Fagudvalget antager derfor, at patienterne i CLL-10 har en bedre prognose end patienterne i CLL-14.

MABLE
Fagudvalget vurderer, at en del af populationen i MABLE stemmer overens med den population, der får bendamustin + rituximab i dansk klinisk praksis. Lidt over 30 % af patienterne i studiet har tidligere modtaget én behandlingslinje, og eftersom man generelt vil forvente en dårligere effekt i anden linje vil det forventeligt medføre en underestimering af effekten af bendamustin + rituximab. Nogle af patienterne har en høj grad af komorbiditet og ville formentligt være behandlet med chlorambucil i kombination med et CD20-antistof i dansk klinisk praksis.

Tabel 5.2: Udvalgte baselinekarakteristika for studierne, der indgår i sammnenligningen mellem venetoclax + obinutuzumab og bendamustin + rituximab

Karateristika	**Venetoclax + obinutuzumab (CLL14)**	**Bendamustin + rituximab (Alliance)**	**Bendamustin + rituximab (CLL10)**	**Bendamustin + rituximab (MABLE) N = 121**
Alder, median (range)	72 (43-89)	70 (65-86)	61 (54-69)	72 (41-86)
Binet-stadie (%) A B C Mangler	 21,3 35,6 43,1	NR	 22 38 39	 5 60 31 4
Rai-stadie (%) 0 I II III IV	NR	 46 (intermediate I/II) 54 (high-stage III/IV)	 5 14 37 15 29	NR
ECOG (%) 0 1 2	 41 46 13	 54 41 5	 64 36 <1%	 51 41 7
Deletion17p-mut (%)	8,5	8	NR*	8
TP53-mut (%)	11,1	9	NR	NR
IGHV (%) Muteret Ikke muteret Ikke evaluerbar/ ikke testet	 38 60,5 1,5	 42 58	 32 68	 34 60 3

CIRS, median	8	NR	2	NR
Komorbiditeter, median (range)	NR	2 (0-14)	NR	3 (0-12)

NR = *not reported*, ikke rapporteret. * del17p var et eksklusionskriterium i CLL10.

Komparator

Fagudvalget vurderer, at doseringen af bendamustin + rituximab i studierne er i overensstemmelse med dansk klinisk praksis.

5.2.2 Databehandling og analyse

Det har ikke været muligt for ansøger at foretage statistiske analyser til sammenligning af venetoclax + obinutuzumab med bendamustin+ rituximab, hvorfor fagudvalget ikke kan foretage en formel kategorisering. Fagudvalgets vurdering vil derfor bero på en narrativ sammenligning. Der vil kun blive afrapporteret data fra venetoclax + obinutuzumab og bendamustin + rituximabarmen i de inkluderede studier. Hvis ikke andet er anført er det angivne data fra ITT-populationen.

Overlevelse/PFS

I nogle af studierne er overlevelses-/PFS-rater ikke opgjort. Hvor det er muligt er disse aflæst direkte på Kaplan-Meier-kurven. Data for 3-årsraterne er umodne, hvilket øger usikkerheden yderligere i den narrative sammenligning. I MABLE er medianopfølgningstiden på 23,5 måneder og derfor for kort til, at 3-årsraterne er anvendelige.

Bivirkninger

Ansøger har indsendt data vedrørende grad 3-4 hændelser samt produktresuméer til narrativ gennemgang som angivet jf. protokollen. I Alliancestudiet er hændelser opgjort separat for grad 3, grad 4 og grad 5.

Livskvalitet

Effektmålet er enten ikke indgået i studierne for komparator eller er ikke opgjort på en måde, der tillader nogen narrativ sammenligning med komparator.

5.2.3 Evidensens kvalitet

Der er ikke foretaget en GRADE-vurdering af evidensens kvalitet, da der er tale om en narrativ sammenligning. Kvaliteten af disse sammenligninger vil altid være meget lav.

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte observerede effekter for hhv. venetoclax + obinutuzumab i CLL-14 samt bendamustin + rituximab i hhv. Alliance, CLL10 samt MABLE. Da sammenligningen er narrativ, kan værdien ikke kategoriseres jf. Medicinrådets metode. Derfor er der ikke angivet foreløbige, aggregerede og samlede kategorier.

Tabel 5.3: Resultater for klinisk spørgsmål 1b – venetoclax + obinutuzumab sammenlignet med bendamustin + rituximab

Effekt-mål	Måle-enhed	Venetoclax + obinutuzumab (CLL-14)	Bendamustin + rituximab (Alliance)	Bendamustin + rituximab (CLL10)	Bendamustin + rituximab (MABLE)
Over-levelse	2-års overlevelse	91,8 %	95 %	-	89 %*
	3-års overlevelse	88,9 %	88%*	92 %	-**
	2-års PFS	88,2 %	74 %	79 %*	79 %*
	3-års PFS	81,9 %	61 %*	56%*	-**
Bivirk-ninger	Grad 3-4 hændelser	79 %		79 %	75 %

*Aflæst på Kaplan-Meier-kurven. **data er ikke modent.

Overlevelse

3-årsoverlevelse er sammenlignelige på tværs af studierne. For venetoclax + obinutuzumab i CLL14 er den 88,9 % mod hhv. 88 % og 92 % for bendamustin + rituximab i Alliance og CLL10. Både patienterne i Alliance og CLL10 er patienter med en bedre prognose. På den korte tidshorisont er det ikke forventeligt, at der kan ses nogen forskel i overlevelse, da der vil være meget få patienter, der dør som følge af deres CLL-sygdom i dette tidsrum, og der er effektiv behandling, der kan anvendes ved progression. Derfor inddrages data for PFS som supplement til data for overlevelse.

PFS

For 3-års PFS er denne 81,9 % i CLL14 for venetoclax + obinutuzumab mod hhv. 61 % og 56 % for bendamustin + rituximab i Alliance og CLL10. Data tyder derfor på, at behandling med venetoclax + obinutuzumab er forbundet med en bedre PFS end bendamustin + rituximab, især når det også tages i betragtning, at patienter har bedre prognose i CLL10, fordi patienterne er væsentlig yngre eller uden væsentlig komorbiditet.

IGHV-status

PFS-rater ved 2 og 3 år er 88,2 % og 81,9 % for patienter behandlet med venetoclax + obinutuzumab. Subgruppeanalyser på IGHV-status med henblik på differentieret effekt viser, at 2-års PFS er 89,4 % og 90,3 % for patienter behandlet med venetoclax + obinutuzumab med hhv. umuteret og muteret IGHV-status. IGHV-status ser derfor ikke ud til at påvirke effekten af venetoclax +obinutuzumab.

Tilsvarende er 3-års PFS-rate 42,8 % og 77,5 % for patienter behandlet med bendamustin + rituximab med hhv. umuteret og muteret IGHV-status i CLL10. I appendix til Alliance er der PFS-kurver for IGHV-subgrupper, hvorfra 3-årsraten kan aflæses. Hos den umuterede gruppe er den ca. 54 % og i den muterede gruppe ca. 78 %. Der er ikke rapporteret estimater for PFS-rater for IGHV-subgrupperne i MABLE. PFS-raterne indikerer på linje med sammenligningen med chlorambucil + obinutuzumab, at patienter med umuteret IGHV-status responderer dårligere på konventionel kemoimmunoterapi herunder bendamustin + rituximab.

Bivirkninger

Andel der oplever en eller flere grad 3/4 uønskede hændelser:

Grad 3-4 hændelser blev rapporteret hos 79 % af patienter behandlet med venetoclax + obinutuzumab i CLL14 mod 75 % og 79 % af patienterne behandlet med bendamustin + rituximab i hhv. MABLE og CLL10.

Kvalitativ gennemgang af bivirkningsprofilen

Det er vanskeligt at sammenligne hændelser på tværs af de studier i en narrativ sammenligning, da der kan være forskellige måder og praksis for at indsamle disse data. Sammenligningen vanskeliggøres yderligere, når populationerne og opfølgningstiden ikke er ens. Overordnet set var der sammenlignelige grad 4 infektioner i studierne, mens grad 3 var højere for bendamustin + rituximab i CLL10-studiet. Febril neutropeni var højere for bendamustin + rituximab i Alliance end for venetoclax + obinutuzumab i CLL-14.

Tabel 5.4: Udvalgte grad 3 og 4 hændelser i studierne, der indgår i sammenligningen mellem venetoclax + obinutuzumab og bendamustin + rituximab

	Venetoclax + obinutuzumab (CLL14)	Bendamustin + rituximab (Alliance)	Bendamustin + rituximab (CLL10)
Infektioner (%)			
Grad 3	14,6	10	22
Grad 4	2,8	3	2
Febril neutopeni	5,2	7	NR

Behandling med bendamustin er kendt for at være forbundet med en øget risiko for udvikling af sekundær malignitet i form af myelodysplastisk syndrom samt akut myeloid leukæmi. Derudover øger bendamustin risikoen for særligt alvorlige opportunistiske infektioner af typen bakteriel pneumoni, cytomegalovirus, varicella zoster virus samt pneumocystis jirovecii, der kan give anledning til alvorlige komplikationer samt lange indlæggelser [20]. Fagudvalget vurderer, at de hændelser, der er forbundet med bendamustin + rituximab, er mere alvorlige og komplicerede. På baggrund af alvorligheden af bivirkninger ved bendamustin + rituximab foretrækker fagudvalget bivirkningsprofilen for venetoclax + obinutuzumab.

Livskvalitet

Der er ikke data tilgængelig for komparator, der tillader en sammenligning. Effektmålet kan derfor ikke kategoriseres.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af venetoclax + obinutuzumab sammenlignet med bendamustin + rituximab til tidligere ubehandlede patienter med kronisk lymfatisk leukæmi uden deletion17p-/TP53-mutation ikke kan kategoriseres. Dette skyldes, at vurderingen beror på en narrativ vurdering, hvilket ikke giver mulighed for at foretage en formel kategorisering af venetoclax + obinutuzumab sammenlignet med bendamustin + rituximab.

Fagudvalget vurderer, at venetoclax + obinutuzumab samlet set ikke har en dårligere sikkerhedsprofil end bendamustin + rituximab og mener, at data indikerer, at behandling med venetoclax + obinutuzumab vil forårsage færre infektioner end bendamustin + rituximab. På baggrund af alvorligheden af de potentielle infektioner ved bendamustin + rituximab foretrækkes bivirkningsprofilen for venetoclax + obinutuzumab.

Overlevelsesrater ved 3 år er ikke tilstrækkeligt til at afgøre, hvorvidt venetoclax + obinutuzumab tilbyder en overlevelsesgevinst. Dette er forventeligt i en population med en god prognose for deres CLL-sygdom, og hvor der efter progression kan tilbydes flere effektive behandlingslinjer. Fagudvalget bemærker dog, at der er en væsentlig forskel på 3-års PFS-rater. Baseret på subgruppeanalyser vurderer fagudvalget, at data indikerer, at venetoclax + obinutuzumab tilbyder et bedre behandlingsalternativ end bendamustin + rituximab, hvad angår effekt i den umuteret IGHV-subpopulation. Patienterne progredierer hurtigere efter endt behandling med bendamustin + rituximab og må derfor også opstarte ny behandling, der i dag enten vil være to-årig behandling med venetoclax + rituximab eller kontinuert behandling med ibrutinib. Som i sammenligningen med chlorambucil + obinutuzumab forventes venetoclax + obinutuzumab derfor også at tilbyde en væsentlig længere behandlingsfri periode, hvilket fagudvalget vurderer er en stærk

patientpræference.

5.3 Klinisk spørgsmål 1c: Patienter uden deletion17p/TP53, hvor venetoclax og obinutuzumab er sammenlignet med fludarabin, cyclofosfamid og rituximab

5.3.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udover CLL-14-studiet angivet i klinisk spørgsmål 1a, og CLL10 angivet i klinisk spørgsmål 1b, udvalgt yderligere 1 fuldtekstartikel, der rapporterer resultater fra 1 studie, E1912. CLL10 og E1912 er randomiserede studier, hvori den relevante komparator fludarabin + cyclofosfamid + rituximab indgår som én af de to behandlingsarme.

Reference (titel, forfatter, tidsskrift, årstal, indeksering)	**Navn på klinisk forsøg**	**Intervention**	**Komparator**	**Opfølgningstid, median**
First-line chemoimmuno therapy 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. Eichhorst B, et al. Lancet Oncol. 2016. [18]	CLL10 (NCT00769522)	Bendamustin + rituximab	Fludarabin + cyclofosfamid + rituximab	36 mdr.
Ibrutinib–rituximab or chemoimmuno therapy for chronic lymphocytic leukemia. Shanafelt TD, et al. N Engl J Med. 2019;381(5):432–43.[21]	E1912 (NCT02048813)	Ibrutinib + rituximab	Fludarabin + cyclofosfamid + rituximab	33,6 mdr.

CLL10

Se afsnit 5.2.1. for en gennemgang af studiet.

CLL14

Se afsnit 5.1.1. for en gennemgang af studiet.

E1912

E1912 er et fase III, open-label, multicenter, randomiseret studie udført hos voksne patienter med tidligere ubehandlet CLL, der er kandidater til fludarabin + cyclofosfamid + rituximab med alder < 70 år. Opfølgningstiden var 33,6 måneder.

Patienter blev randomiseret i et forhold på 2:1 hhv. til ibrutinib + rituximab (n = 354) og fludarabin + cyclofosfamid + rituximab (n = 175).

Behandlinger blev doseret som beskrevet i afsnit 4, hvilket stemmer overens med dansk klinisk praksis.

Det primære endepunkt var PFS og det sekundære endepunkter var overlevelse.

Population

CLL10

Fagudvalget vurderer, at populationen i CLL10 stemmer overens med den population, der får fludarabin + cyclofosfamid + rituximab i dansk klinisk praksis, dvs. fortrinsvis yngre patienter i god almen tilstand uden alvorlig komorbiditet. Patientpopulationen i CLL10 stemmer derfor heller ikke overens med studiepopulationen i CLL-14 (ældre patienter med komorbiditet) med en median alder på 72 mod 61 år i CLL-10. Fagudvalget formoder derfor også, at patienterne i CLL-10 har en bedre prognose end patienterne i CLL-14.

E1912

Som ved populationen i CLL10 vurderer fagudvalget, at populationen i E1912 stemmer overens med den population, der får fludarabin + cyclofosfamid + rituximab i dansk klinisk praksis, dvs. fortrinsvis unge patienter i god almen tilstand uden alvorlig komorbiditet. De formodes derfor også at have en bedre prognose end patienterne i CLL14.

Tabel 5.5: Udvalgte baseline karakteristika for studiepopulationerne, der indgår i sammenligningen mellem venetoclax + obinutuzumab og fludarabin + cyclofosfamid +rituximab

Karateristika	Venetoclax + obinutuzumab (CLL14)	Fludarabin + cyclofosfamid +rituximab (CLL10)	Fludarabin cyclofosfamid + rituximab (E1912)
Alder, median (range)	72 (43-89)	62 (65-67)	57
Binet-stadie (%) A B C Mangler	 21,3 35,6 43,1	 22 37 41	NR
Rai-stadie (%) 0 I-II III-IV	NR	 3 52 45	 5,1 53,7 41,1
ECOG (%) 0 1 2	NR 41 46 13	 64 34 2	 62 36 1,7
Deletion17p-mut	8,5	NR*	0
TP53-mut	11,1	NR	NR
IGHV Muteret Ikke muteret Ikke evaluerbar/ikke testet	 38 60,5 1,5	 55	 38,3 61,7
CIRS, median	9	2	NR

Komorbidi-teter, median (range)	NR	NR	NR

NR = *not reported*, ikke rapporteret. * Del17p var et eksklusionskriterium i studiet.

Komparator

Fagudvalget vurderer, at fludarabin + cyclofosfamid + rituximab-regimet, der anvendes i de to studier CLL10 og E1912, er sammenligneligt med dansk klinisk praksis, om end behandlingen hovedsageligt administreres peroralt i Danmark.

5.3.2 Databehandling og analyse

Ansøger har ikke indsendt statistiske analyser til sammenligning af venetoclax + obinutuzumab med fludarabin + cyclofosfamid + rituximab. Denne vurdering vil derfor bero på den narrativ vurdering. Der vil kun blive rapporteret data fra venetoclax + obinutuzumab og fludarabin + cyclofosfamid + rituximab-armen i disse studier.

Nedenunder beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål. Hvis ikke andet er anført er det angivne data fra ITT-populationen.

Overlevelse/PFS

I nogle af studierne er overlevelses-/PFS-rater ikke beregnet i studierne. Hvor det er muligt og forsvarligt ift. datamodenhed, er disse aflæst direkte på Kaplan-Meier-kurven.

Bivirkninger

Ansøger har indsendt data vedrørende grad 3-4 hændelser samt produktresuméer til narrativ gennemgang som angivet jf. protokollen. I E1912 er der afrapporteret grad 3-5, hvilket giver en højere hændelsesrate end for CLL14, hvor der er opgjort grad 3-4. I CLL10 er der afrapporteret, hvor mange patienter der hhv. har haft en grad 3, 4 og 5 hændelse. I tabellen nedenfor er grad 3 summeret med grad 4, hvilket medfører en risiko for en lille overestimering af andel, der oplever grad 3-4, da samme patient godt kan tælle med i hver af de individuelle opgørelser.

Livskvalitet

Effektmålet er ikke indgået i studierne for komparator, hvorfor effektmålet ikke kan belyses.

5.3.3 Evidensens kvalitet

Der er ikke foretaget en GRADE-vurdering af evidensens kvalitet, da der er tale om en narrativ sammenligning. Kvaliteten af sammenligninger vil altid være meget lav.

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte observerede effekter for hhv. venetoclax + obinutuzumab i CLL-14 samt fludarabin + cyclofosfamid + rituximab i hhv. E1912 og CLL10. Da sammenligningen er narrativ, kan værdien ikke kategoriseres jf. Medicinrådets metode. Derfor er der ikke angivet foreløbige, aggregerede og samlet kategori.

Tabel 5.6. Effektestimater for sammenligningen mellem venetoclax + obinutuzumab og fludarabin + cyclofosfamid + rituximab (fludarabin + cyclofosfamid + rituximab)

Effektmål	Måleenhed	CLL-14 (venetoclax + obinutuzumab)	E1912 (fludarabin+ cyclofosfamid + rituximab)	CLL10 (fludarabin+ cyclofosfamid + rituximab)
Overlevelse	3-års overlevelse	88,9 %	91,5 %	91 %
	3-års PFS	81,9 %	72,9 %	68 %
Bivirkninger	Grad 3-4 hændelser	79 %	79 %*	89**

*Indeholder også grad 5, hvilket overestimerer raten. **Summeret grad 3 og grad 4 hvilket kan give en overestimering af andel, der oplever grad 3-4, da samme patient godt kan tælle med i hver af de individuelle opgørelser.

Overlevelse

3-årsoverlevelse er 88,9 % for patienter behandlet med venetoclax + obinutuzumab i CLL14 mod hhv. 91,5 % og 91 % behandlet med fludarabin+ cyclofosfamid + rituximab i E1912 og CLL10. Både patienterne i E1912 og CLL10 har en bedre prognose grundet ung alder og ingen komorbiditet end patienterne i CLL14. På denne korte tidshorisont er det ikke forventeligt, at der kan ses nogen forskel i overlevelse, da der vil være meget få patienter der dør af deres CLL-sygdom i dette tidsrum.

PFS

3-års PFS er 81,9 % for patienter behandlet med venetoclax + obinutuzumab i CLL14 mod hhv. 72,9 % og 68 % i E1912 og CLL10 for fludarabin + cyclofosfamid + rituximab. Den lavere PFS-rate for patienter behandlet med fludarabin + cyclofosfamid + rituximab skal ses i lyset af, at patienter har bedre prognose i E1912 og CLL10, fordi patienterne er hhv. væsentlig yngre eller uden væsentlig komorbiditet. Derfor tyder data på, at behandling med venetoclax + obinutuzumab giver en bedre PFS end fludarabin+ cyclofosfamid + rituximab, hvilket er væsentlig for patienterne.

IGHV-status

For 2- og 3-års PFS er 88,2 % og 81,9 % for patienter behandlet med venetoclax + obinutuzumab. Subgruppeanalyser på IGHV-status med henblik på differentieret effekt viser, at 24-måneders PFS er 89,4 % og 90,3 % for patienter behandlet med venetoclax + obinutuzumab med hhv. umuteret og muteret IGHV-status. IGHV-status ser derfor ikke ud til at påvirke effekten af venetoclax + obinutuzumab.

Tilsvarende er 3-års PFS-rate 59,1 % og 82,4 % for patienter behandlet med fludarabin + cyclofosfamid + rituximab med hhv. umuteret og muteret IGHV-status i CLL10-studiet. I E1912 er 3-års PFS-rate 62,5 % for umuterede vs. 90,7 % for muterede blandt de fludarabin + cyclofosfamid + rituximab-behandlede patienter. Dette viser i overensstemmelse med de foregående sammenligninger, at patienter med umuteret IGHV-status responderer dårligere på konventionel kemoimmunoterapi herunder fludarabin + cyclofosfamid + rituximab.

Bivirkninger

Andel der oplever en eller flere grad 3-4 uønskede hændelser:

Grad 3-4 hændelser blev rapporteret for 79 % af patienter behandlet med venetoclax + obinutuzumab i CLL14 mod 79 % behandlet med fludarabin + cyclofosfamid +rituximab i E1912. Der var 28 måneders opfølgningstid i CLL14 mod 33 måneder i E1912, hvilket bidrager med usikkerhed til sammenligningen.

Kvalitativ gennemgang af bivirkningsprofilen

Tabel 5.7: Væsentligeste grad 3-4 hændelser i de anvendte studier for venetoclax + obinutuzumab og fludarabin + cyclofosfamid + rituximab

Hændelsestype	venetoclax + obinutuzumab (CLL14)	Fludarabin + cyclofosfamid + rituximab (E1912)	Fludarabin + cyclofosfamid + rituximab (CLL10)	Venetoclax + obinutuzumab (CLL14)	Fludarabin + cyclofosfamid + rituximab (E1912)	Fludarabin + cyclofosfamid + rituximab (CLL10)
	Grad 3			**Grad 4**		
Hæmatologiske hændelser (%)						
Neutropeni	24,4	22,2	23	28,3	22,8	62
Leukocytopenia	2,4	49,4*	42	0	34,9*	39
Thrombocytopenia	9,4	10,1**	13	4,2	5,1**	8
Anaemia	7,5	10,8	10	0,5	3,8	4
Febril neutropeni	3,3	13,3	NR	1,9	2,5	NR
Total sum						
Inkfektioner	14,6	5,7	35	2,8	3,2	3

I E1912 er hændelserne rapporteret som, **white-cell count decreased* + *lymphocyte count decreased* og ***platelet count decreased.*

Opfølgningstiden var 28,1 måneder i CLL14, 33,6 måneder i E1912 og 37,4 måneder i CLL10, og flere hændelser forventes derfor opfanget i CLL10 og E1912 grundet længere opfølgningstid. Overordnet set giver fludarabin + cyclofosfamid + rituximab væsentlig højere grad af leukocytopeni, som formentlig er relateret til lymfopeni associeret med fludarabinbehandling. Øvrige cytopenier også er højere hos patienter behandlet med fludarabin + cyclofosfamid + rituximab, men ikke i samme grad.

Livskvalitet

Der er ikke data tilgængelig for komparator, der tillader en sammenligning. Effektmålet kan derfor ikke kategoriseres.

5.3.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af venetoclax + obinutuzumab sammenlignet med fludarabin + cyclofosfamid + rituximab til tidligere ubehandlede patienter med kronisk lymfatisk leukæmi uden deletion 17p-/TP53-mutation **ikke kan kategoriseres.** Dette skyldes, at vurderingen beror på en narrativ vurdering, hvilket ikke giver mulighed for at foretage en formel kategorisering af venetoclax + obinutuzumab sammenlignet med fludarabin + cyclofosfamid + rituximab. Fagudvalget vurderer, at venetoclax + rituximab samlet set ikke har en dårligere sikkerhedsprofil end fludarabin + cyclofosfamid + rituximab, og at data indikerer, at behandling med venetoclax + obinutuzumab vil forårsage færre tilfælde af leukocytopeni.

Overlevelsesrater ved 3 år er ikke tilstrækkeligt til at afgøre, hvorvidt venetoclax + obinutuzumab tilbyder en overlevelsesgevinst. Dette er forventeligt i en population med en god prognose for deres CLL-sygdom, og hvor der efter progression kan tilbydes flere effektive behandlingslinjer. Baseret på subgruppeanalyser vurderer fagudvalget dog, at data indikerer, at venetoclax + obinutuzumab tilbyder et bedre behandlingsalternativ end fludarabin + cyclofosfamid + rituximab, hvad angår effekt i den umuterede IGHV-subpopulation. Her ses der markant hurtigere progression hos patienter behandlet med fludarabin +

cyclofosfamid + rituximab, som derfor også hurtigere må opstarte ny behandling, der i dag enten vil være 2-årig behandling med venetoclax + rituximab eller kontinuert behandling med ibrutinib. Som for de forudgående sammenligninger må venetoclax + obinutuzumab derfor forventes også at tilbyde en væsentlig længere behandlingsfri periode hos de umuterede patienter, hvilket fagudvalget vurderer er en stærk patientpræference.

5.4 Klinisk spørgsmål 2 – Patienter med deletion17p/TP53-mutation, sammenligning med ibrutinib

5.4.1 Litteratur

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udover CLL-14 studiet angivet i klinisk spørgsmål 1a udvalgt yderligere 3 fuldtekstartikler med data for effekten af ibrutinib, der rapporterer resultater fra 3 studier, beskrevet i tabellen nedenfor. Mato- og Ahn-studiet er single-arm-studier, hvor Mato er et retrospektivt kohortestudie, der er lavet på baggrund indsamling af data fra medicinske journaler og Ahn er en prospektivt studie. RESONATE-studiet er et randomiseret forsøg, hvori den relevante komparator ibrutinib indgår som én af de to behandlingsarme.

Reference (titel, forfatter, tidsskrift, årstal, indeksering)	Navn på klinisk forsøg	Intervention	Komparator	Opfølgningstid
Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. Mato AR, et al. Am J Hematol. 2018;93(11):1394–401 [22]	Mato-studiet (Ikke registeret, retrospektivt-studie)	Ibrutinib	Ingen	13,8 mdr.
Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Ahn, et al. Blood. 2018;131(21):2357–66. [23]	Ahn-studiet (NCT01500733)	Ibrutinib	Ingen	58 mdr.
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. Burger JA, et al. Leukemia. 2020;34(3):787–98. [24]	RESONATE-2 (NCT01722487)	Ibrutinib	Chlorambucil	60 mdr.

Fagudvalget ekskluderer Mato-studiet fra evidensgrundlaget på grund af det retrospektive studiedesign og korte opfølgningstid. Sammenligningen mellem venetoclax + obinutuzumab og ibrutinib vil således basere sig på CLL-14, Ahn og RESONATE-2.

Ahn-studiet

Ahn-studiet er et single-arm, open-label, singlecenter studie udført hos voksne patienter med tidligere ubehandlet CLL, der enten havde deletion17p/TP53-mutation eller var 65 år eller ældre. Studiets mediane opfølgningstid var ca. 58 måneder (4,8 år).

Patienter fik alle ibrutinib som beskrevet i afsnit 4, hvilket stemmer overens med dansk klinisk praksis.

Det primære endepunkt var responsrate og de sekundære endepunkter var overlevelse, PFS og bivirkninger.

RESONATE-2

RESONATE-2 er et fase III, open-label, multicenter, randomiseret studie udført hos voksne patienter med tidligere ubehandlet CLL med alder under 65 år og uden væsentlig komorbiditet (CIRS < 6). Median opfølgningstid var 60 måneder (5 år).

Patienter blev randomiseret i et forhold på 1:1 til ibrutinib (n = 136) eller chlorambucil (n = 133).

Ibrutinib blev doseret som beskrevet i afsnit 4 og stemmer overens med dansk klinisk praksis.

Det primære endepunkt var: investigatorbedømt PFS.

De sekundære endepunkter var: overlevelse, bivirkninger.

Population:

CLL-14

CLL-14-studiet inkluderer meget få patienter (< 10 %) med deletion17p/TP53-mutation, hvorfor populationen stemmer dårligt overens med populationen i det kliniske spørgsmål. Patienter med deletion 17p/TP53-mutation har generelt en dårligere prognose, også selvom effekten af venetoclax er uafhængig af deletion17p/TP53. Fagudvalget vurderer derfor, at patienterne i CLL14 er bedre prognostisk stillet end patienter i dansk klinisk praksis med del17p/TP53, og at der er risiko for, at effekten af venetoclax + obinutuzumab overestimeres i sammenligning med effekter i studiepopulationer, der udelukkende består af patienter med del17p/TP53.

Ahn-studiet

Fagudvalget vurderer, at populationen i Ahn-studiet stemmer overens med en del af den population, der får ibrutinib i dansk klinisk praksis, da studiet fortrinsvis inkluderede patienter med del17p/TP53-mutation. Dog indeholdt studiet også en andel patienter (38 %), der havde relaps/refraktær sygdom. Disse patienter er også kandidater til ibrutinib i dansk klinisk praksis, men har en dårligere prognose, som vil føre til en underestimering af effekten af ibrutinib som behandling i 1. linje. Patienter med del17p/TP53 har også generelt en dårligere prognose. Patientpopulationen stemmer derfor ikke overens med studiepopulationen i CLL-14.

RESONATE-2

Fagudvalget vurderer, at populationen i RESONATE-studiet ikke stemmer overens med den population, der får ibrutinib i dansk klinisk praksis, da studiet fortrinsvis inkluderede patienter uden deletion17p/TP53-mutation (del17p blev ekskluderet), og patienterne derfor formentlig har en bedre prognose end de danske patienter og en studiepopulation med højere andel af patienter med del17p/TP53-mutation. Patientpopulationen er derfor ikke direkte sammenlignelig med studiepopulationen i CLL-14, hvor der desuden var flere patienter med komorbiditet (CIRS > 6).

Tabel 5.8. Udvalgte baselinekarakteristika for studierne, der indgår i sammenligningen mellem venetoclax + obinutuzumab og ibrutinib

Karateristika*	**Venetoclax + obinutuzumab (CLL14)**	**Ibrutinib (Ahn)**	**Ibrutinib (RESONATE-2)**
Alder, median/gns (range)	72 (NR)	66 (35-85)	73 (65-89)
Binet-stadie, % A B C Mangler	 21,3 35,6 43,1	NR	NR
Rai-stadie, % III-IV	NR	62,7	44
Deletion17p-mut, %	8,5	58,1	0

TP53-mut, %	11,1	4,7	10
IGHV, % Muteret Ikke muteret Ikke evaluerbar/ikke testet	 38 60,5 1,5	 33,3 66,7	 57 43
CIRS > 6, %	86,1	NR	31

NR = *not reported*, ikke rapporteret.
*Karakteristika er fra de samlede studiepopulationer, og ikke fra de deletion17p/TP53-populationer der indgår i de nedenstående resultater, da disse informationer ikke er tilgængelige.

Komparator:
Fagudvalget vurderer, at ibrutinib-regimet, der anvendes i Ahn og RESONATE-2, er identisk med dansk klinisk praksis.

5.4.2 Databehandling og analyse

Ansøger har ikke indsendt statistiske analyser til den kliniske vurdering af sammenligningen af venetoclax + obinutuzumab med ibrutinib. Denne vurdering vil derfor bero på en narrativ vurdering af data fra studiearmene med venetoclax og ibrutinib i de ovenfornævnte studier.

Nedenunder beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål. Hvis ikke andet er anført er det angivne data fra ITT-populationen.

Overlevelse/PFS
Der er inkluderet data for PFS for de relevante subgrupper, som er opgjort lidt forskelligt på tværs af studier. Overlevelses- og PFS-rater er ikke rapporteret i alle de inkluderede studier. Hvor det har været muligt og forsvarligt i forhold til datamodenhed er raterne aflæst direkte på Kaplan Meier-kurven. De meget små patientantal i subgrupperne med deletion17p/TP53-mutation gør, at estimaterne er forbundet med stor usikkerhed, men gør sammenligningen mere uafhængig af de forskelle, der er mellem studiernes ITT-populationer.

Bivirkninger
Ansøger har indsendt data vedrørende grad 3-4 hændelser, samt produktresuméer til narrativ gennemgang som angivet jf. protokollen. Disse data er dog fra hovedpopulationer og ikke specifik for deletion17p/TP53. Dette vurderer fagudvalget er uden betydning, da mutationsstatus ikke er betydende for, hvilke eller hvor mange bivirkninger patienterne oplever af behandlingen.

Livskvalitet
Effektmålet har ikke været undersøgt i studierne for komparator, hvorfor effektmålet ikke kan belyses.

5.4.3 Evidensens kvalitet

Der er ikke foretaget en GRADE-vurdering af evidensens kvalitet, da der er tale om en narrativ sammenligning. Kvaliteten af sammenligninger vil altid være meget lav.

5.4.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte observerede effekter for hhv. venetoclax + obinutuzumab i CLL-14 samt ibrutinib i hhv. Ahn og RESONATE-2. Da sammenligningen er narrativ, kan værdien ikke kategoriseres jf. Medicinrådets metode. Derfor er der ikke angivet foreløbige, aggregerede og samlet kategori.

Tabel 5.9. Effektestimater for sammenligningen mellem venetoclax + obinutuzumab og ibrutinib

Effektmål	Måleenhed	Studie			
		Ahn N = 34, TP53 Ibrutinib	**RESONATE-2 N = 12, TP53 Ibrutinib**	**RESONATE-2 N = 136 Ibrutinib**	**CLL14 deletion17p/TP53 N= 17/ N= 24 Venetoclax + obinutuzumab**
Opfølgningstid	Median, mdr	58 mdr.	60 mdr.	60 mdr.	24 mdr.
Overlevelse	PFS (2 år)	85 %*	-	-	64,7 % / 73,9%
	PFS (3 år)	-	-	82*	-
	PFS (5-år)	74,4 %	56 % (5 år)	70 % - 5-års	-
Bivirkninger	Grad 3-4 hændelser	83 %	83 %**	83 %	79 %**

*ikke opgjort, aflæst direkte af Kaplan-Meier-graf. **For alle patienter i studiet.

Overlevelse

Der er ikke estimater for overlevelse tilgængelige for deletion17p/TP53-subgrupperne. Derfor anvendes PFS som surrogat.

I deletion17p/TP53-populationen i CLL14, var 2-års PFS 64,7/73,9 % for patienter behandlet med venetoclax + obinutuzumab mod hhv. 2-års PFS på 85 % for ibrutinib i Ahn og 56 % for 5-års PFS for TP53-subpopulationen i RESONATE-2. Subpopulationen i Ahn kan forventes at have en bedre prognose grundet væsentlig lavere alder (62 år) og mindre komorbiditet. Dog inkluderede Ahn-studiet patienter i 2. linje, hvilket trækker i den modsatte retning. Patienter i RESONATE havde sammenlignelig alder, men væsentlig mindre komorbiditet. Den bedre prognose for patienterne i RESONATE forventes at favorisere effektestimaterne for ibrutinib.

Data fra de enkelte studier viser at både venetoclax + obinutuzumab og ibrutinib har en bedre effekt på PFS end konventionel kemoterapi hos patienter med deletion17p/TP53-mutation, og fagudvalget vurderer, at det på baggrund af det foreliggende datagrundlag ikke er muligt at skelne mellem de to behandlinger, som derfor kan betragtes som klinisk ligeværdige behandlingsalternativer, hvad angår overlevelse.

Bivirkninger

Andel der oplever en eller flere grad 3/4 uønskede hændelser:

Grad 3-4 hændelser blev rapporteret for 79 % af patienter behandlet med venetoclax + obinutuzumab i CLL14 mod 83 % behandlet med ibrutinib i Ahn og RESONATE. Der var 28 måneders opfølgningstid i CLL14 mod hhv. 58 og 60 måneder i Ahn og RESONATE-2. Dette indikerer, at venetoclax + obinutuzumab kan være forbundet med flere grad 3-4 hændelser pga. den store forskel i opfølgningstiden.

Kvalitativ gennemgang af bivirkningsprofilen

Der er flere hæmatologiske bivirkninger ved behandling med venetoclax + obinutuzumab (særligt neutropeni) end med ibrutinib. Patienter i behandling med ibrutinib kan opleve hjerteflimmer medførende behov for antikoagulationsbehandling. Dette kan kompliceres af en generelt øget tendens til blødninger blandt disse patienter. Herudover er ibrutinib forbundet med generende bivirkninger i form af diarré og hududslæt. Fagudvalget vurderer, at sikkerheden af lægemidlerne er sammenlignelig, men at der er væsentlige forskelle i bivirkningsprofilerne, og dette kan have betydning for den enkelte patients præference og egnethed.

Livskvalitet
Der er ikke data tilgængelig for komparator, der tillader en sammenligning.

5.4.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af venetoclax + obinutuzumab sammenlignet med ibrutinib til patienter med tidligere ubehandlede patienter med kronisk lymfatisk leukæmi med deletion 17p-/TP53-mutation ikke kan kategoriseres. Dette skyldes, at vurderingen beror på en narrativ vurdering, hvilket ikke giver mulighed for at foretage en formel kategorisering af venetoclax + obinutuzumab sammenlignet med ibrutinib. Fagudvalget vurderer dog, at venetoclax + obinutuzumab samlet set ikke har dårligere effekt eller sikkerhedsprofil end ibrutinib. Fagudvalget vurderer, at ibrutinib og venetoclax i kombination med obinutuzumab er klinisk ligestillede behandlingsvalg.

6 Andre overvejelser

6.1 Indflydelse på efterfølgende behandling

Fagudvalget ønskede i protokollen, at ansøger skulle bidrage med information om, hvordan det vil påvirke efterfølgende behandlinger, hvad angår type, varighed og forventet effekt at flytte anvendelse af venetoclax til 1.-linjebehandling. Ansøger har bidraget med information fra et retrospektivt studie, hvor næsten alle patienterne var relaps-/refraktære patienter (96 %), og hvor de fleste havde modtaget flere tidligere behandlinger, før de fik venetoclax (0-11). Data vurderes derfor ikke at være repræsentative eller anvendelige for denne vurdering, hvad angår påvirkningen af at flytte venetoclaxbehandling til første linje.

Vedrørende klinisk spørgsmål 1 vurderer fagudvalget, at anvendelse af venetoclax + obinutuzumab hos de IGHV-umuterede patienter vil udelukke senere brug af kemoimmunterapi hos disse patienter. De vil derfor behandles med ibrutinib i anden linje.

Hos IGHV-muterede patienter, hvor fagudvalget vurderer, at det på det foreliggende datagrundlag ikke er muligt at skelne mellem værdien af kemoimmunterapi og venetoclax + obinutuzumab, vil behandling i 2. linje afhænge af, hvilken behandling der er givet i første linje, herunder effekt og bivirkninger heraf.

Hvis patienterne er behandlet med kemoimmunoterapi i 1. linje, vil 2.-linjebehandling være venetoclax + rituximab eller ibrutinib i henhold til tidligere vurderingsrapport. Hvis de er behandlet med venetoclax + obinutuzumab i 1. linje, så vil behandlingen i 2. linje være ibrutinib, da viden om brug af kemoimmunterapi efter targeteret behandling er sparsomme.

6.2 Genbehandling med VEN

Der er meget begrænset erfaring med genbehandling med venetoclax + rituximab og ingen med venetoclax + obinutuzumab. Resultater fra 3 genbehandlende patienter indikerer, at der kan opnås respons på venetoclax + rituximab efter en længere periode uden behandling [25]. Fagudvalget anser resultaterne for at være for usikre til at drage konklusion eller være vejledende for valg mellem genbehandling med venetoclax. Genbehandling med venetoclax vil kunne overvejes ved relaps efter > 3 år.

6.3 Differentieret effekt baseret på IGHV-status

Dette er belyst særskilt under hvert klinisk spørgsmål. Resultaterne peger entydigt på, at der ses en væsentlig kortere PFS ved umuteret IGHV-status for kemoimmunoterapi, og fagudvalget anser derfor venetoclax +

obinutuzumab som en bedre behandlingsmodalitet for denne patientpopulation. Den korte PFS for patienter med umuterede IGHV behandlet med kemoimmunoterapi betyder i praksis, at de hurtigere må overgå til næste behandling. Dette betyder, at tid til næste behandling bliver kort, og patienterne må tolerere et mere intensivt behandlingsforløb, hvor kemoimmunoterapi tilbyder begrænset effekt i forhold til bivirknings- og behandlingsbyrden. Derudover bemærker fagudvalget, at såfremt patienter ikke får venetoclax i første linje, så består andenlinjebehandling af to års behandling med venetoclax + rituximab, modsat venetoclax + obinutuzumab, der kun doseres i ét år.

6.4 Venetoclax i kombination med obinutuzumab eller rituximab

Fagudvalget havde i protokollen efterspurgt, at ansøger belyste, hvorvidt der forventes nogen forskel i den kliniske effekt ved tillæg af de to anti-CD20-antistoffer, hhv. obinutuzumab og rituximab. For nuværende er der ikke nogen data tilgængelig, der tillader sammenligning mellem venetoclax + rituximab og venetoclax + obinutuzumab i første linje, og fagudvalget har ikke noget grundlag for at vurdere, om det ene antistof er at foretrække fremfor et andet. Chlorambucil + obinutuzumab har vist bedre PFS og OS end chlorambucil + rituximab i en population, der er sammenlignelig med populationen i CLL14, men dette kan ikke direkte videreføres til venetoclax [26].

Der pågår et studie, GAIA (NCT02950051), der bl.a. undersøger venetoclax + rituximab og venetoclax + obinutuzumab overfor bendamustin + rituximab og fludarabin + cyclofosfamid + rituximab i første linje, hvorfor en eventuel konklusion om, hvorvidt de to regimer er ligeværdige, først kan drages efter disse resultater er rapporteret.

7 Samlet konklusion

7.1 Klinisk spørgsmål 1 – patienter uden del17p/TP53-mutation

Samlet set vurderer fagudvalget at værdien af venetoclax + obinutuzumab sammenlignet med kemoimmunterapi **ikke kan kategoriseres** hos patientpopulationen uden del17p/TP53-mutation. Evidensens kvalitet er **meget lav**.

Mængden og typen af bivirkninger for venetoclax + obinutuzumab er sammenlignelig med chlorambucil + obinutuzumab, mens fagudvalget foretrækker bivirkningsprofilen for venetoclax + obinutuzumab i sammenligning med både bendamustin + rituximab og fludarabin + cyclofosfamid + rituximab.

Fagudvalget vurderer baseret på data for PFS, at der med venetoclax + obinutuzumab er en behandlingsgevinst i subpopulationen af patienter der er IGHV-umuterede sammenlignet med kemoimmunoterapi.

7.2 Klinisk spørgsmål 2 – patienter med del17p/TP53-mutation

Samlet set vurderer fagudvalget, at værdien af venetoclax + obinutuzumab sammenlignet med ibrutinib **ikke kan kategoriseres** hos patientpopulationen med del17p/TP53-mutation. Evidensens kvalitet er **meget lav**.

Mængden og typen af bivirkninger er sammenlignelig for de to behandlinger, og data for effekt giver ikke anledning til at skelne mellem de to behandlinger, som fagudvalget derfor betragter som klinisk ligestillede behandlingsalternativer.

8 Relation til behandlingsvejledning

Der findes ikke en behandlingsvejledning fra Medicinrådet. Medicinrådet har tidligere besluttet, at der skal udarbejdes en behandlingsvejledning for CLL i Medicinrådet.

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kronisk lymfatisk leukæmi (CLL)

Formand	**Indstillet af**
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Medlemmer	**Udpeget af**
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11 Versionslog

Version	Dato	Ændring
1.1	3. november 2020	s. 18: obintuzumab er rettet til rituximab i sætningen: *Det vil i dag enten være venetoclax + rituximab eller ibrutinib, som er henholdsvis en to-årig eller kontinuert behandling.*
1.0	21. oktober 2020	Godkendt af Medicinrådet.

12 Bilag 1: Evidensens kvalitet

12.1 Cochrane, Risk of Bias

Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool.

	Risiko for bias i randomiseringsprocessen	**Risiko for bias grundet afvigelser fra tilsigtet intervention** **(effekt af tildeling til intervention)**	**Manglende data for effektmål**	**Risiko for bias ved indsamlingen af data**	**Risiko for bias ved udvælgelse af resultater der rapporteres**	**Overordnet risiko for bias**
CLL-14	Lav	Lav	Lav	forbehold	Lav	Forbehold

GRADE-profil

Klinisk spørgsmål 1

Venetoclax + obinutuzumab sammenlignet med chlorambucil + obinutuzumab

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gilteritinib	Kemoterapi	Relative (95 % CI)	Absolute (95 % CI)		
3-års overlevelse (follow up: median 17,8 months)												
1	randomised trials	not serious	serious [a]	not serious	Very serious [b]	none	192/216 (88,9 %)	190/216 (88 %)	**HR 1,03** (0,60-1,75)	-	⨁◯◯◯ MEGET LAV	CRITICAL
Grad 3-4 hændelser												
1	randomised trials	serious[c]	serious [a]	not serious	Very serious [b]	none	167/212 (79 %)	164/214 (77 %)	**RR 1,03** (0,93-1,14)	**2,0 % [-5,7 % til 10 %]**	⨁◯◯◯ MEGET LAV	IMPORTANT
Livskvalitet (follow up: median 28,1 mdr)												
1	randomised trials	serious[c]	serious [a]	not serious	Very serious [b]	none	216	216	-	-0,7-point	⨁◯◯◯ MEGET LAV	IMPORTANT

Forklaring:

a. Kun ét studie indgår i vurderingen af dette effektmål.
b. Konfidensintervallet indeholder både positive og negative værdier.
c. Risiko for bias, da studiet er open-label, og der er et subjektivt element i målingen af effektmålet.

abbvie

Application for the assessment of clinically added value of Venclyxto in combination with obinutuzumab for previously untreated patients with chronic lymphocytic leukemia

3rd August 2020

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2 Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical

Proprietary name	Venclyxto®	
Generic name	Venetoclax	
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany	
ATC code	L01XX52	
Pharmacotherapeutic group	Other antineoplastic agents	
Active substance(s)	venetoclax	
Pharmaceutical form(s)	Film-coated tablet (10mg, 50 mg and 100mg)	
Mechanism of action	Venetoclax is a potent, selective inhibitor of B cell lymphoma (BCL)-2, an anti-apoptotic protein.	
Dosage regimen	Dosage in combination with obinutuzumab: Obinutuzumab i.v., cycle 1: 100 mg day 1, 900 mg day 2 and 1.000 mg day 8 and day 15, cycle 2-6: 1.000 mg day 1 Venetoclax p.o., cycle 1: 20 mg day 22-28, cycle 2: 50 mg day 1-7, 100 mg day 8-14, 200 mg day 15-21 and 400 mg day 22-28. Cycle 3-12: 400 mg day 1-28.	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.	
Other approved therapeutic indications	1. Venclyxto® in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) 2. Venclyxto® in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. 3. Venclyxto® monotherapy is indicated for the treatment of CLL: o in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or o in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.	
Patient population	Incidence: From 2011-2015, on average 398 persons were diagnosed each year (ref cancer.dk)	Prevalence: By the end of 2015, there was a total of 3.677 patients in Denmark
Will dispensing be restricted to hospitals?	Yes	
Combination therapy and/or co-medication	Obinutuzumab	
Packaging – types, sizes/number of units, and concentrations	Carton, film-coated tablets, 7-day pack, 10 mg, 14 film-coated tablets Carton, film-coated tablets, 7-day pack, 50 mg, 7 film-coated tablets	

	Carton, film-coated tablets, 7-day pack, 100 mg, 7 film-coated tablets Carton, film-coated tablets, 7-day pack, 100 mg, 14 film-coated tablets Carton multipack, 100 mg film-coated tablets, 112 (4 x 28) film-coated tablets
Orphan drug designation	No

3 Abbreviations

AD: Absolute difference

AE: Adverse events

BCL-2: B-Cell lymphoma-2

BM: Bone marrow

BR: Bendamustin in combination with rituximab

BSH: British Society for Heamotology

BTKi: Bruton's Tyrosine Kinase inhibitor

CI: Confidence Interval

CI_low: Lower confidence Interval

CI_high: Higher confidence Interval

CIRS: Cumulative illness rating scale

CIT: Chemoimmunotherapy

GClb: Chlorambucil in combination with obinutuzumab

CLL: Chronic lymphocytic leukemia

CR: Complete remission

DC: Discontinuation

EMA: European Medicines Agency

EORCT QLQ-C30: the European Platform of Cancer Research Quality of Life questionnaire

FCR: Fludarabin, cyclofosfamid in combination with rituximab

FTD: Fixed treatment duration

HR: Hazard ratio

IBR: Ibrutinib monotherapy

ITT: Intention to treat

iwCLL: International workshop on chronic lymphocytic leukemia

MRD: Minimal residual disease

ORR: Overall response rate

OS: Overall survival

PD: Progression of disease

PFS: Progression-free survival

PI3Ki: Phosphoinositide 3-kinase inhibitor

PR: Partial remission

SAE: Serious Adverse Event

SD: Standard Disease

SmPC: Summary of product Characteristics

TLS: Tumor lysis syndrome

VenG: Venetoclax in combination with obinutuzumab

VenR: Venetoclax in combination with obinutuzumab

4 Summary

Venetoclax® is a first-in-class targeted medicine that selectively binds and inhibits the B-cell lymphoma-2 (BCL-2) protein. In chronic lymphocytic leukemia (CLL), BCL-2 prevents cancer cells from undergoing their natural death or self-destruction process, called apoptosis. Venetoclax targets and inhibits the BCL-2 protein and works to help restore the process of apoptosis. In 12 months, fixed duration therapy Venetoclax has in combination with 6 cycles of obinutuzumab demonstrated first-in-class efficacy, with the achievement of unparalleled deep response as measured by minimal residual disease negativity at similar and manageable safety profile to competitors.

On 9th March 2020 venetoclax in combination with 6 cycles obinutuzumab received EMA approval as the first fixed duration, targeted, chemotherapy-free combination for the treatment of adult patients with previously untreated chronic lymphocytic leukemia. The approval was based on the CLL14 Phase 3 clinical trial in which venetoclax plus obinutuzumab reduced the risk of disease progression or death by 69 percent compared to chlorambucil in combination with rituximab. Most patients (75.5 percent) treated with venetoclax plus obinutuzumab achieved MRD negativity in peripheral blood compared to 35.2 percent of patients who received chlorambucil plus obinutuzumab.

Current treatment options in first line treatment of CLL entail either fixed duration chemoimmunotherapy or continuous indefinite targeted therapy. Venetoclax plus obinutuzumab is the first and only approved fixed duration targeted therapy with a favorable safety profile and substantial clinical benefit.

The Medicines Council outlined 2 clinical questions to be answered in this application for recommendation to be used as standard of care in Danish hospitals:

Clinical question 1: What is the clinically added value of venetoclax in combination with obinutuzumab compared to chemotherapy in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?

> Overall a clear benefit on PFS for VenG was shown vs. chemotherapy in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation. This benefit is realized with similar rates of serious adverse events compared to BR and GClb, and at lower rates of serious adverse events compared to FCR.

Clinical question 2: What is the clinically added value of venetoclax in combination with obinutuzumab compared to ibrutinib for patients with previously untreated chronic lymphocytic leukemia with deletion17p/p53-mutation?

> PFS and OS were found to be on par between VenG and IBR considering the vast difference in follow-up time and patient demographics between trials. Higher rates of grade 3-4 AEs were observed in the VenG arm of the CLL14 compared to the IBR treated patients in the Ahn et al. and Mato et al. studies. However, 5 years of continuous therapy with IBR in the RESONATE 2 trial meant that 83% of patients had experienced AEs of grade 3 or higher.

In conclusion, VenG represents an important additional therapy option for patients with previously untreated chronic lymphocytic leukemia that compared to present standard therapy for patients without deletion17p/p53-mutation offers superior efficacy at similar or better safety and includes the option to stop therapy for patients with deletion17p/p53-mutation at similar efficacy and safety.

5 Literature search

A systematic literature search was conducted on 15/6 2020 according to the criteria set out by the Medicines Council protocol for venetoclax in first line CLL to retrieve data to answer the 2 clinical questions. Details of the searches including in- and exclusion criteria, search terms and strategy can be found in Appendix A.

The PRISMA flow diagram is shown in appendix 7.1.2. A total of 861+172 potentially relevant references were identified through searching MEDLINE and CENTRAL (see Appendix 7.1). A total of 112 reference duplicates were identified and 921 references were subsequently screened. 896 records were excluded based on titles and abstracts and 25 published full-text papers were subsequently assessed for eligibility. Of these, 15 references were excluded in full text review. In total, 10 references reporting results of 6 studies were included.

To answer the 1st clinical question a hand search for references reporting on the updated results for the CLL14 trial (36 months estimates) was performed. This hand search added 2 conference abstract references.

Furthermore, to answer the 2nd clinical question a hand search for studies of ibrutinib in first line del17/TP53 patients was performed. This hand search added 2 studies/references (Ahn et al. and Mato et al.):

1. CLL14 trial, NCT02242942
2. E1912 trial, NCT02048813
3. Alliance trial, NCT01886872
4. CLL10 trial, NCT00769522
5. MaBle trial, NCT01056510
6. RESONATE-2, NCT01722487
7. Ahn et al. trial, NCT01500733
8. Mato et al. study, no NCT

Please note that these studies and references were included to answer the clinical questions only. All other references referred to in the sections 5.3 Other considerations and 5.4 Discussion were included ad hoc.

5.1 Relevant studies

Clinical question 1: Venetoclax + obinutuzumab vs. chemoimmunotherapy in CLL patients without del17p/TP53 who have not previously been treated

Table 4.1: Relevant studies included in the assessment of VenG vs. GClb, BR and FCR

Reference (title, author, journal, year)	Trial name	NCT number	Dates of trial (start and expected completion date)	Relevant for clinical question
Fisher et al., 2019(1) Al-Sawaf et al, 2020(2) Al-Sawaf et al, 2019(3)	CLL14	NCT02242942	Start: December 31, 2014 End: September 1, 2020	Q1
Shanafelt et. al(4)	E1912	NCT02048813	Start: February 20, 2014 End: June 9, 2026	Q1
Woyach et al.(5)	Alliance	NCT01886872	Start: December 9, 2013 End: August 7, 2018	Q1
Eichhorst et al.(6) Kutsch et al.(7)	CLL10	NCT00769522	Start: October 2, 2008 End: January 2018	Q1
Michallet et al. 2018(8)	MaBle	NCT01056510	Start: March 2010 End: March 2014	Q1

Clinical question 2: Venetoclax + obinutuzumab vs. ibrutinib in CLL patients with del17p/TP53 who have not previously been treated

Table 4.2: Relevant studies included in the assessment of VenG vs. IBR

Reference (title, author, journal, year)	Trial name	NCT number	Dates of trial (start and expected completion date)	Relevant for clinical question
Fisher et al., 2019(1) Al-Sawaf et al, 2020(2) Al-Sawaf et al, 2019(3)	CLL14	NCT02242942	Start: December 31, 2014 End: September 1, 2020	Q2
Ahn et al. 2018 (9)	Ahn et al. trial	NCT01500733	Start: November 28, 2011 May 1, 2025	Q2
Mato et al.(10)	Mato et al. study	NA	Start: Publication august 2018 End: Publication august 2018	Q2
Burger et al. 2020(11) Burger et al.(12) Barr et al.(13)	Resonate 2	NCT01722487	Start: March 2013 End: May 2015	Q2

5.2 Main characteristics of included studies

Please see sections for each clinical question and Appendix 7.1.4. for details on trial characteristics.

6 Clinical questions

Clinical question 1: *What is the clinically added value of venetoclax in combination with obinutuzumab compared to chemotherapy in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?*

- Intervention: venetoclax in combination with obinutuzumab
  - Obinutuzumab i.v., cycle 1: 100 mg day 1, 900 mg day 2 and 1.000 mg day 8 and day 15, cycle 2-6: 1.000 mg day 1
  - Venetoclax p.o., cycle 1: 20 mg day 22-28, cycle 2: 50 mg day 1-7, 100 mg day 8-14, 200 mg day 15-21 and 400 mg day 22-28. Cycle 3-12: 400 mg day 1-28.
- Comparator (Q1a): Chlorambucil in combination with obinutuzumab (GClb)
  - Chlorambucil p.o. cycle 1-6: 0,5 mg/kg day 1 and 15
  - Obinutuzumab i.v. cycle 1: 100 mg day 1, 900 mg day 2 and 1.000 mg day 8 and 15, 1.000 mg day 1 in cycle 2-6.
- Comparator (Q1b): Bendamustin in combination with rituximab (BR)
  - Bendamustin i.v. 70-90 mg/m^2 day 1 and 2, cycle 1-6
  - Rituximab i.v. 375 mg/m^2 day 1 in cycle 1, thereafter i.v. 500 mg/m^2 day 1 in cycle 2-6
- Comparator (Q1c): Fludarabin, cyclofosfamid in combination with rituximab (FCR)
  - Fludarabin 25 mg/m^2 i.v. dag 1-3 in cycle 1-6
  - Cyclofosfamid 250 mg/m^2 i.v. dag 1-3 in cycle 1-6
  - Rituximab i.v. 375 mg/m^2 day 1 in cycle 1, thereafter i.v. 500 mg/m^2 day 1 in cycle 2-6

Clinical question 2: *What is the clinically added value of venetoclax in combination with obinutuzumab compared to ibrutinib for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?*

- Comparator: Ibrutinib monotherapy (IBR)
  - Ibrutinib p.o. 420 mg daily until progression

Outcomes:

- *Overall survival (OS)*
- *Progression free survival (PFS)*
- *Grade 3-4 adverse events*
- *EORTC QLQ-C30*

The Medicines Council protocol posed 2 questions involving 4 comparators. The only identified direct comparative trial was the CLL14 trial in which VenG was directly compared to GClb. Thus, only clinical question 1a was answered using direct comparison from this trial. All other clinical questions would have to rely on narrative analysis in accordance with the *Handbook of the Medicines Council's process and methodologies for new pharmaceuticals and indication expansions version 2.6 (14).*

6.1 Clinical question 1

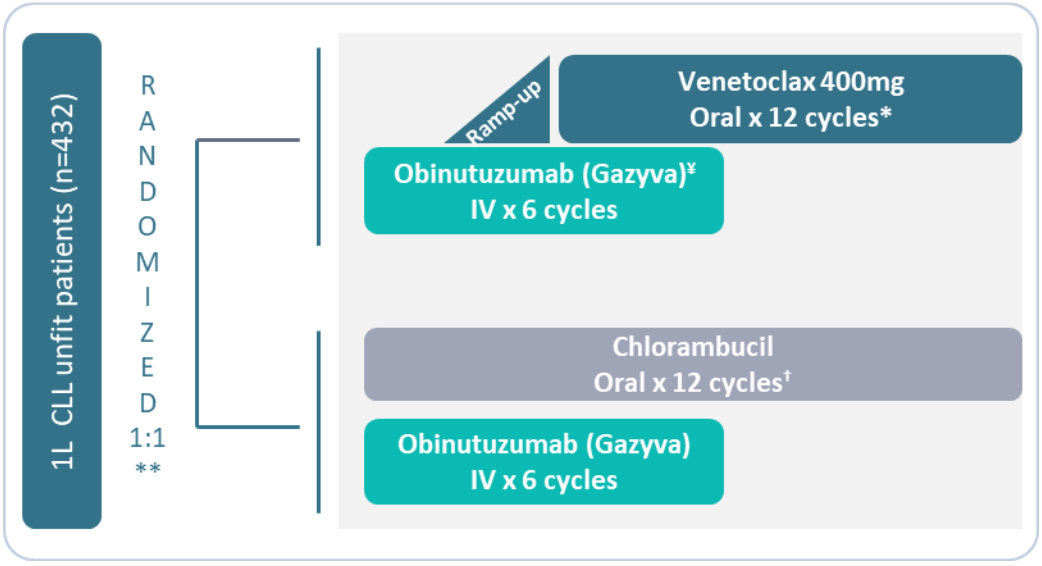
What is the clinically added value of venetoclax in combination with obinutuzumab compared to chemotherapy in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?

6.1.1 Presentation of relevant studies

6.1.2 CLL14

The CLL14 trial was an open-label, randomized trial, that enrolled 432 elderly patients, with co-existing conditions (CIRS > 6 or CrCl <70 ml/min), who had previously untreated CLL, had been diagnosed in accordance with the criteria of the International Workshop on CLL (iwCLL) and had been determined by the treating clinician and confirmed during the central screening process to require therapy (Binet stage C [low hemoglobin or platelet count from bone marrow infiltration of CLL cells] or symptomatic disease). Because new treatment options were approved during the recruitment period, patients with TP53 deletion or mutation were enrolled at the investigator's discretion. A notification letter was sent to all the investigators about the enrollment of such patients. Patients were randomly assigned in a 1:1 ratio to receive either venetoclax–obinutuzumab or chlorambucil–obinutuzumab. 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. The primary end point was investigator-assessed progression-free survival, defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause. Secondary end points were progression-free survival as assessed by an independent review committee, minimal residual disease negativity, overall and complete response, minimal residual disease negativity in patients with complete response, and overall survival.

Figure 5.1: Trial design CLL14 trial



For further details, please see appendix 7.1.4.

6.1.3 Alliance trial

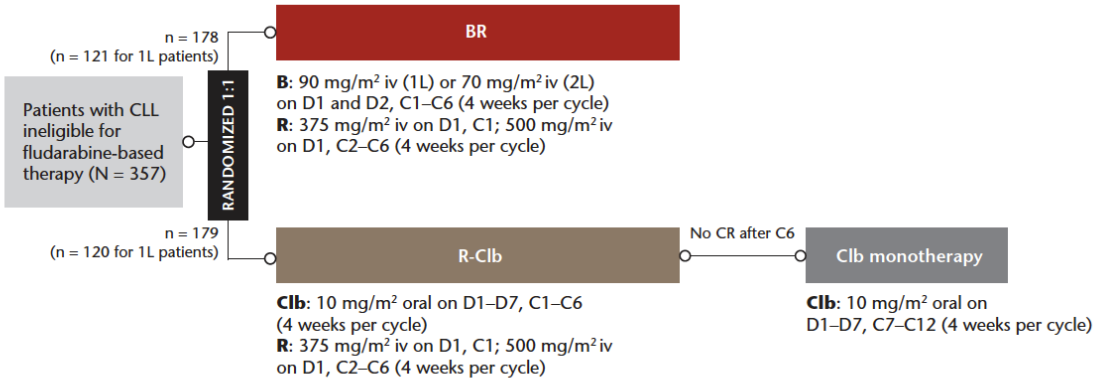
The Alliance trial was a phase 3 trial were patients aged 65 or older with previously untreated CLL received. Patients were randomly assigned, in a 1:1:1 ratio to receive Bendamustine plus rituximab, ibrutinib or ibrutinib plus rituximab. The Primary endpoint was progression-free survival. Secondary endpoints was overall survival, overall response and safety among others. A total of 547 patients underwent randomization. Subgroups were defined according to various baseline characteristics such as IgHV mutation-status, del(17p) status etc.

For further details, please see appendix 7.1.4.

6.1.4 MaBle trial

MaBle investigated the efficacy and safety of rituximab plus bendamustine or rituximab plus chlorambucil in fludarabine-ineligible patients with chronic lymphocytic leukemia. 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 progression-free survival, overall survival, minimal residual disease, and safety. The trial was conducted between 23 February 2010 and 31 March 2014. Of the 357 patients in the ITT population, comprising 241 1st line patients (R-B, n=121; R-Clb, n=120) and 116 2nd line patients (R-B, n=57; R-Clb, n=59), 355 patients received treatment (R-B, n=177; R-Clb, n=178).

Figure 5.2: Trial design MABLE trial



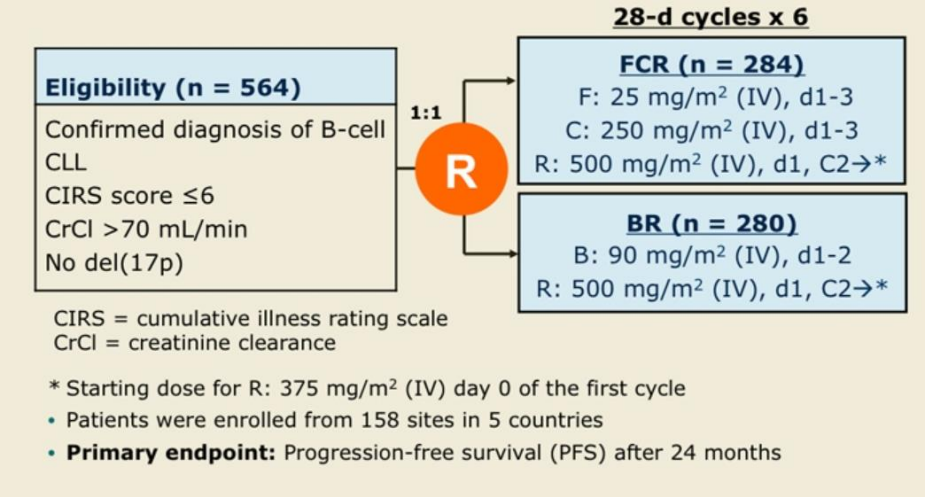
1L = first-line; 2L = second-line; B = bendamustine; BR = bendamustine plus rituximab; C = cycle; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; D = day; iv = intravenous; R = rituximab; R-Clb = chlorambucil plus rituximab

For further details, please see appendix 7.1.4.

6.1.5 CLL10 trial

Treatment-naive fit patients (564) with chronic lymphocytic leukemia (aged 33–81 years) without del(17p) were enrolled after undergoing a central screening process. Patients were randomly assigned (1:1) with a computer-generated randomization list using randomly permuted blocks with a block size of eight and were stratified according to participating country and Binet stage. Patients were allocated to receive six cycles of intravenous fludarabine (25 mg/m² per day) and cyclophosphamide (250 mg/m² per day) for the first 3 days or to intravenous bendamustine (90 mg/m² per day) for the first 2 days of each cycle. Rituximab 375 mg/m² was given intravenously in both groups on day 0 of cycle 1 and was subsequently given at 500 mg/m² during the next five cycles on day 1. The primary endpoint was progression-free survival whereas secondary endpoints included overall survival, overall response, minimal residual disease, event-free survival and EORTC-C30.

Figure 5.3: Trial design CLL10 trial

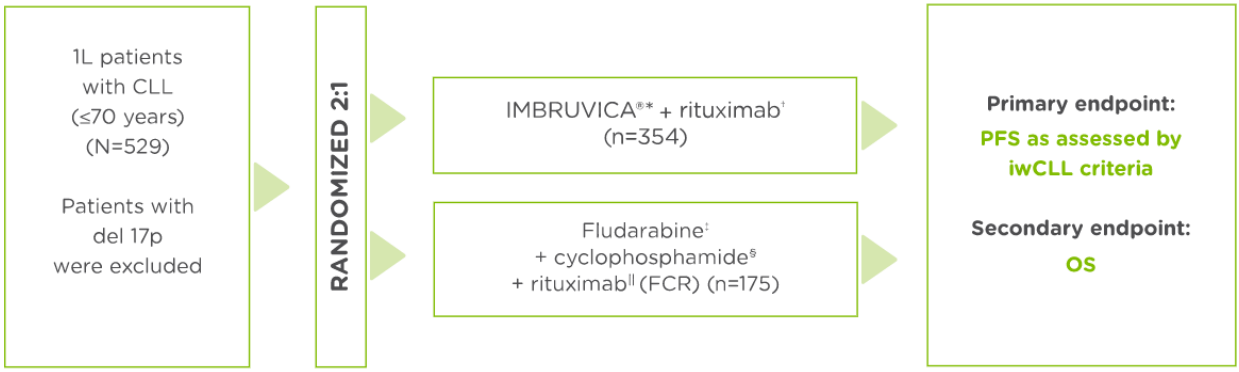


For further details, please see appendix 7.1.4.

6.1.6 E1912 trial

The E1912 phase 3 trial randomly assigned (in a 2:1 ratio) 529 patients 70 years of age or younger, with non del 17p and previously untreated CLL to receive either ibrutinib and rituximab (n=354) for six cycles (after a single cycle of ibrutinib alone), followed by ibrutinib until disease progression, or (n=175) six cycles of chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab. The primary end point was progression-free survival and overall survival was a secondary end point.

Figure 5.4: Trial design E1912 trial



6.1.7 Results per trial

CLL14

Table 5.1: Relevant results from the CLL14 trial, VenG vs. GClb in first line CLL patients

OUTCOMES in MR protocol	VenG (216)	GClb (216)	HR	CI	P-value	Source
OS, 24 md	91.80%	93.30%	1.24	[0.64-2.40]	0.52	Fisher et al. 2019(1)
OS, 36 md	88.9%	88.0%	1.03	[0.602-1.753]	0.921	Al-Sawaf et al. 2020(2)
PFS, 24 md	88.2%	64.1%	0.35	[0.23-0.53]	<0,001	Fisher et al. 2019(1)
PFS, 36 md	81.9%	49.5%	0.31	[0.22-0.44]	<0,001	Al-Sawaf et al. 2019(2)
AE grade 3-4 (safety population; VenG=212, GClb=214)	79%	77%	n.a.	n.a.	n.a.	Fisher et al. 2019(1)
EORTC QLQ-C30, Global Health Status, improvement 30 months	12.7	13.4	n.a.	n.a.	n.a.	Al-Sawaf et al. 2019(3)

Note: Improvement 30 months in EORTC QLQ-C30 Global Health Status; 30 months read in graph as VenG=73, GClb=77, Baseline was 60.3 and 63.6, Improvement calculated as 12.7 and 13.4 respectively

Table 5.2: Relevant results from the Alliance trial, IBR vs. IBR+R vs. BR in first line CLL patients

OUTCOMES in MR protocol	BR (176)	CI	Ibrutinib (178)	CI	Ibrutinib + R (170)	CI	HR; IBR vs. BR, IBR+R vs. BR	CI; IBR vs. BR, IBR+R vs. BR	P-value	Source
OS, 24 md	95%	0.91-0.98	90%	0.85-0.94	94%	0.89-0.97	n.a.	n.a.	0.64	Woyach et al. 2018(5)
PFS, 24 md	74%	0.66-0.80	87%	0.81-0.92	88%	0.81-0.92	0.39; 0.38	[0.26-0.58]; [0.25-0.59]	<0,001	Woyach et al. 2018(5)
Hematological AE grade 3-4	61%		41%		39%		n.a.	n.a.	<0,001	Woyach et al. 2018(5)
Non-Hematological AE grade 3-4	63%		74%		74%		n.a.	n.a.	0.04	Woyach et al. 2018(5)
EORTC QLQ-C30, Global Health Status	NR									

Table 5.3: Relevant results from the MaBle trial, BR vs. Clb+R in first line CLL patients

OUTCOMES in MR protocol	BR (121)	CI	Clb+R (120)	CI	HR	CI	P-value	Source
PFS median	39.6 months		29.9 months		0.52	[0.339-0.806]	0.003	Michallet et al. 2018(8)
OS median	43.8 months		NR		0.98	[0.505-1.880]	0.939	Michallet et al. 2018(8)
AE grade 3-4*Pooled analysis	132 (75%)		113 (64%)		n.a.	n.a.	n.a.	Michallet et al. 2018(8)
EORTC QLQ-C30, Global Health Status	NR							

Table 5.4: Relevant results from the CLL10 trial, BR vs. FCR in first line CLL patients

OUTCOMES in MR protocol	BR (279)	CI	FCR (282)	CI	HR	CI	P-value	Source
OS, 36 md	92%	[0.887-0.956]	91%	[0.87-0.942]	1.03	[0.62-1.724]	0.897	Eichhorst et al. 2016(6)
OS, 60 md	80%		81%		1.11	[0.755-1.627]	0.599	Eichhorst et al. 2016(6)
Median PFS, md	41.7 months	[34.9-45.3]	55.2 months	NE	1.64	[1.308-2.064]	n.a.	Eichhorst et al. 2016(6)
Median PFS, md (extension)	42.3 Months		57.6 Months		1.59	[1.271-1.996]	<0.0001	Eichhorst et al. 2016(6)
AE grade 3-4 (>=3)	84%		94%		n.a.	n.a.	n.a.	Eichhorst et al. 2016(6)
EORTC QLQ-C30, Global Health Status	NR							

Table 5.5: Relevant results from the E1912 trial, IBR vs. IBR+R vs. BR in first line CLL patients

OUTCOMES in MR protocol	IBR+R (354), saftey 352	CI	FCR (175), saftey 158	CI	HR	CI	P-value	Source
PFS, 36 md	89.4%	0,86-0.93	72.9%	0,653-0,813	HR: 0,35	0,22-0,56	<0,001	Shanafelt et al. 2019(4)
OS, 36 md	98.8%	0,976-1,0	91.5%	0,862-0,97	HR: 0,17	0,05-0,54	<0,001	Shanafelt et al. 2019(4)
Grade 3 or higher AE, 36 md	(282) 80.1%		(126) 79.7%					Shanafelt et al. 2019(4)
EORTC QLQ-C30, Global Health Status, improvement 30 months*	NR							

6.1.8 Comparative analysis

6.1.8.1 Clinical question 1a

What is the clinically added value of venetoclax in combination with obinutuzumab compared to chlorambucil in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?

Table 5.6: Comparative analysis VenG vs. GClb

Outcome	VenG/GClb HR			Absolute difference (AD) assuming event rate GClb from CLL14 trial			Event rate GClb
	HR	CI_low	CI_high	AD	CI_low	CI_high	
OS, 24 md	1.24	0.64	2.4	-1.50%	n.a.	n.a.	93.30%
OS, 36 md	1.03	0.602	1.753	0.9%	n.a.	n.a.	88.00%
PFS, 24 md	0.35	0.23	0.53	24.10%	n.a.	n.a.	64.10%
PFS, 36 md	0.31	0.22	0.44	32.40%	n.a.	n.a.	49.50%
AE grade 3-4	1.03	0.93	1.14	2.3%	-5.4%	10.7%	76.64%
EORTC QLQ-C30, Global Health Status, Difference	- 0.70	n.a.	n.a.	- 0.70	n.a.	n.a.	na

The comparative analysis in table 5.6 is performed using data from the CLL14 trial on VenG vs. GClb for OS, PFS, SAE and EORTC.

Overall survival was numerically lower for VenG compared to GClb at both 24 and 36 months (HR 1.24 and 1.03 respectively), however not significant as the confidence interval included 1. Progression free survival was considerably higher for VenG compared to GClb at both assessments and statistically significant (HR 0.35 and 0.31 respectively). The estimated absolute difference in progression free survival at 36 months was 32.4% for VenG vs. GClb. VenG had a numerically higher proportion of patients with grade 3-4 adverse events compared to GClb (HR 1.03), however the HR was not significant as the confidence interval included 1. Patients in VenG therapy experienced an improvement from baseline in EORTC QLQ-C30 of 12.7, which was 0.7 points lower than the improvement experienced by patients in GClb therapy on the 100-point scale of the EORTC QLQ-C30 scale.

6.1.8.2 Clinical question 1b

What is the clinically added value of venetoclax in combination with obinutuzumab compared to bendamustine in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?

Table 5.7: Comparative analysis VenG vs. BR

Outcome	BR (Alliance)	BR (CLL10)	BR (MaBle)	VenG (CLL14)
OS, 24 md	95%	NR	NR	91.8%
PFS, 24 md	74%	NR	NR	88.2%
OS, 36 md	NR	92%	NR	88.9%
PFS, 36 md	NR	NR	NR	81.9%
PFS median	NR	42.3 months	39.6 months	NR
OS median	NR		43.8 months	NR
Hematological AE grade 3-4	61%	NR	NR	NR
Non-Hematological AE grade 3-4	63%	NR	NR	NR
AE grade 3-4*Pooled analysis (>3 CLL10)	NR	84%	75%	79%
EORTC QLQ-C30, Global Health Status, improvement 30 months	NR	See Figure 5.5	NR	12.7

The systematic literature review did not reveal any head to head studies or network meta-analyses for VenG vs BR in first line CLL patients. Therefore, the BR arms in the Alliance, CLL10 and MaBle studies were compared naïve to the VenG arm of the CLL14 trial.

Considerable differences exist between patient populations recruited in the 4 included trials. The Cll10 trial recruited fit patients (CIRS≤6) of younger age as the comparator was FCR. Median age in the CLL10 trial was 61 years in the BR arm. The E1912 trial recruited patients below 70 years of age and mean age in the trial was 56.7 years, whereas the Alliance trail had patients with median age 71 years and high-risk disease in 54% of randomized patients. The CLL14 trial recruited elderly patients with co-morbidity (CIRS>6) and median age was 72 years in the VenG arm of the trial. These differences should be observed when comparing results between trials.

In the Alliance trial overall survival after 24 months for the BR arm was 95% (CI 91%-98%), compared to 91.8% after 24 months in the VenG arm of the CLL14 trial, and thus a numerical higher OS for BR compared to GClb however not statistically significant. At 24 months follow-up the rate of progression free survival was 88.2% for the VenG arm of the CLL14 trial compared to 74% (CI 66%-80%) for the BR arm of the Alliance trial and thus a significantly higher PFS for VenG vs. GClb. PFS after 36 months in the VenG arm of the CLL14 trial was 81.9% compared to a median PFS of 39.6 months in the BR arm of the MaBle trial, and thus an expected considerably higher rate of PFS for VenG compared to BR. At 36 months follow up in the CLL10 trial 143 patients out of 279 had not progressed and the PFS rate was thus 51.3% in the CLL10 trial(7). The rate of grade 3-4 adverse events in the VenG arm of the CLL14 trial was 79% compared to 75% in the BR arm of the MaBle trial and 84% having a grade 3 or higher adverse event in the BR arm of the CLL10 trial. In the Alliance trial the BR arm had rates of hematologic- and non-hematologic AEs grade 3-5 of 61% and 63% respectively. The EORTC QLQ-C30 outcome was not included in the Alliance and MaBle studies and subsequently no comparisons could be performed for this outcome. The CLL10 trial included EORTC QLQ-C30 but did only report graphically (see figure 5.6). During the active therapy phase of the trial, the global health status diminished to improve up to the end of follow-up for both active arms of the trial.

Figure 5.5: EORTC QLQ-C30 Global Health status and Fatigue subscale, FCR and BR, CLL10(7)

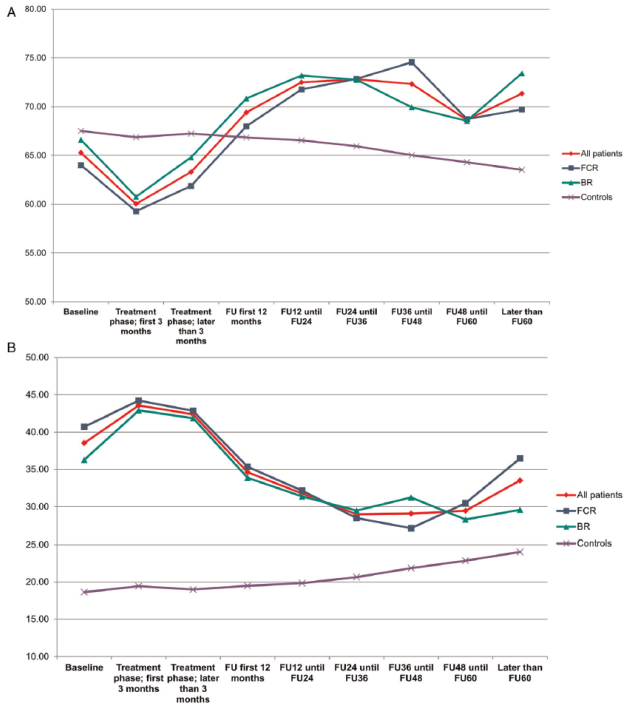


Figure 4. **(A) Global health status in all patients vs healthy controls (B) fatigue in all patients vs healthy controls (C) global health status in both treatment arms and different age groups (D) fatigue in both treatment arms and different age groups.**

6.1.9 Clinical question 1c

What is the clinically added value of venetoclax in combination with obinutuzumab compared to fludarabine, cyclophosphamide and rituximab combination therapy for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?

Table 5.8: Comparative analysis VenG vs. FCR

Outcome	FCR (E1912)	FCR (CLL10)	VenG (CLL14)
OS, 36 md	91.5%	91%	88.9%
OS, 60 md	NR	80.9%	NR
PFS, 36 md	72.9%	68%	81.9%
Median PFS, md	NR	55.2 months	NR
Median PFS, md (extension)	NR	57.6 Months	NR
AE grade 3-4*	79.7%	94%	79%
EORTC QLQ-C30, Global Health Status, improvement 30 months	NR	NR	12.70

Note: *AE grade >=3 was reported in the E1912 and CLL10 trials

The systematic literature review did not reveal any head to head studies or network meta-analyses for VenG vs. FCR in first line CLL patients. Therefore, the FCR arm in the E1912 and CLL10 trials was compared naïve to the VenG arm of the CLL14 trial.

Considerable differences exist between patient populations recruited in the 3 included trials. The Cll10 trial recruited fit patients (CIRS⩽6) of younger age as the comparator was FCR. Median age in the CLL10 trial was 62.1 years with 30% being older than 65 years in the FCR arm. The E1912 trial recruited patients below 70

years of age and mean age in the trial was 56.7 years. The CLL14 trial recruited elderly patients with co-morbidity (CIRS>6) and median age was 72 years in the VenG arm of the trial. These differences should be observed when comparing results between trials.

In the E1912 and CLL10 trials overall survival after 36 months for the FCR arms was 92% and 91% respectively compared to 88.9% after 36 months for VenG in the CLL14 trial. This suggests that the therapy options are on par in this respect. Median progression free survival in the extension of the CLL10 trial was 57.6 months for the FCR arm. At 36 months follow-up in the E1912 and CLL10 trials the PFS rate was 73% and 68% respectively. This should be compared to 82% PFS rate at 36 months in the VenG arm of the CLL14, suggesting substantially longer time to progression or death for VenG compared to FCR. The rate of grade 3-4 adverse events in the VenG arm of the CLL14 trial was 79% compared to 94% of patients having a grade 3 or higher adverse event in the FCR arm of the CLL10 trial and 79.7% in the E1912 trial, suggesting a lower rate of serious adverse events with VenG compared to FCR. The CLL10 trial included EORTC QLQ-C30 but did only report graphically (see figure 5.6). During the active therapy phase of the trial, the global health status diminished to improve up to end of follow-up for both active arms of the trial. This should be compared to the improvement of 12.7 points on the 100-point scale of the global health status EORTC QLQ-C30.

Conclusion

The clinically added value of venetoclax in combination with obinutuzumab has been assessed directly compared to chlorambucil in combination with obinutuzumab in the CLL14 trial, which based on 39.6 months follow-up found a substantial benefit on progression free survival. On the other included outcomes in the Medicines Council protocol, the results of the CLL14 trial shows similarity in the rate of grade 3-4 adverse events, similarity in improvement in global health status from base line and data are too immature to show any difference in the rate of overall survival for VenG vs Clb+O.

The clinically added value of venetoclax in combination with obinutuzumab has been assessed narratively compared to bendamustine in combination with rituximab (BR) and fludarabine, cyclophosphamide and rituximab combination therapy (FCR). This assessment strongly suggests a substantial benefit on progression free survival versus both BR and FCR. Overall survival seems on par between VenG, BR and FCR after 36 months follow-up. Serious adverse events seem higher for FCR than for BR and VenG, whereas the little data found on quality of life suggest that the therapy options are similar in this respect.

Overall a clear benefit on PFS for VenG was shown vs. chemotherapy in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation. This benefit is realized with similar rates of serious adverse events compared to BR and Clb+O, and at lower rates of serious adverse events compared to FCR.

6.2 Clinical question 2

What is the clinically added value of venetoclax in combination with obinutuzumab compared to ibrutinib for patients with previously untreated chronic lymphocytic leukemia with deletion17p/p53-mutation?

Single agent ibrutinib in patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation has been studied in only one randomized trial – the Alliance trial had a subgroup of patients with del17p (n=9). In addition single agent ibrutinib in first line 17p/TP53 CLL has been studied in two single arm studies; Ahn et al. (9) where results for a subgroup of 51 patients with TP53 were reported, Mato et al. (10) where results for a subgroup of 110 patients with 17p deletion were reported and the RESONATE 2 trial where a subgroup of 12 patients with TP53 was included (11).

6.2.1 Presentation of relevant studies

6.2.1.1 CLL14 trial

Please see section 5.1.2

6.2.1.2 Ahn et al. study

In 2018 Ahn et al. published the 5-year follow-up from a single arm, phase 2, open-label, single-center trial of ibrutinib monotherapy. The trial followed two cohorts labeled: Elderly cohort and a TP53 cohort. Eligibility criteria included active CLL or small lymphocytic lymphoma requiring therapy, and del(17p) by fluorescence in situ hybridization in 10% or more of nuclei or TP53 mutation for the TP53 cohort or age 65 years or older for the elderly cohort. The primary end point was response after 6 cycles of therapy. Secondary end points included safety, tolerability, overall survival (OS), PFS and best response.

6.2.1.3 Mato et al. study

Mato et al. published a multicenter, retrospective cohort trial of 391 CLL patients treated with ibrutinib in first line at 20 community and academic cancer centers in 2018. Investigators utilized chart review, electronic medical records, and related databases to obtain required information. Patients were categorized based on key inclusion criteria for the RESONATE-2 trial: younger than 65 years of age at time of starting ibrutinib (<65) vs. ≥65, and chromosome del(17p13) present vs. del (17p13) absent. In addition, patients were stratified based on the presence or absence of TP53 mutation in those where this testing was available, although this was not an exclusion in RESONATE-2 and not specifically tested or reported, and the presence or absence of somatic hypermutation of the B-cell receptor (IGHV mutated vs. unmutated).

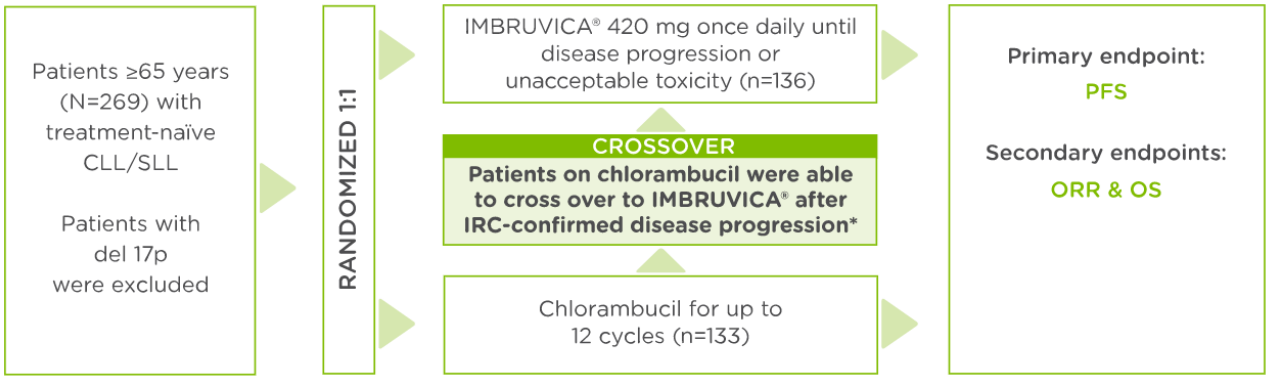
The primary end point was PFS stratified by age at ibrutinib initiation and del(17p13) status (both categorical variables). PFS was defined as time from ibrutinib initiation to progression or death from any cause as per the Kaplan Meier method. Three patients were otherwise censored at the time of last follow-up. Secondary

end points included ORR, complete remission (CR), OS, toxicity profile, reasons for discontinuation, and subsequent therapies following discontinuation. OS was defined as time from initiation of ibrutinib to death.

6.2.1.4 RESONATE 2 trial

The RESONATE 2 trial was a multicenter, open-label, randomized phase 3 trial. Patients were randomly assigned, in a 1:1 ratio, to receive either oral ibrutinib until disease progression or development of an unacceptable level of toxic effects or up to 12 cycles of chlorambucil with the objective 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. Though patients with del(17p) CLL were excluded from the study, 12 ibrutinib-treated patients had TP53 mutation and where reported on in the 5-year update to the study.

Figure 5.6: Trial design RESONATE 2 trial



6.2.2 Results per trial

Table 5.9: CLL14(1), del17p and TP53 subgroups, 24 months follow-up

Outcome	Subgroup	n	VenG	GClb	HR vs. GClb	CI_L	CI_H
PFS	All	216, 216	88.1%	64.1%	0.34	0.23	0.53
	del17p	17, 14	64.7%	23.1%	0.33	0.12	0.89
	TP53	24, 22	73.9%	32.7%	0.31	0.13	0.76
Grade 3 or higher AE	Safety population	212, 214	79%	77%	1.03	0.93	1.14

Note: data from the S3 table of the supplement to Fischer et. al. 2019(1), se table A2 Cll14

Table 5.10: Ahn et al. study (9) IBR by Elderly or TP53 cohorts, 60 months follow-up

Outcome	Subgroup	N	Result	CI_L	CI_H
PFS	TP53	35	74.4%	60.2%	92.1%
	Elderly	18	64.8%	43.9%	95.7%
OS	TP53	35	85.3%	74.2%	98.1%
	Elderly	18	71.6%	51.2%	100.0%
Grade 3 or higher AE	TP53 or Elderly (1st line and R/R)	86	28%		

Table 5.11: Mato et al. study (10) IBR del17p cohort, 12 months follow-up

Outcome	Subgroup	n	Result	HR vs. all	p-value
PFS	All	391	92.0%	1.9	0.04
PFS	del17p	110	87.0%		
OS	All	391	95.0%	3.9	0.001
OS	del17p	110	89.0%		

Table 5.12: Mato et al. study safety, 12 months follow-up

AE	Grade 3-4
Arthralgia	1.5%
Fatigue	1.8%
Rash	1.8%
Bruising	N/A
Diarrhea	0.3%
Infection (all sources combined)	3.8%
Bleeding	1.8%
Cytopenias, combined	2.5%
Atrial fibrillation	4.1%
Hypertension	0.5%
Peripheral edema	1.0%
Pneumonitis	1.0%
Renal dysfunction	1.3%
Peripheral neuropathy	0.5%
Liver dysfunction	0.3%
Congestive heart failure	0.3%

Table 5.13: RESONATE 2 trial IBR vs. Clb, TP53 subpopulation, 60- and 12-months follow-up

Type	Follow-up	Arm	n	Result
PFS	60 months	IBR, All	136	70%
PFS	60 months	IBR, TP53	12	56%
OS	60 months	IBR, All	136	83%
OS	60 months	IBR, TP53	12	NR
Grade 3 or higher AE	60 months	IBR, All	135	83%
Grade 3 or higher AE	12 months	IBR, All	135	58%

6.2.3 Comparative analysis

Table 5.14: Comparative analysis VenG vs. IBR, CLL patients with del17p/TP53 mutation

Outcome	**IBR (Mato, n=110, del17p)**	**IBR (Ahn n=34, TP53)**	**IBR (RESONATE 2, n=12, TP53)**	**VenG (n=17, 17p)**	**VenG (n=24, TP53)**
Follow up	12 md	60 md	60 md	24 md	24 md
PFS	87.0%	74.4%	56.0%	64.7%	73.9%
OS	89.0%	85.3%	NR	NR	NR
Grade 3 or higher AE*	NR	28%	12 md=58%, 60 md=83%	79%	79%

Note *For all patients in respective studies

The systematic literature review did not reveal any head to head studies or network meta-analyses for VenG vs. IBR in first line CLL patients with del17p/TP53 mutation. Therefore, the results for the subpopulations with del17p and TP53 mutation respectively from the CLL14 trial was compared naively to the results for the del17p subpopulation in the Mato et al. study and to the TP53 mutation subpopulation in the Ahn et al. study.

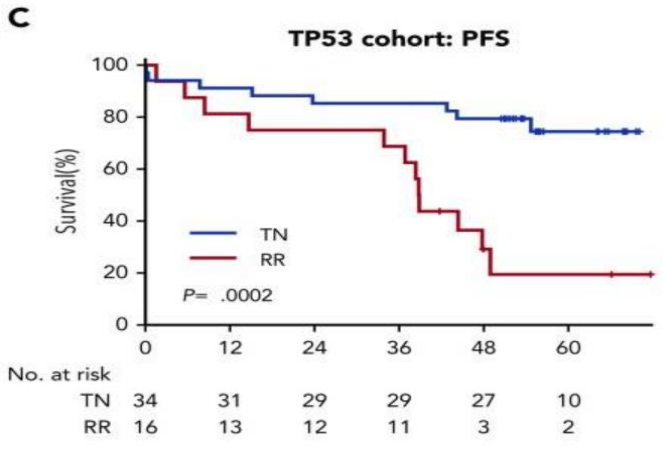
Follow-up time was substantially different with 60 months in the Ahn et al. study and RESONATE 2 trial, but 12 months in the Mato et al. study and this should be considered when interpreting results.

In addition, demographics were considerably different between the studies. Mato et al. recruited patients who would have been excluded in the RESONATE 2 study. The median age at start of IBR therapy in the Mato et al. study was 68 years (range 36–96) and 41% of patients were below 65 years. The Ahn et al. study TP53 subpopulation had a median age of 62 years (range 33-82) and 58% were below 65 years. The median age in the CLL14 VenG arm was 72 years (range 43-89) and 33.3% were 75 years or older. For reference Danish men aged 72 years have a 2.16 factor higher mortality compared to 62-year old men and the corresponding factor for women is 2.54 (2019 death panel, Statistics Denmark www.dst.dk). Age specific general mortality alone would account for more than 1% difference in PFS per year between cohorts that like in the Ahn et al. study and CLL14 trial has a 10-year difference in age of patients. The RESONATE 2 trial recruited patients at 65 years of age or older, and median age was 73 years with 70% of the patients being 70 years of age or older and thus similar to the patient population recruited in the CLL14 trial.

In the CLL14 trial PFS after 24 months follow-up was 64.7% and 73.9% for the del17p and TP53 mutation sup-populations, respectively. In the Mato et al. study the del17p cohort had a 12 months PFS of 87%. It is important to note the difference in follow-up time between the CLL14 trial (24 months) and the Mato et al. study (12 months) as well as the younger patient population in the Mato et al. study. In addition, PFS curves over time exhibits a pattern of a plateau where progression occurs more rapidly in the first years than later when the plateau has been reached (se figure 5.8), as it is well known from many trials in CLL and other cancers. In the Ahn et al. study at 60 months follow-up the PFS rate was 74.4%, compared to 73.9% after 24 months follow up in the CLL14 trial. It is again noted that there was a 10-year age difference in the patient populations between the Ahn et al. study and the CLL14 trial. PFS for the TP53 subpopulation in the RESONATE trial after 5 years was 56%.

Overall survival has not been published for the del17p and TP53 subpopulations in the CLL14 trial specifically, but the OS in the VenG arm was 88.9% at 36 months or 9% mortality over 3 years, equivalent to 3.1% annual mortality rate. The 1-year OS for the del17p cohort in the Mato et al. study was 89% or 11% mortality over one year. In the Ahn et al. study TP53 mutation subpopulation the 60-month OS was 85.3% or 14.7% mortality over 5 years, equivalent to 3.13% annual mortality rate in this group.

Figure 5.7: Ahn et al. PFS over time, 0-60 months, Treatment naïve (TN) and relapse/refractory (RR) CLL patients with TP53 mutation



Grade 3-4 adverse events were registered for 79% of all patients in the safety population of the CLL14 trial. Grade 3 or higher AEs were registered for 58% of patients in the first year of the RESONATE 2 trial, with additionally 39% being registered in the 2nd year of the trial. After continuous IBR therapy in the RESONATE trial for 5 years 83% of all patients in the IBR arm had experienced a grade 3 or higher AE. In the Ahn et al. study 29% of patients experienced a grade 3-4 AE and a similar proportion was observed in the Mato et al. study as summed up in table 5.12.

Conclusion

The clinically added value of venetoclax in combination with obinutuzumab in the subgroup of del17p/TP53 mutation has been assessed. Results for the subpopulations with del17p (n=17) and TP53 (n=24) mutation respectively from the CLL14 trial that were compared naively to the results for the del17p subpopulation in the Mato et al. study (n=110), the TP53 mutation subgroup of the RESONATE 2 trial (n=12) and the TP53 mutation subpopulation in the Ahn et al. study (n=34).

PFS and OS were found to be on par between VenG and IBR considering the vast difference in follow-up time and patient demographics between trials. Higher rates of grade 3-4 AEs were observed in the VenG arm of the CLL14 compared to the IBR treated patients in the Ahn et al. and Mato et al. studies, however 5 years continuous therapy with IBR in the RESONATE 2 trial meant that 83% of patients had experienced AEs of grade 3 or higher.

6.3 Other considerations

6.3.1 Safety considerations

Following the Medicines Council protocol for VenG in first line CLL, the SmPCs of venetoclax, chlorambucil, fludarabine, cyclophosphamide, bendamustine, rituximab, obinutuzumab and ibrutinib has been attached to this application.

Safety based on the CLL14 trial of venetoclax in combination with obinutuzumab vs. chlorambucil in combination with obinutuzumab

In the CLL14 trial of VenG vs. GClb grade 3-4 infections were recorded in 17.5% and 15% in the VenG and GClb arms, respectively. Neutropenia grade 3-4 were seen in 52.8% and 5.2% had febrile neutropenia in the VenG arm vs. in 48.1% and 3.7% respectively for GClb. Leukocytopenia grade 3-4 was present in 2.4% in the VenG arm vs. 4.7% in the GClb arm. Diarrhea grade 3-4 was recorded in 4.2% and 0.5% for VenG and GClb respectively. Tumor lysis syndrome was reported in 3 patients in the VenG arm and all cases occurred during treatment with obinutuzumab and before treatment with venetoclax was initiated. In comparison 5 patients had TLS in the chlorambucil–obinutuzumab group(1).

Fisher et al. concluded regarding safety*; "The safety profile of both treatments in this trial showed no new safety signals or higher incidences of known toxic effects. The toxic effects in the two treatment groups were similar in severity, and significant differences were detected only in the incidence of metabolism disorders and gastrointestinal disorders*" (1).

And

"In contrast to the findings in a previous trial, we did not find that venetoclax–obinutuzumab was associated with a higher frequency of tumor lysis syndrome. (15) This finding suggests that the safety measures implemented in this trial, such as prophylactic treatment after risk stratification, weekly dose ramp-up of venetoclax, and starting the treatment with obinutuzumab allowed for effective prevention of tumor lysis syndrome" (1).

And

"Recently, three trials reported that continuous ibrutinib therapy was superior to fixed-duration chemoimmunotherapy with regard to progression-free survival among young (16) and elderly (5, 17) patients with previously untreated CLL. In contrast, the current trial evaluated a fixed-duration, noncytotoxic regimen, venetoclax–obinutuzumab. The fixed duration venetoclax–obinutuzumab combination regimen warrants a comparison with continuous ibrutinib monotherapy (12, 13). Venetoclax–obinutuzumab proved to be effective and to have a low incidence of high-grade toxic effects in patients with relevant coexisting conditions, as shown by the completion of treatment by almost 80% of patients. In contrast, recent data indicate that up to 41% of patients discontinue treatment with ibrutinib after a median of 7 months; of these patients, approximately 60% discontinue because of toxic effects" (1, 10, 18-20).

Safety based on the CLL10 trial of fludarabine, cyclophosphamide and rituximab vs. bendamustine and rituximab

In the CLL10 trial of FCR vs. BR in first line CLL patients grade 3 infections were recorded for 35% and grade 4 for 3% of patients treated with FCR vs. 22% and 2% for BR patients. Neutropenia grade 3 was seen in 23% and for grade 4 in 62% of FCR patients vs. 24% and 35% for BR patients. Leukocytopenia grade 3 was present in 42% and for grade 4 Leukocytopenia in 39% of FCR patients vs. 37% and 11% for BR patients (6).

These results suggest that BR is associated with higher rates of infections and hematological toxic effects compared to GClb and VenG based on the CLL14 trial of elderly patients with high rates of co-morbidity. FCR is associated with considerably higher infections and hematological toxic effects in younger patients with less co-morbidity compared to GClb and VenG.

Safety outcomes for ibrutinib

Based on the 5-year follow-up from the RESONATE 2 trial 83% of IBR patients experienced a grade 3 or higher AE. Neutropenia was seen in 13% of patients with pneumonia, hypertension and anemia accounting for 12%, 8%, and 7% respectively (11). As ibrutinib is the most mature novel targeted therapy, its safety profile is also most mature. Ibrutinib therapy is associated with well-known risk of atrial fibrillation(AF) and bleeding, and AF has been reported in 6-16% of ibrutinib patients (21). Brown et al. published a pooled analysis of atrial fibrillation in 2017 based on 4 trials covering 1,505 chronic lymphocytic leukemia and mantle cell lymphoma patients. Brown et al. concluded*; "AF incidence was 6.5% [95% Confidence Interval (CI): 4.8, 8.5] for ibrutinib at 16.6-months versus 1.6% (95%CI: 0.8, 2.8) for comparator and 10.4% (95%CI: 8.4, 12.9) at the 36-month follow up; estimated cumulative incidence: 13.8% (95%CI: 11.2, 16.8). Ibrutinib treatment, prior history of AF and age 65 years or over were independent risk factors for AF. Multiple AF events were more common with ibrutinib (44.9%; comparator, 16.7%) among patients with AF. Most (85.7%) patients with AF did not discontinue ibrutinib and more than half received common anticoagulant/antiplatelet medications on study. Low-grade bleeds were more frequent with ibrutinib, but serious bleeds were uncommon (ibrutinib, 2.9%; comparator, 2.0%). Although the AF rate among older non-trial patients with comorbidities is likely underestimated by this dataset, these results suggest that AF among clinical trial patients is generally manageable without ibrutinib discontinuation"*(21). Toxicity in clinical practice was investigated by Mato et al. in 2018 based on data for 616 IBR treated patients with 17 months follow-up the authors concluded*; "In the largest reported series on ibrutinib- treated chronic lymphocytic leukemia patients, we show that 41% of patients discontinued ibrutinib. Intolerance as opposed to chronic lymphocytic leukemia progression was the most common reason for discontinuation. Outcomes remain excellent and were not affected by line of therapy or whether patients were treated on clinical studies or commercially. These data strongly argue in favor of finding strategies to minimize ibrutinib intolerance so that efficacy can be further maximized. Future clinical trials should consider time-limited therapy approaches, particularly in patients achieving a complete response, in order to minimize ibrutinib exposure"*(19).

6.3.2 Later line therapy

Mato et al. (2019) evaluated clinical responses in subsequent lines of therapy after venetoclax use in earlier lines of therapy. The multicenter study was conducted retrospectively across 31 centers in the US, EU, and South America in partnership with the UK CLL Forum and CORE registry. Patients included in the analysis could have discontinued venetoclax for any reason (22).

Of 326 patients, who discontinued venetoclax in the first line (4%) or R/R (96%) setting, 58% were treated with a subsequent therapy (of the remaining patients 61 were alive and untreated and 77 patients died prior to a subsequent therapy). Post venetoclax therapy focused on BTKi, PI3Ki, and cellular therapy (CAR-T or alloHSCT). Overall response rates to BTKi therapy were 84% (n=44) in BTKi naïve vs. 54% (n=30) in BTKi exposed patients (*P*<0.001, estimated median PFS of 32 months for BTKi naïve, 4 months for BTKi resistant, and NR in BTKi intolerant) (see table 5.16). ORR to PI3Ki was 47% in PI3Ki naïve patients following venetoclax therapy, though responses were not deemed durable (PFS of 5 months). 66% of patients responded to CAR-T therapy post venetoclax (n=18) with a median PFS of 9 months. Median PFS was not reached in 19 patients who underwent alloHSCT after venetoclax therapy.

Table 5.16: Response to subsequent therapy in CLL patients previously treated with venetoclax

Post-Ven Therapy	BTKi	BTKi	PI3Ki	CAR-T	Anti-CD20 ab
Agents	Ibrutinib Acalabrutinib	Ibrutinib Acalabrutinib Non-covalent BTKi	Idelalisib Duvelisib	Anti-CD19	Rituximab Obinutuzumab Ofatumumab
Pre-Ven exposure	BTKi Naïve	BTKi Exposed 33% BTK intolerant; 67% BTK resistant	PI3Ki Naïve BTKi Exposed	BTKi Exposed	
Patient number	44	30	17	18	19
ORR	83.9%	53.4%	46.9%	66.6%	32%
CR	9.0%	10.0%	5.9%	33.3%	16%
PR	56.8%	26.7%	35.2%	33.3%	16%
PR-L	18.1%	16.7%	5.8%	0%	0%
SD	11.6%	23.3%	23.7%	5.7%	32%
PD	4.5%	23.3%	29.4%	27.7%	36%
Median PFS (months)	32	12	5	9	2
DC rate	38%	38%	78%	NA	72%
Reasons for DC (% discontinuation)					
CLL progression	21.5%	66.6%	58.3%	--	61.9%
Adverse event	14.3%	8.4%	35%	--	15.3%
Transformation	14.3%	--	16.7%	--	7.5%
Planned cellular tx	14.3%	--	--	--	--
Second cancer	--	--	--	--	--
Unrelated death	7.1%	8.4%	--	--	--
Sudden death on tx	7.1%	8.4%	--	--	--
Pt preference	7.1%	--	--	--	--
Other	14.3%	--	--	--	15.3%

Source: Mato et al. 2019(22)

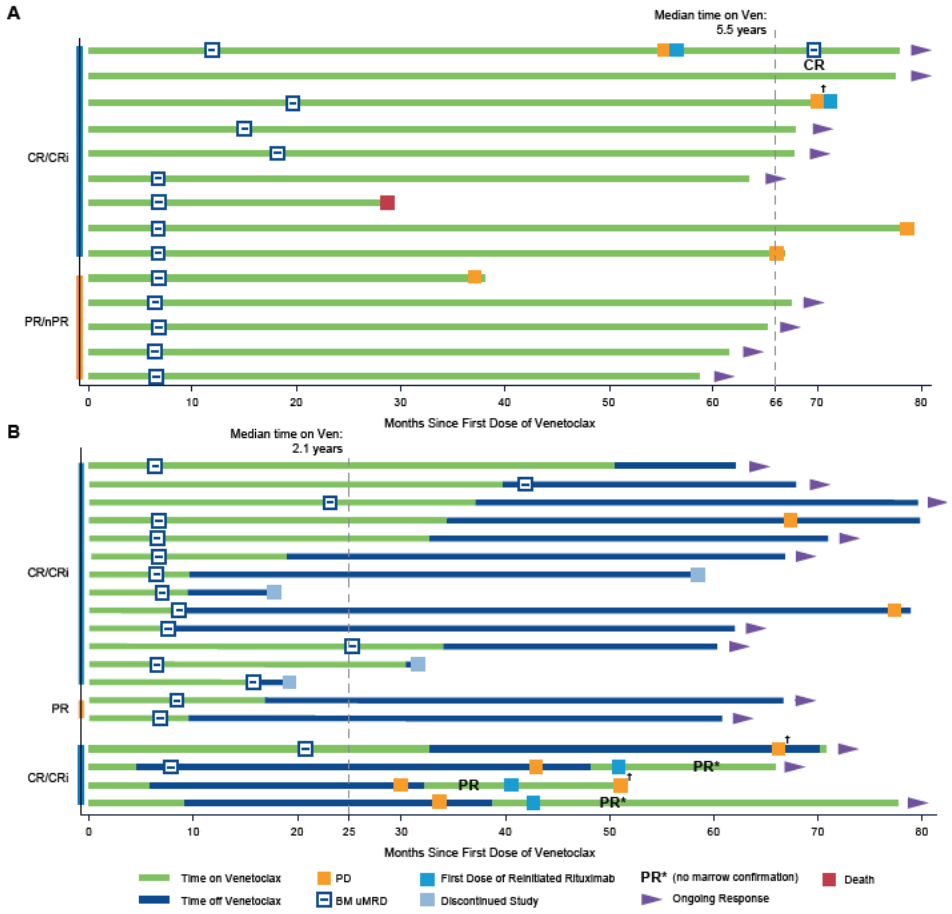
CR= complete remission; BTKi= Bruton's Tyrosine Kinase inhibitor; DC= discontinuation; ORR= overall response rate; PD= progression of disease; PI3Ki= phosphoinositide 3-kinase inhibitor; PR= partial remission, PR-L= partial remission with lymphocytosis, SD= stable disease, Tx= therapy, Ven= venetoclax

The 4-year follow-up to the Murano trial in 2nd line CLL patients Seymour et al. (2019) reported that 42 patients out of 64, who had progressed since completion of 2 year VenR therapy, had received anti-CLL therapy after progression. Of these, 28 received novel targeted therapies (BTKis, n=12; PI3Kis, n=1; BH3-only mimetics, n=14; IMPs, n=1) and the response rate to these treatments was 9/28 (32%). Fourteen of the VenR arm patients with PD subsequently received Ven or were re-treated with VenR, producing an overall

response rate of 2/14 (14%). It should be noted that 10/14 VenR patients (71%) were without an evaluable or available response (23).

Brander et al (2019) reported on a phase 1b study (NCT01682616 N=49) in patients with relapsed CLL who received VenR. Of the 18 patients who stopped Ven in deep response, the median time on Ven prior to cessation was 16 months (5 - 40) and median time off Ven was 40.3 months (1.1 - 70.0). Four patients had PD after stopping Ven at 25.5, 29.0, 33.3 and 42.0 months off Ven and have been re-treated with VenR or Ven-mono, and 3 have been re-evaluated for response. All achieved at least PR (2 without BM assessment so unevaluable for CR), with 2 having ongoing response. One patient with PR but residual BM infiltrate had subsequent PD 18 months later. The fourth patient was recently re-treated with Ven-mono; response is pending. Two additional patients had PD off Ven and had not been re-treated as of the data cutoff; both remain on study.

Figure 5.8: Disease Response and Treatment Status in Deep Responders Who Continued Ven (A) or Received Limited-Duration Ven (B)



BM, bone marrow; CR, complete remission; CRi, CR with incomplete hematologic recovery; MRD, minimal residual disease; nPR, nodular PR; PD, progressive disease; PR, partial remission; Ven, venetoclax; uMRD, undetectable MRD.
†Patients were either allowed to retreat due to MRD increase or were not included in the clinical database at the time of the data cutoff.

Source: Brander et al. 2019 (24)

The authors concluded*: "Re-treatment of patients with Ven or VenR re-exposure has resulted in response in some patients. In addition to long PFS, which represents time to first PD or death, patients who cease Ven in deep response have the opportunity for further disease control through reintroduction of Ven"* (24).

6.3.3 The effect of IGHV-mutation status

Progression free survival after 24 months follow-up in the CLL14 trial by IGHV-mutation status was 89.4% and 90.3% respectively for VenG patients with unmutated and mutated IGHV status, compared to 51.0% and 85.6% respectively for GClb. HR for VenG vs. GClb was 0.22 [CI 0.12-0.36] for IGHV unmutated and HR = 0.64 [CI 0.26-1.46] for IGHV mutated patients (1).

Median PFS by IGHV-mutation status after 60 months follow up in the CLL10 trial was 42.7 months (CI 36.2–55.2) and not reached in the FCR arm for unmutated and mutated, respectively. In the BR arm median PFS was 33.6 months (CI 30.3–38.4) and 55.4 months (CI not evaluable) for IGHV-unmutated and -mutated respectively(6).

Progression free survival after 60 months follow-up in the RESONATE 2 trial by IGHV-mutation status was 67% and 81% respectively for IBR patients with unmutated and mutated IGHV status, compared to 6% and 24% respectively for Clb treated patients. HR for IBR vs. Clb was HR = 0.105 [CI 0.058-0.190] for IGHV unmutated and HR = 0.153 [CI 0.067-0.349] for IGHV mutated patients. For reference the PFS rate after 24 months in the RESONATE 2 was 89% and 90% respectively for IBR patients with unmutated and mutated IGHV status, compared to 22% and 43% respectively for Clb treated patients (13).

In conclusion the prognosis regarding PFS for IGHV unmutated 1st line CLL patients treated with chemoimmunotherapy is very low compared to patients with IGHV mutation. For chlorambucil monotherapy median PFS is as low as 9 months. The two targeted therapies have little and non-significant difference in PFS rates depending on IGHV mutational status.

For the other included outcomes, OS, EORTC QLQ-C30 and Grade 3-4 AEs no published subgroup analysis was found.

6.3.4 Obinutuzumab vs. rituximab combination therapy

In the CLL11 trial, chlorambucil in combination with rituximab (Clb+R) was trialed against chlorambucil in combination with obinutuzumab (GClb) and vs. chlorambucil alone. The conclusion from this trial was that the addition of a CD20 antibody to chlorambucil improved outcome for patients, and that obinutuzumab was superior to rituximab when combined with chlorambucil. In the primary analysis conducted in 2013 a significant benefit on PFS was observed with GClb vs. Clb+R where the median PFS was 26.7 months for GClb and 15.2 months for Clb+R (HR, 0.39; 95% CI, 0.31-0.49; P <0.001). In addition, a higher proportion of complete responses was found in the GClb arm compared to Clb+R (20.7% vs. 7%) (25). In the extension with a median follow-up time of 59.4 months, the median PFS for GClb was 28.9 months vs. 15.7 months for Clb+R (HR, 0.49; 95% CI, 0.41-0.58; P <0.0001). The median OS for was not reached for GClb vs. 73.1 months for Clb+R (HR, 0.76; 95% CI, 0.60-0.97; P <0.0245). These findings led the authors to conclude; *"These findings support the use of G-Clb as first-line treatment for CLL patients with comorbidities, and suggest G as the preferred anti-CD20 antibody in future combination regimens for CLL"* (26). Very little data exist on the effects of venetoclax in combination with rituximab in elderly first line CLL patients and it is therefore uncertain if results of using Ven+R would be similar to results for VenG, however this combination is presently being studied in the CLL13 trial.

6.4 Discussion

Fixed duration, target therapy in CLL

Fixed-treatment duration (FTD) regimens have historically been the standard of care in CLL treatment. However, while allowing for treatment-free intervals for the patient, the termination of these treatments have been a necessity ruled by the tolerability and severe toxicity of historical FTD-treatment options. Data from the CLL14 and MURANO trials demonstrate, for the first time, how a non-chemo based CLL treatment can be safely terminated after a fixed number of cycles with maintained treatment effect (1, 27). Even if a proportion of patients are ultimately destined to develop PD by iwCLL criteria and require subsequent treatment a number of years off drug would have quality-of-life, toxicity, and societal economic benefits. This would also minimize clonal selection pressure relevant with other targeted therapies (19, 28, 29).

Minimal Residual Disease in CLL

In the CLL14 trial MRD was considered negative if the result was less than 1 CLL cell in 10,000 leukocytes (MRD value <0.0001 OR 10-4). In the intention-to-treat population higher percentages of patients in the venetoclax–obinutuzumab group than in the chlorambucil–obinutuzumab group were negative for minimal residual disease in peripheral blood (75.5% vs. 35.2%, P<0.001) and in bone marrow (56.9% vs. 17.1%, P<0.001) three months after treatment completion (1).

MRD is an established surrogate outcome in chemoimmunotherapy. Multiple studies have demonstrated that achieving MRD below 10^{-4} CLL cells in the blood and/or bone marrow (i.e. undetectable MRD or MRD negativity) correspond to longer PFS(30-32).

In December 2015, the European Medicines Agency (EMA) has included undetectable MRD as an intermediate endpoint in a revision document to appendix 4 to the guideline on the evaluation of anticancer medicinal products in humans. EMA states that *"undetectable MRD in patients with CLL in clinical complete remission (= MRD response rate) after induction therapy may be used as an intermediate endpoint for licensure in randomised well controlled studies designed to show superiority in terms of PFS"* (33).

The CLL guidelines of the British Society for Haematology (BSH) present MRD as a factor which affects prognosis based on studies reporting longer remission, improved OS, and PFS for patients with undetectable MRD (34). Furthermore, the updated International Workshop on CLL (iwCLL) guidelines in March 2018, underscores the importance of MRD in CLL: According to the iwCLL update; "*Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome*"(35).

Therapy-free intervals affects development of toxicity

As CLL is still an incurable disease, life-long treatment is the reality for the vast majority of CLL patients where treatment is needed. Treatment affects quality of life in many ways and in particular in terms of therapy-related toxicity (36-38). Although newer, targeted treatments have a milder toxicity-profile than CIT, they require continuous treatment until progression. Long-term safety follow-up of ibrutinib treated patients demonstrate that tolerability is a major reason for discontinuation and is higher in clinical practice compared

to clinical trial settings (19, 39). Thus, treatment-free intervals are an effective way of alleviating the burden of treatment-emergent toxicity and thus increase quality of life. An added benefit of FTD therapy, such as venetoclax plus obinutuzumab, is to protect the efficacy of subsequent treatments since prolonged therapy also exerts strong selective pressure, which can promote the eventual outgrowth of resistant subclones (29). As with any cancer cell, CLL cells have high intrinsic ability to adapt and find ways to survive. The most fit clones are being selected under the pressure of treatment and may result in the domination of more aggressive or treatment-resistant clones which in turn can reduce the efficacy of subsequent treatments needed (29).

A unique combination

Current treatment options in first line treatment of CLL entail either fixed-duration CIT or continuous indefinite targeted therapy. Venetoclax plus obinutuzumab is the first and only approved first line fixed-duration targeted therapy with a favorable safety profile and substantial clinical benefit. Venetoclax plus obinutuzumab have achieved among the highest rates of MRD negative responses observed so far in a randomized prospective trial in first line CLL. Even if a proportion of patients are ultimately destined to develop PD by iwCLL criteria and require treatment a number of years off drug would have quality-of-life, toxicity, and societal economic benefit.

7 Conclusion

The Medicines Council outlined 2 clinical questions to be answered in this application for venetoclax in combination with obinutuzumab to be recommended for standard of care in Danish hospitals:

Clinical question 1: What is the clinically added value of venetoclax in combination with obinutuzumab compared to chemotherapy in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation?

> Overall a clear benefit on PFS for VenG was shown vs. chemoimmunotherapy in combination with CD20-antibody for patients with previously untreated chronic lymphocytic leukemia without deletion17p/p53-mutation. This benefit is realized with similar rates of serious adverse events compared to BR and GClb and at lower rates of serious adverse events compared to FCR.

Clinical question 2: What is the clinically added value of venetoclax in combination with obinutuzumab compared to ibrutinib for patients with previously untreated chronic lymphocytic leukemia with deletion17p/p53-mutation?

> PFS and OS were found to be on par between VenG and IBR considering the vast difference in follow up time and patient demographics between trials. Higher rates of grade 3-4 AEs were observed in the VenG arm of the CLL14 compared to the IBR treated patients in the Ahn et al. and Mato et al. studies, however 5 year continuous therapy with IBR in the RESONATE 2 trial meant that 83% of patients had experienced AEs of grade 3 or higher.

In conclusion, VenG represents an important additional therapy option for patients with previously untreated chronic lymphocytic leukemia that compared to present standard therapy for patients without deletion17p/p53-mutation offers superior efficacy at similar or better safety and includes the option to stop therapy for patients with deletion17p/p53-mutation at similar efficacy and safety.

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8 Appendices

8.1 Literature search

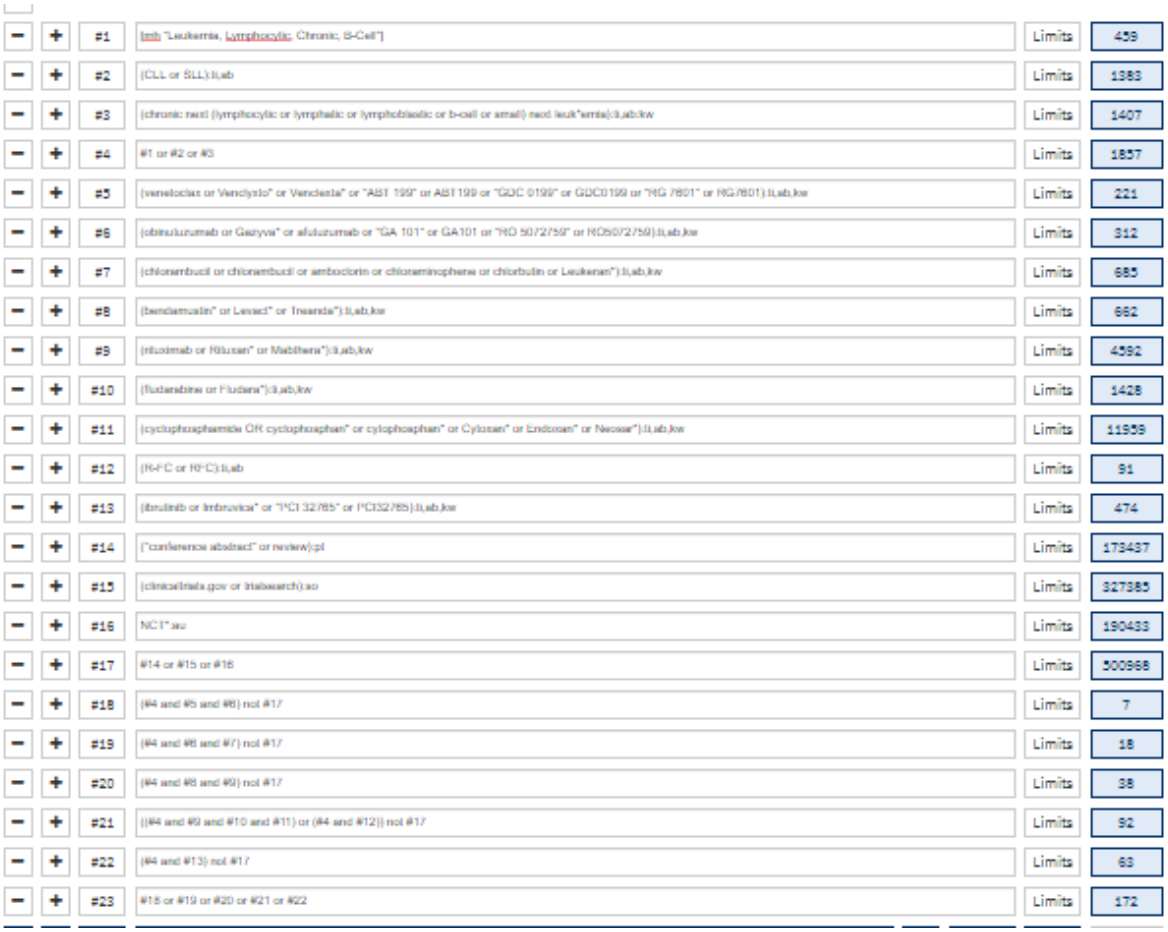
Table A1: Inclusion and exclusion criteria

Search strategy: MEDLINE (Pubmed) and CENTRAL (Cochrane Library) Date: 15-06, 2020

PubMed Results

Search	Query	Items found
1	Leukemia, Lymphocytic, Chronic, B-Cell[mh]	16100
2	CLL[tiab]	14652
3	chronic lymphocytic leukemia[tiab] OR chronic lymphocytic leukaemia[tiab]	19917
4	chronic lymphatic leukemia[tiab] OR chronic lymphatic leukaemia[tiab]	1381
5	chronic lymphoblastic leukemia[tiab] OR chronic lymphoblastic leukaemia[tiab]	78
6	chronic b-cell leukemia[tiab] OR chronic b-cell leukaemia[tiab]	80
7	SLL[tiab] OR small lymphocytic lymphoma[tiab] OR small cell lymphoma[tiab]	1905
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	27440
9	venetoclax[nm] OR venetoclax[tiab] or Venclyxto*[tiab] or Venclexta*[tiab]	962
10	obinutuzumab[nm] OR obinutuzumab[tiab] or Gazyva*[tiab] or afutuzumab[tiab]	502
11	Chlorambucil[mh] OR chlorambucil[tiab] OR amboclorin*[tiab] OR chloraminophene[tiab] OR chlorbutin*[tiab] OR Leukeran*[tiab]	5154
12	Bendamustine Hydrochloride[mh] OR bendamustin*[tiab] OR Levact*[tiab] OR Treanda*[tiab]	1313
13	Rituximab[mh] OR rituximab[tiab] OR Rituxan*[tiab] OR Mabthera*[tiab]	23562
14	fludarabine[nm] OR fludarabine[tiab] OR Fludara*[tiab]	5881
15	Cyclophosphamide[mh] OR cyclophosphamide[tiab] OR cyclophosphan*[tiab] OR cytophosphan*[tiab] OR Cytoxan*[tiab] OR Endoxan*[tiab] OR Neosar*[tiab]	74308
16	R-FC[tiab] OR RFC[tiab]	2051
17	PCI 32765[nm] OR ibrutinib[tiab] OR Imbruvica*[tiab] OR PCI-32765[tiab] OR PCI32765[tiab]	2125
18	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	6309620
19	(#8 AND #9 AND #10) NOT #18	24
20	(#8 AND #10 AND #11) NOT #18	46
21	(#8 AND #12 AND #13) NOT #18	138
22	(#8 AND #13 AND #14 AND #15) NOT #18	230
23	(#8 AND #16) NOT #18	26
24	(#8 AND #17) NOT #18	525
25	#19 OR #20 OR #21 OR #22 OR #23 OR #24	861

Results from the Cochrane Central Trials

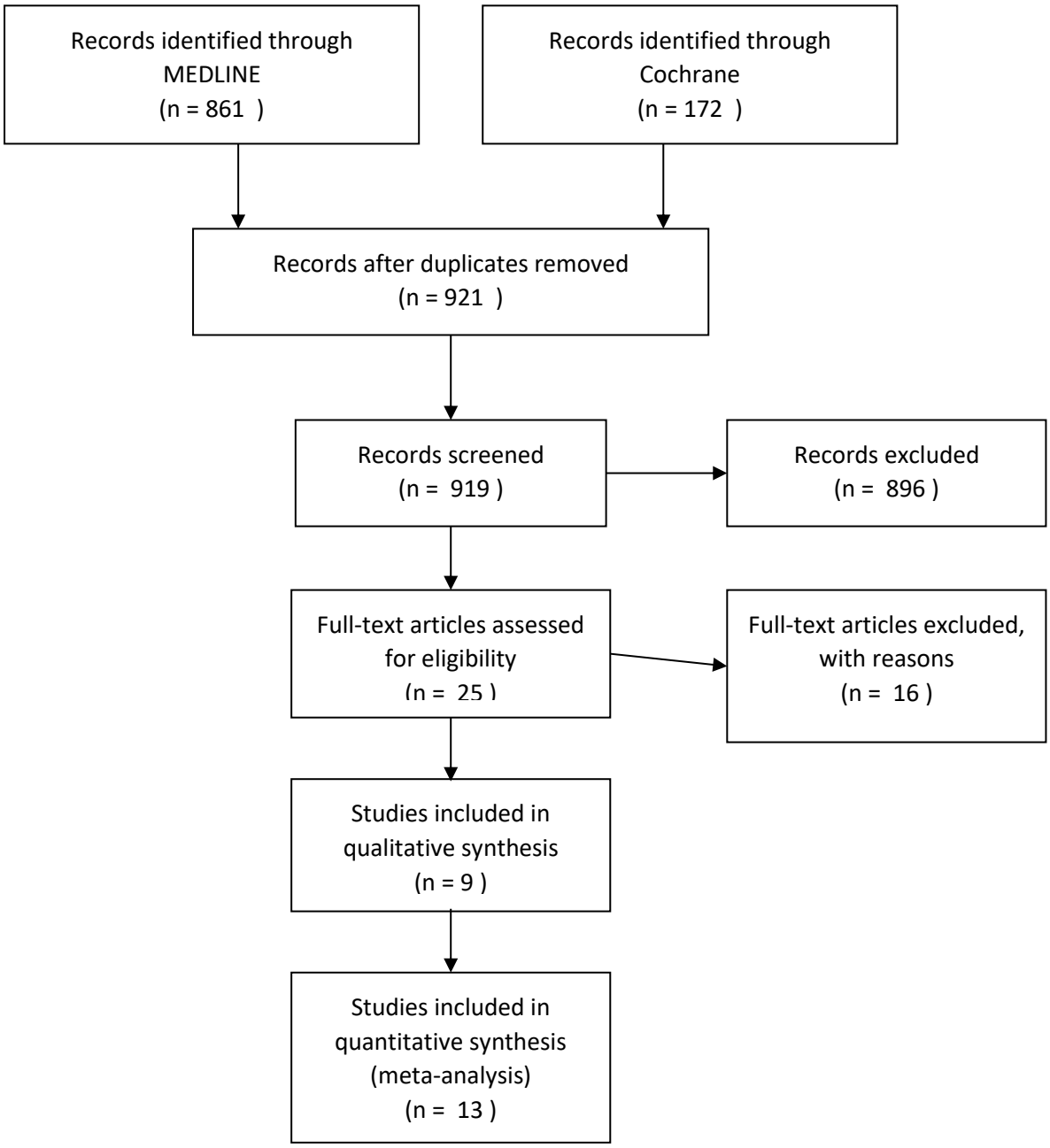


#1	[mh "Leukemia, Lymphocytic, Chronic, B-Cell"]	Limits	459
#2	(CLL or SLL):ti,ab	Limits	1383
#3	(chronic next (lymphocytic or lymphatic or lymphoblastic or b-cell or small) next leuk*emia):ti,ab,kw	Limits	1407
#4	#1 or #2 or #3	Limits	1857
#5	(venetoclax or Venclyxto* or Venclexta* or "ABT 199" or ABT199 or "GDC 0199" or GDC0199 or "RG 7601" or RG7601):ti,ab,kw	Limits	221
#6	(obinutuzumab or Gazyva* or afutuzumab or "GA 101" or GA101 or "RO 5072759" or RO5072759):ti,ab,kw	Limits	312
#7	(chlorambucil or chlorambucil or amboclorin or chlorameniphene or chlorbutin or Leukeran*):ti,ab,kw	Limits	685
#8	(bendamustin* or Levact* or Treanda*):ti,ab,kw	Limits	662
#9	(rituximab or Rituxan* or Mabthera*):ti,ab,kw	Limits	4592
#10	(fludarabine or Fludara*):ti,ab,kw	Limits	1428
#11	(cyclophosphamide OR cyclophosphan* or cytophosphan* or Cytoxan* or Endoxan* or Neosar*):ti,ab,kw	Limits	11559
#12	(R-FC or RFC):ti,ab	Limits	91
#13	(ibrutinib or Imbruvica* or "PCI 32765" or PCI32765):ti,ab,kw	Limits	474
#14	("conference abstract" or review):pt	Limits	173437
#15	(clinicaltrials.gov or trialsearch):so	Limits	327385
#16	NCT*:au	Limits	190433
#17	#14 or #15 or #16	Limits	500968
#18	(#4 and #5 and #6) not #17	Limits	7
#19	(#4 and #6 and #7) not #17	Limits	18
#20	(#4 and #8 and #9) not #17	Limits	38
#21	((#4 and #9 and #10 and #11) or (#4 and #12)) not #17	Limits	92
#22	(#4 and #13) not #17	Limits	63
#23	#15 or #19 or #20 or #21 or #22	Limits	172

8.1.1 List of excluded articles

Publication	Reason for exclusion
Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia, Burger J.A et al., Blood - Volume 133, 2018	Wrong intervention and comparator.
A phase 3 trial comparing the efficacy and safety of acalabrutinib in combination with venetoclax with or without obinutuzumab, compared with investigator's choice of chemoimmunotherapy in patients with previously untreated chronic lymphocytic leukemia (CLL) without del(17p) or tp53 mutation, Brown J.R et al., Blood, 2019	Wrong comparator. Already have head to head study with VEN-G.
Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL, Brown J.R., Leukemia, 2018	Wrong population. Patients are R/R
Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions, Goede V. et al., N Engl J Med, 2014	We have Head to head study with OBI+Chlorambucil vs. Ven-G
Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial, Hallek M et al,. Lancet, 2010	Comparator not of interest
Frontline treatment with the combination obinutuzumab +/- chlorambucil for chronic lymphocytic leukemia outside clinical trials: Results of a multinational, multicenter study by ERIC and the Israeli CLL study group, Herishanu Y. et al., Am journal of hematology, 2020	Wrong study design. Not randomized trial.
Ibrutinib and Venetoclax for First-Line Treatment of CLL, Jain N. et al., N Engl J med, 2019	Wrong study design. This is a phase 2 study. Wrong intervention
Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial, Knauf W.U et al., Br J Haemtology, 2012	Wrong interventions.
Ofatumumab-based chemoimmunotherapy is effective and well tolerated in patients with previously untreated chronic lymphocytic leukemia (CLL), Shanafelt T et al., Cancer, 2013	Wrong study design. Not a randomized trial.
Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial, Moreno C et al., Lancet oncology, 2018	Wrong intervention.
Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIIb GREEN study, LeBlond V et al., Haematologica, 2018	Already have head to head study for Obinutuzumab + Chlorambucil vs VEN-G.
Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax, Tausch E et al., Blood, 2020	Not original data. Data already included in included study.
Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia, Tam C.S et al., Blood, 2008	Wrong study design. Not a comparative trial.
Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab, Byrd J.C, Blood, 2019	Wrong population. Patients are R/R

8.1.2 PRISMA Flow Diagram



8.1.3 Included references

For direct and narrative assessments for Q1a, Q1b, Q1c and Q2

1st author and reference	Title	Trial arms		Clinical Question
Fischer et al.(1)	Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions	VenG GClb		All
Shanafelt et al.(4)	Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia	IBR+R FCR		Q1c
Woyach et al.(5)	Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL	IBR IBR+R BR		Q1b
Eichhorst et al.(6)	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	FCR BR		Q1b and Q1c
Kutsch et al.(7)	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)	FCR BR		Q1b and Q1c
Michallet et al.(8)	Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study	BR Clb+R		Q1b
Burger et al.(11)	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	IBR Clb		Q2
Burger et al.(12)	Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia	IBR Clb		Q2
Barr et al.(13)	Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2	IBR Clb		Q2
Hand searched references for direct and narrative assessments for Q1a, Q1b, Q1c and Q2				
Mato et al.(10)	Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial	IBR		Q2
Ahn et al.(9)	Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study	IBR		Q2
Al-Sawaf et al.(3)	Rapid Improvement of Patient-Reported Outcomes with Venetoclax Plus Obinutuzumab in Patients with Previously Untreated CLL and Coexisting Conditions: A Prospective Analysis from the CLL14 Trial.	VenG GClb		All
Al-Sawaf et al.(2)	Fixed-Duration Venetoclax-Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia: Follow-Up of Efficacy and Safety Results from the Multicenter, Open-Label, Randomized, Phase 3 CLL14 Trial	VenG GClb		All

Note: IBR=Ibrutinib, R=Rituximab, B=bendamustine, G= obinutuzumab, VEN=venetoclax, IDA=idealisib, FC= fludarabine-cyclophosphamide, Clb= chlorambucil

Note: all other references are included as hand searches for sections 5.3 “Other considerations”, and 5.4 “Discussion”.

8.1.4 Main characteristics of included studies

Table 2A: CLL14 trial

Trial name	*CLL14*
NCT number	*NCT02242942*
Objective	*To evaluate whether venetoclax–obinutuzumab is superior to chlorambucil–obinutuzumab in previously untreated patients with CLL and coexisting conditions.*
Publications – title, author, journal, year	*Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions, K. Fischer, O. Al-Sawaf, J. Bahlo et al. N Engl J Med, 2019*
Trial type and design	*Open-label, randomized trial. The trial was conducted in 21 countries at 196 sites. The initial safety and side-effect profile of venetoclax–obinutuzumab had been established during a safety run-in phase. Patients were randomly assigned in a 1:1 ratio. The treatment duration in both groups consisted of 12 cycles lasting 28 days each; no crossover was allowed.*
Follow-up time	*Median follow-up: 28.1 months*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Documented previously untreated CLL according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria* • *CLL requiring treatment according to IWCLL criteria* • *Total Cumulative Illness Rating Scale (CIRS score) greater than (>) 6* • *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* • *Adequate liver function* • *Life expectancy > 6 months* • *Agreement to use highly effective contraceptive methods per protocol* *Exclusion Criteria:* • *Transformation of CLL to aggressive Non-Hodgkin's lymphoma (Richter's transformation or pro-lymphocytic leukemia)* • *Known central nervous system involvement* • *Participants with a history of confirmed progressive multifocal leukoencephalopathy (PML)* • *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* • *Participants with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia* • *Inadequate renal function* • *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* • *Use of investigational agents or concurrent anti-cancer treatment within the last 4 weeks of registration* • *Participants with active bacterial, viral, or fungal infection requiring systemic treatment within the last two months prior to registration* • *History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products*

	• *Hypersensitivity to chlorambucil, obinutuzumab, or venetoclax or to any of the excipients* • *Pregnant women and nursing mothers* • *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)* • *Participants with known infection with human immunodeficiency virus (HIV) or human T-cell leukemia virus-1 (HTLV-1)* • *Requires the use of warfarin, marcumar, or phenprocoumon* • *Received agents known to be strong and moderate Cytochrome P450 3A inhibitors or inducers within 7 days prior to the first dose of trial drug* •
Intervention	*Venetoclax – Obinutuzumab:* *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. 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 – Obinutuzumab:* *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. 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.*

Baseline characteristics	**Table 1. Selected Patient Demographic and Disease Characteristics at Baseline (Intention-to-Treat Population).***

Characteristic	Venetoclax–Obinutuzumab (N=216)	Chlorambucil–Obinutuzumab (N=216)
Age ≥75 yr — no. (%)	72 (33.3)	78 (36.1)
Male sex — no. (%)	146 (67.6)	143 (66.2)
Binet stage — no. (%)†		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumor lysis syndrome risk category — no. (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6 — no. (%)‡	186 (86.1)	177 (81.9)
Calculated creatinine clearance <70 ml/min — no./total no. (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup — no./total no. (%)§		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)
No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status — no./total no. (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status — no./total no. (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)

* There were no significant differences between the groups at baseline. Percentages may not total 100 because of rounding.
† Binet stages indicate the degree of advancement of chronic lymphocytic leukemia and are based on organ and lymph-node involvement, hemoglobin levels, and platelet counts.
‡ Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems.
§ Cytogenetic subgroups were determined according to the hierarchical model of Döhner at al.[18]

Primary and secondary endpoints	*Primary Endpoint* *Investigator-assessed PFS* *Secondary endpoint:* *IRC-Assessed PFS* *MRD* *Overall response* *Complete Response* *Overall survival* *Duration of response* *Time to new antileukemic treatment* *Event-free survival.*
Method of analysis	*All efficacy end points were analyzed in the intention-to-treat population. For patients who were alive and had not had disease progression or relapse, the data for progression-free survival were censored on the date of the last disease assessment. In the analysis of minimal residual disease negativity and response to treatment, patients without a sample or response assessment that*

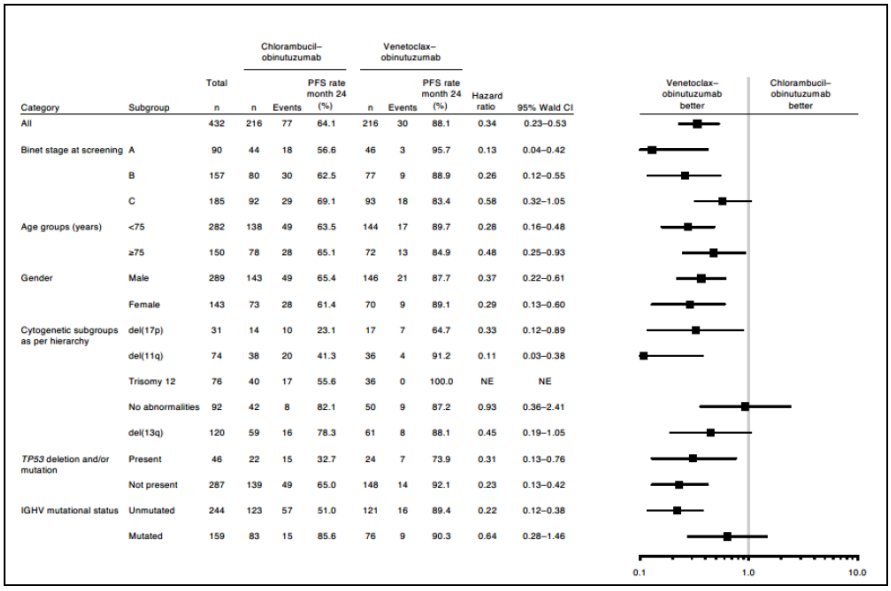
	could be evaluated were counted as not being negative for residual disease or as not having a response, respectively. To control for multiplicity, the above-listed key secondary efficacy end points were analyzed with a prespecified hierarchical testing procedure after a fallback procedure
Subgroup analyses	**Figure S3. Investigator-assessed progression-free survival by prognostic subgroup.**  Hierarchical order of cytogenetic subgroups according to Döhner et al. NEJM 2000

Table 2A: E1912 trial

Trial name	*A Randomized Phase III Trial of Ibrutinib (PCI-32765)-Based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients With Chronic Lymphocytic Leukemia (CLL)*
NCT number	*NCT02048813*
Objective	*To evaluate the efficacy and safety of treatment with ibrutinib in combination with six cycles of rituximab, as compared with fludarabine–cyclophosphamide–rituximab, in previously untreated patients with CLL who were 70 years of age or younger.*
Publications – title, author, journal, year	*Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia, T D Shanafelt, X V Wang, N E Kay et al., N Engl J Med, 2019*
Trial type and design	*open- label, randomized, phase 3 trial. The trial was monitored twice annually by a standing data and safety monitoring board that included persons from both within and outside ECOG–ACRIN.* *eligible participants underwent randomization, which was stratified according to the age of the patients (<60 years vs. 60 to 70 years), ECOG performance-status score (0 or 1 vs. ≥2; scores are on a 5-point scale, with higher numbers indicating greater disability), Rai stage (0 to II [low or intermediate risk] vs. III or IV [high risk]), and the presence or absence of chromosome 11q22.3 deletion on fluorescence in situ hybridization analysis. Patients were randomly assigned in a 2:1 ratio to receive either ibrutinib–rituximab or chemoimmunotherapy with fludarabine–cyclo-phosphamide–rituximab.*
Follow-up time	*median follow-up of 33.6 months*
Population (inclusion and exclusion criteria)	*Eligible participants were previously untreated patients with CLL or the small lymphocytic lymphoma (SLL) subtype of CLL who were 70 years of age or younger and who would be appropriate candidates for treatment according to the Inter- national Workshop on Chronic Lymphocytic Leukemia (IWCLL) Working Group criteria.* *Patients with chromosome 17p13 deletion were excluded from the trial be- cause of the poor response of CLL in these patients to fludarabine–cyclophosphamide–rituximab therapy.* *See appendix or Clinicaltrials.gov for a comprehensive list of inclusion- and exclusion criteria*
Intervention	*Patients were randomly assigned in a 2:1 ratio to receive either ibrutinib–rituximab or chemoimmunotherapy with fludarabine–cyclophosphamide–rituximab.* *Patients who were randomly assigned to the ibrutinib–rituximab group received ibrutinib (at a dose of 420 mg per day until disease progression or an unacceptable level of side effects occurred) and rituximab (50 mg per square meter of body-surface area on day 1 of cycle 2; 325 mg per square meter on day 2 of cycle 2; and 500 mg per square meter on day 1 of cycles 3 through 7); each cycle was 28 days. Patients who were randomly assigned to the chemoimmunotherapy group received six cycles of intravenous fludarabine (at a dose of 25 mg per square meter) and cyclophosphamide (250 mg per square meter) on days 1 through 3 with rituximab (50 mg per square meter on day 1 of cycle 1; 325 mg per square meter on day 2 of cycle 1; and 500 mg per square meter on day 1 of cycles 2 through 6) every 28 days.*

Baseline characteristics	**Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).***

Characteristic	Ibrutinib–Rituximab Group (N=354)	Chemoimmunotherapy Group (N=175)	Total (N=529)
Age			
Mean	56.7±7.5	56.7±7.2	56.7±7.4
≥60 yr — no. (%)	145 (41.0)	70 (40.0)	215 (40.6)
Sex — no. (%)			
Female	118 (33.3)	55 (31.4)	173 (32.7)
Male	236 (66.7)	120 (68.6)	356 (67.3)
Rai stage — no. (%)			
Low risk, 0	11 (3.1)	9 (5.1)	20 (3.8)
Intermediate risk, I or II	187 (52.8)	94 (53.7)	281 (53.1)
High risk, III or IV	156 (44.1)	72 (41.1)	228 (43.1)
ECOG performance-status score — no. (%)†			
0	226 (63.8)	109 (62.3)	335 (63.3)
1	119 (33.6)	63 (36.0)	182 (34.4)
2	9 (2.5)	3 (1.7)	12 (2.3)
$Beta_2$ microglobulin — mg/liter			
Mean	4.0±2.1	4.0±1.9	4.0±2.0
Median	3.6	3.4	3.6
Interquartile range	2.6–4.6	2.7–4.8	2.6–4.7
Dohner classification — no. (%)			
Chromosome 17p13 deletion‡	2 (0.6)	0	2 (0.4)
Chromosome 11q22.3 deletion	78 (22.0)	39 (22.3)	117 (22.1)
Trisomy 12	70 (19.8)	27 (15.4)	97 (18.3)
Normal	69 (19.5)	37 (21.1)	106 (20.0)
Chromosome 13q deletion	121 (34.2)	58 (33.1)	179 (33.8)
Other	14 (4.0)	14 (8.0)	28 (5.3)
IGHV mutation status — no./total no. (%)§			
Mutated	70/280 (25.0)	44/115 (38.3)	114/395 (28.9)
Unmutated	210/280 (75.0)	71/115 (61.7)	281/395 (71.1)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive ibrutinib–rituximab or chemoimmunotherapy with fludarabine–cyclophosphamide–rituximab. Data include patients with small lymphocytic lymphoma (SLL); overall, 11.4% of the patients (11.7% in the ibrutinib–rituximab group and 10.9% in the chemoimmunotherapy group) had the SLL subtype of chronic lymphocytic lymphoma. Percentages may not total 100 because of rounding. More detailed information regarding the characteristics of the patients at baseline is provided in Table S1 in the Supplementary Appendix.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability.

‡ Two patients with chromosome 17p13 deletion were enrolled and randomly assigned to the ibrutinib–rituximab group but were later found to be ineligible on the basis of fluorescence in situ hybridization analysis.

§ Immunoglobulin heavy-chain variable region (*IGHV*) mutation status was tested in the 436 patients (82.4% of the overall population) who agreed to participate in the correlative study component of the trial and who provided a research sample. Among the 436 patients who underwent testing, *IGHV* status could be determined in 395.

Primary and secondary endpoints	*Primary endpoint:* *Progression-free survival* *Secondary endpoints:* *Overall survival* *Safety* *MRD in Bone marrow and peripheral blood*

Method of analysis	*Stratified log-rank tests were used to com- pare time-to-event distributions. Hazard ratios were estimated with the use of stratified Cox proportional-hazards models. The frequency of response and the incidence of adverse events were compared between the two groups with the use of Fisher's exact test. Descriptive statistics were used to summarize the characteristics of the patients. Time-to-event distributions were estimated with the use of the Kaplan–Meier method. The primary analysis was conducted in the intention-to-treat population, which included all the patients who had undergone randomization, regardless of eligibility or treatment status. P values are two-sided, and 95% confidence intervals are presented.*
Subgroup analyses	*A subgroup of patients with 11q22.3 deletions were analysed.* *Patients were also stratified according to IGHV mutation status.*

Table 2A: Alliance trial

Trial name	*A Randomized Phase III Trial of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients (>/= 65 Years of Age) With Chronic Lymphocytic Leukemia (CLL)*
NCT number	*NCT01886872*
Objective	*among older patients with untreated CLL, is treatment with ibrutinib or ibrutinib plus rituximab superior to treatment with bendamustine plus rituximab?* *does the addition of rituximab to single-agent ibrutinib lead to increased efficacy?*
Publications – title, author, journal, year	*Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL, Jennifer A. Woyach, Amy S. Ruppert, Nyla A. Heerema et al., N Engl J Med 2018*
Trial type and design	*Phase 3 randomized trial. Before each patient underwent randomization, a blood sample was submitted for central testing for methylation at the promoter region of the ZAP70 gene. The following risk factors for CLL were used for stratification: ZAP70 methylation status on central testing (unmethylated [<20%] vs. methylated [≥20%]), risk category according to modified Rai stage (intermediate vs. high), and status with regard to del(17p13.1) or del(11q22.3) on local FISH analysis (absent vs. present).* *Patients were randomly assigned, in a 1:1:1 ratio. Patients in the bendamustine plus-rituximab group who had disease progression could cross over to receive ibrutinib within 1 year after progression*
Follow-up time	*Median follow up of 38 months.*
Population (inclusion and exclusion criteria)	*Eligible patients were 65 years of age or older and had untreated CLL for which treatment was indicated, as defined by International Workshop on CLL (IWCLL) criteria. The IWCLL criteria and a full list of eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.*
Intervention	*Patients were randomly assigned, in a 1:1:1 ratio to receive:* • *Bendamustine plus rituximab. 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). At the investigator's discretion, the cycle 1 dose of bendamustine could be 70 mg per square meter.* • *Ibrutinib. Ibrutinib was administered at a dose of 420 mg daily until the patient had unacceptable toxic effects or disease progression.* • *Ibrutinib plus rituximab. Ibrutinib-plusrituximab therapy consisted of ibrutinib (administered as described previously and given before rituximab on days when they were administered together) plus rituximab (administered at a dose of 375 mg per square meter weekly for 4 weeks starting on day 1 of cycle 2 and then on day 1 of cycles 3 through 6).*

Baseline characteristics	**Table 1. Characteristics of the Patients at Baseline.**

Characteristic	All Patients (N = 547)	Bendamustine+ Rituximab (N = 183)	Ibrutinib (N = 182)	Ibrutinib+ Rituximab (N = 182)	P Value*
Age — yr					0.53
Median	71	70	71	71	
Range	65–89	65–86	65–89	65–86	
Male sex — no. (%)	367 (67)	119 (65)	123 (68)	125 (69)	0.75
High-risk disease according to modified Rai stage — no. (%)	296 (54)	99 (54)	99 (54)	98 (54)	0.99
ECOG performance-status score — no. (%)†					0.06
0	271 (50)	98 (54)	87 (48)	86 (47)	
1	259 (47)	75 (41)	90 (49)	94 (52)	
2	17 (3)	10 (5)	5 (3)	2 (1)	
FISH analysis according to hierarchical classification of Döhner et al. — no./total no. (%)‡					0.99
Del(17p13.1)	34/542 (6)	14/181 (8)	9/181 (5)	11/180 (6)	
Del(11q22.3)	105/542 (19)	33/181 (18)	35/181 (19)	37/180 (21)	
Trisomy 12	118/542 (22)	40/181 (22)	40/181 (22)	38/180 (21)	
None	90/542 (17)	29/181 (16)	32/181 (18)	29/180 (16)	
Del(13q14.3)	195/542 (36)	65/181 (36)	65/181 (36)	65/180 (36)	
Mutated *TP53* — no./total no. (%)	51/510 (10)	16/174 (9)	15/168 (9)	20/168 (12)	0.60
Complex karyotype — no./total no. (%)§	143/499 (29)	44/166 (27)	39/165 (24)	60/168 (36)	0.04
Unmethylated *ZAP70* — no./total no. (%)	287/546 (53)	95/182 (52)	96/182 (53)	96/182 (53)	0.99
Unmutated IgVH gene — no./total no. (%)¶	218/360 (61)	71/123 (58)	77/122 (63)	70/115 (61)	0.69

* 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.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
‡ Central fluorescence in situ hybridization (FISH) analysis was performed with the use of the hierarchical classification method established by Döhner et al.[20]
§ Complex karyotype was defined as the presence of at least three unrelated abnormalities as assessed by central review.
¶ IgVH denotes immunoglobulin variable heavy chain.

Primary and secondary endpoints	*Primary endpoint:* *PFS* *Secondary endpoints:* *OS* *Overall response* *Complete response* *MRD in Bone marrow* *Safety*
Method of analysis	*For the comparisons of ibrutinib and ibrutinib plus rituximab with bendamustine plus rituximab, three interim efficacy and futility analyses were planned. For the comparison of ibrutinib plus rituximab with ibrutinib, two interim efficacy and futility analyses were planned. In May 2018, the Alliance Data and Safety Monitoring Board made the decision to release these data on the basis of the results of the protocol-specified second interim analysis for the comparisons of the two ibrutinib-containing regimens with bendamustine plus rituximab and the protocol-specified first interim analysis for the comparison of ibrutinib plus rituximab with ibrutinib.* *In accordance with the protocol, the primary analysis of progression-free survival included all patients who underwent randomization except those who, after randomization, were determined to have not met the eligibility criteria at screening. P values for the primary analysis are one-sided. Secondary analyses included all patients who underwent randomization, regardless of eligibility. P values for all secondary analyses are two-sided. Prespecified and exploratory subgroup analyses were also performed.*
Subgroup analyses	*See "Trial type and design" for risk factors, by which subgroups were defined.*

Table 2A: CLL10 trial

Trial name	*CLL10*
NCT number	*NCT00769522*
Objective	*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.* *To compare the incidence of major side effects (e.g., myelosuppression) associated with these regimens in these patients.* *To compare the rate of infections and secondary neoplasias in patients treated with these regimens.*
Publications – title, author, journal, year	*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, B. Eichhorst, A. Fink, J. Bahlo et al. The Lancet Oncology, July 2016* *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), Kutsch, N.; Bahlo, J.; Robrecht, S. et al. Hemasphere, Feb 2020*
Trial type and design	*A randomised, open-label, phase 3, non-inferiority trial in previously untreated fit patients aged 33–81 years with advanced chronic lymphocytic leukaemia who required treatment according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and had an Eastern Cooperative Oncology Group (ECOG) status of 0–2. Treatment-naive patients diagnosed with chronic lymphocytic leukaemia were registered for central screening, which was done by the German CLL Trial Group central trial office (Cologne, Germany) and included immunophenotyping for confirmation of the diagnosis, fluorescence-in-situ hybridisation (FISH) to determine del(17p) status, evaluation of the comorbidity burden, and renal function. After the central screening process, eligible patients were randomly assigned (1:1) using a computer-generated randomisation list. In patients whose blood counts had not recovered adequately within 28 days or still showed signs of an active infection, the next treatment was postponed and further cycles of therapy continued with a 25% dose reduction. After two dose reductions to a total dose reduction of 50%, treatment was stopped in case there was any further treatment delay due to adverse events.*
Follow-up time	*Median follow-up for FCR: 37.4 months* *Median follow-up for BR: 36.0 months* *Median follow-up in extension: 58.2 months*
Population (inclusion and exclusion criteria)	*Overall Criteria according to Clinicaltrials.gov¨* *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 ≥ 1 of the following:* • *B-symptoms (e.g., night sweats, weight loss ≥ 10% within the past 6 months, fevers > 38°C or 100.4°F for ≥ 2 weeks without evidence of infection) or constitutional symptoms (e.g., fatigue)* o *Progressive lymphocytosis, defined as peripheral lymphocyte count > 5 x 10^9/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 ≥ 6 months* • *Total bilirubin ≤ 2 times upper limit of normal (ULN) (unless directly attributable to CLL)* • *AST and ALT ≤ 2 times ULN (unless directly attributable to CLL)* • *Creatinine clearance ≥ 70 mL/min (creatinine clearance is to be calculated only in patients with serum creatinine ≥ 1.1 mg/dL)* • *Not pregnant or nursing* • *Negative pregnancy test* • *Fertile patients must use effective contraception during and for ≥ 6 months after completion of trial 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 trial or the required follow-up* • *PRIOR CONCURRENT THERAPY:* • *No prior CLL specific-chemotherapy, radiotherapy, and/or immunotherapy* ○ *Prednisolone administered immediately prior to initiation of trial therapy allowed for very high lymphocyte counts* • *No concurrent participation in another clinical trial*
Intervention	*Six 28-day cycles of intravenous fludarabine (25 mg/m2 per day) and cyclophosphamide (250 mg/m2 per day) on the first 3 days of each cycle.* *Or:* *Treatment with bendamustine (90 mg/m2 per day) was given intravenously on the first 2 days of each of the six 28-day cycles.* *Rituximab 375 mg/m2 was given to both groups intravenously on day 0 of cycle 1 and subsequently during the next five cycles rituximab 500 mg/m2 was given on day 1 of each cycle*

Baseline characteristics		**Fludarabine, cyclophosphamide, and rituximab (n=282)**	**Bendamustine and rituximab (n=279)**
	Age (years)	62·1 (55·0–67·0)	61·0 (54·0–69·0)
	>65 years	86 (30%)	108 (39%)
	>70 years	28 (10%)	51 (18%)
	Sex		
	Male	201 (71%)	207 (74%)
	Female	81 (29%)	72 (26%)
	Median time from diagnosis to study entry (months)	21·6 (4·0–52·6)	24·6 (6·2–50·1)
	Binet stage		
	A	63 (22%)	62 (22%)
	B	105 (37%)	107 (38%)
	C	114 (41%)	110 (39%)
	Rai stage		
	0	7/221 (3%)	11/224 (5%)
	I	29/221 (13%)	32/224 (14%)
	II	86/221 (39%)	84/224 (37%)
	III	44/221 (20%)	34/224 (15%)
	IV	55/221 (25%)	65/224 (29%)
	ECOG performance status		
	0	180/281 (64%)	177/276 (64%)
	1	95/281 (34%)	98/276 (36%)
	2	6/281 (2%)	1/276 (<1%)
	B-symptoms present	116 (41%)	113 (41%)
	Median CIRS	2·0 (1·0–3·0)	2·0 (0–3·0)
	Total CIRS ≤3	240 (85%)	234 (84%)
	Number of involved CIRS categories ≤1	163 (58%)	149 (53%)
	Median creatinine clearance (mL/min)	87·0 (71·7–106·9)	86·4 (72·6–101·6)
	Thymidine kinase >10 U/L	198/272 (73%)	196/270 (73%)
	β_2-microglobulin >3·5 mg/L	84/272 (31%)	103/270 (38%)
	Cytogenetic abnormalities		
	del(11q)	68 (24%)	63 (23%)
	12q+	33 (12%)	32 (11%)
	del(13q)	155 (55%)	147 (53%)
	Unmutated *IGHV*	152/275 (55%)	183/270 (68%)

Primary and secondary endpoints	*Primary Endpoint:* *PFS* *Secondary endpoints:* *Overall survival* *Overall response* *MRD Status* *Safety* *Event-free survival* *Duration of remission* *EORTC-C30*
Method of analysis	*All statistical tests were two-sided and a p value of less than 0·05 was considered significant. Adjustments for multiple comparisons were not considered for analysing secondary endpoints and exploratory subgroup analyses.* *All analyses were done in the intention-to-treat population. The results of minimal residual disease status at follow-up were calculated based on the intention-to-treat population and based on those patients for whom a sample at follow-up month 12 and month 18 was available.* *Safety analyses were restricted to patients from the intention-to-treat population who received at least one dose of one component of the trial treatment.* *Time-to-event endpoints including 95% CIs were estimated according to the Kaplan-Meier method and survival curves were compared using two-sided non-stratified 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.*
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-rank tests and the calculation of HRs including 95% CIs. Additionally, the interaction with trial treatment was explored for each factor; a term for the interaction between the factor and the trial treatment was included in a Cox regression model. Post hoc matched paired analysis was done for IGHV mutation status and progression-free survival.*

Table 2A: RESONATE-2 trial

Trial name	*Resonate-2*
NCT number	*NCT01722487*
Objective	*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.*
Publications – title, author, journal, year	*Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia, J. A. Burger, A Tedeschi, P. M. Barr et al., N Engl J Med 2015* *Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2, P.M. Barr, T. Robak, A. Tedeschi et al. Haematologica, 2018* *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 trial, J.A. Burger, P.M. Barr, T. Robak et al. Nature Leukemia, 2019*
Trial type and design	*multicenter, open-label, randomized phase 3 trial. Patients were enrolled in the United States, countries in Europe, and other countries. 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, if there was not an unacceptable level of toxic effects) until disease progression, determination of a lack of efficacy (defined as a lack of complete or partial response, as determined by the investigator), or development of an unacceptable level of toxic effects. Patients with disease progression that was confirmed by the independent review committee were enrolled in a separate extension trial (PCYC-1116-CA) for follow-up and second-line treatment according to the investigator's choice. Treatment in the PCYC-1116-CA trial could include ibrutinib for chlorambucil-treated patients who had disease that progressed according to the independent review committee and who had an indication for treatment according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria.*
Follow-up time	*Median follow-up 18.4 months in primary trial* *Median follow-up 29 months in 1st extension* *Median Follow-up 60 months in 2nd extension*

Population (inclusion and exclusion criteria)	*Inclusion Criteria:*
	• *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:*
	  ○ *creatinine clearance < 70 mL/min using the Cockcroft-Gault equation*
	  ○ *platelet count < 100,000/µL or hemoglobin < 10 g/dL*
	  ○ *clinically apparent autoimmune cytopenia (autoimmune hemolytic anemia or immune thrombocytopenia)*
	  ○ *ECOG performance score = 1 or 2*
	• *Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008)*
	• *Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment:*

	○ *Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia Massive, progressive, or symptomatic splenomegaly* ○ *Massive nodes or progressive or symptomatic lymphadenopathy* ○ *Progressive lymphocytosis* ○ *Autoimmune hemolytic anemia and/or immune thrombocytopenia that is poorly responsive to corticosteroids or standard therapy* ○ *Constitutional symptoms* • *Measurable nodal disease by computed tomography (CT)* • *ECOG performance status of 0-2* • *Life expectancy > 4 months from randomization* • *Adequate hematologic function, defined as absolute neutrophil count (ANC) ≥ 1,000/µL (independent of growth factor support for at least 7 days prior to screening) and platelet count ≥ 50,000/µL (independent of transfusion and growth factor support for at least 7 days prior to screening)* • *Adequate hepatic function, defined as serum aspartate transaminase (AST) and alanine transaminase (ALT) < 2.5 x upper limit of normal (ULN), and total bilirubin ≤ 1.5 x ULN* • *Adequate renal function, defined as estimated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation* • *Willingness to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers trial drug for the entire trial* • *Willingness of male patients, if sexually active with a female of childbearing potential, to use an effective barrier method of contraception during the trial and for 3 months following the last dose of trial drug* • *Ability to provide written informed consent and to understand and comply with the requirements of the trial* *Exclusion Criteria:* • *Known involvement of the central nervous system by lymphoma or leukemia* • *History or current evidence of Richter's transformation or prolymphocytic leukemia* • *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* • *Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura* • *Any previous treatment (chemotherapy, radiotherapy, and/or monoclonal antibodies) intended specifically to treat CLL/SLL* • *Received any immunotherapy, vaccine, or investigational drug within 4 weeks prior to randomization* • *Corticosteroid use within 1 week prior to first dose of trial 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.* • *Major surgery within 4 weeks prior to randomization* • *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*

	• *Currently active, clinically significant cardiovascular disease or a history of myocardial infarction within 6 months prior to randomization* • *Inability to swallow capsules or tablets, or disease significantly affecting gastrointestinal function* • *Uncontrolled active systemic fungal, bacterial, viral, or other infection or requirement for intravenous (IV) antibiotics* • *Known history of infection with human immunodeficiency virus (HIV)* • *Serologic status reflecting active hepatitis B or C infection* • *History of stroke or intracranial hemorrhage within 6 months prior to enrollment* • *Current life-threatening illness, medical condition, or organ-system dysfunction that could compromise patient safety or put the trial at risk* • *Requirement for anticoagulation with warfarin* • *Requirement for treatment with a strong CYP3A4/5 and/or CYP2D6 inhibitor*
Intervention	*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* *Or:* *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*

Baseline characteristics	**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*** **Characteristic** / **Ibrutinib (N=136)** / **Chlorambucil (N=133)** Age Median (range) — yr: 73 (65–89) / 72 (65–90) ≥70 yr — no. (%): 96 (71) / 93 (70) Male sex — no. (%): 88 (65) / 81 (61) ECOG performance-status score — no. (%)† 0: 60 (44) / 54 (41) 1: 65 (48) / 67 (50) 2: 11 (8) / 12 (9) Diagnosis — no. (%) Chronic lymphocytic leukemia: 123 (90) / 126 (95) Small lymphocytic lymphoma: 13 (10) / 7 (5) Rai stage III or IV — no. (%): 60 (44) / 62 (47) Bulky disease ≥5 cm — no. (%)‡: 54 (40) / 40 (30) Chromosome 11q22.3 deletion — no. (%): 29 (21) / 25 (19) Unmutated *IGHV* — no. (%): 58 (43) / 60 (45) Cytopenia at baseline — no. (%) Any cytopenia: 72 (53) / 73 (55) Hemoglobin ≤11 g/dl: 51 (38) / 55 (41) Platelet count ≤100,000/mm^3: 35 (26) / 28 (21) Absolute neutrophil count ≤1500/mm^3: 10 (7) / 7 (5) Lactate dehydrogenase Median (range) — U/liter: 199 (52–1188) / 195 (110–1347) >250 U/liter — no. (%): 39 (29) / 31 (23) β_2-Microglobulin Median (range) — mg/liter: 5 (2–20) / 5 (1–39) >3.5 mg/liter — no. (%): 85 (62) / 89 (67) Cumulative Illness Rating Scale score >6 — no. (%)§: 42 (31) / 44 (33) Creatinine clearance <60 ml/min — no. (%): 60 (44) / 67 (50) Median time from initial diagnosis (range) — mo: 31 (1–241) / 31 (1–294) * There were no significant between-group differences at baseline. † Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing disability. ‡ Measurement was based on the longest diameter of the largest lymph node at screening, according to assessment by an independent review committee. § Scores on the Cumulative Illness Rating Scale range from 0 to 52, with higher scores indicating worse health status.
Primary and secondary endpoints	*Primary endpoints:* *IRCC-assessed PFS* *Secondary endpoints:* *Overall survival* *Overall response* *Rate of sustained improvement in hematologic variables* *Safety* *FACIT*
Method of analysis	*Patients were monitored every 2 weeks during cycles 1 and 2, every 4 weeks during cycles 3 through 12, and then every 8 weeks starting at cycle 13. The assessment of response was conducted every 4 cycles until disease progression or until trial closure.*

	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.
Subgroup analyses	*Patients with disease progression that was confirmed by the independent review committee were enrolled in a separate extension trial (PCYC-1116-CA) for follow-up and second-line treatment according to the investigator's choice.*

Table 2A: MABLE trial

Trial name	MABLE
NCT number	NCT01056510
Objective	This trial aims to investigate the efficacy and safety of R-B and R-Clb in fludarabine-ineligible CLL patients.
Publications – title, author, journal, year	Anne-Sophie Michallet, Melih Aktan, Wolfgang Hiddemann, Osman Ilhan, Peter Johansson, Kamel Laribi, Balkis Meddeb, Carol Moreno, João Raposo, Anna Schuh, Ali Ünal, Tom Widenius, Alf Bernhardt, Kerstin Kellershohn, Dimitri Messeri, Stuart Osborne and Véronique Leblond Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE trial. Hematologica. 2018
Trial type and design	Patients received Rituximab and either Bendamustine or Chlorambucil as written below. After treatment completion, patients were followed every three months for one year, then every six months until data cut-off. Treatment was discontinued if the patient had progressive disease.
Follow-up time	Median follow-up was 23.5 months (R-B) and 23.3 months (R-Clb).
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Signed and dated written informed consent • Aged 18 years or older • Tumor cell phenotype consistent with chronic lymphocytic leukemia (CLL) by cell surface marker analyses: CD5+, CD19+, and CD23+ (as per local confirmation of diagnosis) • Patients with active CLL (Binet B and C) who required therapy per criteria according to the National Cancer Institute criteria 2008. Symptomatic Binet A patients and/or patients with low/intermediate Rai stages could also be included • Eastern Cooperative Oncology Group performance status ≤2 • Ineligible for treatment with fludarabine • A negative serum pregnancy test within 1 week before the first cycle of treatment must have been available for women who were 2 years after the onset of menopause and not sterilized surgically Exclusion Criteria: • From amendment No. 2, patients treated second-line (2L) were not allowed to be entered in the trial • 2. Any other concomitant anti-cancer therapy. Corticosteroids were allowed if they were given for reasons other than CLL and the dose was ≤20 mg of prednisolone equivalent per day • Patients with transformation to aggressive B-cell malignancy • Known or suspected central nervous system involvement of CLL • Any other malignancy within 5 years prior to enrollment except curatively treated carcinoma in situ of the cervix, squamous cell carcinoma of the skin, or basal cell skin cancer. Cervical carcinoma stage 1B or less, breast cancer in situ, or localized prostate cancer stage T1c or less was to be considered, provided that the patient was treated with curative intent and was relapse-free for at least 2 years prior to enrollment • Major surgery (excluding lymph node biopsy) within 28 days prior to first cycle of trial treatment • Chronic or ongoing active infectious disease requiring systemic treatment • History of clinically significant cerebrovascular disease with residual sequelae • Patients who had known HIV, active hepatitis B virus, or hepatitis C virus infection • Serious underlying medical conditions that could have impaired the ability of the patient to participate in the trial • Inadequate renal and hepatic function per the following laboratory values: creatinine clearance <30 mL/min, total bilirubin >1.5 × upper limit of normal (ULN), alanine aminotransferase and/or aspartate aminotransferase >2.5 × ULN, and alkaline phosphatase >2.5 × ULN • Inadequate hematologic function, defined as absolute neutrophil count <1.0 × 109/l (1000/µl), platelet count <50 × 109 /l (50,000/µl), or hemoglobin <9.0 g/dl, unless due to involvement of bone marrow (BM) by CLL • Known or suspected hypersensitivity to components of investigational product • Life expectancy less than 6 months • Patients known or suspected of not being able to comply with a trial protocol

Trial name	MABLE
NCT number	NCT01056510
	• Pregnant or breast-feeding patients • Male and female patients with reproductive potential who were not willing to use an effective method of contraception during the trial and 1 year after last dose of trial medication • Patients unable to provide informed consent • Patients with severe autoimmune cytopenia as assessed by the physician (Coombs positive patients without clinical signs of autoimmune hemolytic anemia were eligible for trial entry) • Patients who had received any investigational treatment within 30 days before screening • Medical condition requiring chronic use of oral corticosteroids in doses >20 mg of prednisolone equivalent/day. Inhaled or topical steroids were permitted
Intervention	Patients received rituximab (intravenous 375 mg/m2 Day [D] 1, Cycle [C] 1 and 500 mg/m2 D1, C2-C6) plus B (intravenous 90 mg/m2 [1L] or 70 mg/m2 [2L] D1 and D2, C1-C6) or Clb (oral 10 mg/m2 D1-D7, C1-C6) every four weeks for six cycles. R-Clb patients without CR after C6 received Clb monotherapy for ≤6 additional cycles or until CR

Trial name	MABLE
NCT number	NCT01056510
Baseline characteristics	Table 1. Demographic characteristics for patients receiving 1L therapy.

	1L therapy	
	R-B (N=121)	R-Clb (N=120)
Age (years)		
Median (min, max)	72 (41, 86)	72 (38, 91)
≥65 years, n (%)	86 (71)	90 (75)
≥75 years, n (%)	45 (37)	44 (37)
Sex		
Male, n (%)	70 (58)	80 (67)
Female, n (%)	51 (42)	40 (33)
Active medical conditions, n		
Median (min, max)	3 (0, 12)	3 (0, 18)
Binet stage, n (%)		
A	6 (5)	8 (7)
B	73 (60)	66 (55)
C	37 (31)	43 (36)
Missing	5 (4)	3 (3)
ECOG PS, n (%)		
0	62 (51)	59 (49)
1	50 (41)	51 (43)
2	9 (7)	8 (7)
Missing	0	2 (2)
Body surface area, m^2		
Mean (SD)	1.811 (0.2382)	1.807 (0.1706)
Min, max	1.30, 2.48	1.41, 2.29
IGVH mutational status, n (%)		
Mutated	41 (34)	46 (38)
Unmutated	73 (60)	59 (49)
Other[a]	3 (3)	8 (7)
Not tested	4 (3)	7 (6)
11q status, n (%)		
Heterozygous deletion	24 (20)	19 (16)
Normal	96 (79)	99 (83)
Not tested	1 (1)	2 (2)
17p status, n (%)		
Heterozygous deletion	10 (8)	3 (3)
Normal	110 (91)	114 (95)
Not tested	1 (1)	3 (3)
11q/17p deletion, n (%)		
Heterozygous deletion	32 (26)	22 (18)
Normal	88 (73)	96 (80)
Not tested	1 (1)	2 (2)
13q deletion (S25 or S319 probe)[b], n (%)		
Homozygous deletion	3 (3)	1 (1)
Two clones (one homozygote, one heterozygote)	15 (12)	6 (5)
Heterozygous deletion	42 (35)	5 (4)
Normal	61 (50)	60 (50)
Not tested	1 (1)	2 (2)
Trisomy 12, n (%)		
Trisomy	30 (25)	19 (16)
Normal	90 (74)	99 (83)
Not tested	1 (1)	2 (2)

[a]Other includes polyclonal and oligoclonal. [b]Deletion status according to at least one probe (NB, in the R-B group, one patient with two clones by S319 probe and heterozygous deletion by S25 probe is counted twice). 1L: first-line; ECOG PS: Eastern Cooperative Oncology Group performance status; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil; SD: standard deviation.

Primary and secondary endpoints	Primary endpoints: • Complete response rate in 1st line treated patients after cycle 6 Secondary endpoints: • Complete response rate in 2nd line treated patients after cycle 6 • Progression-free survival • Overall survival • Time to next leukemic treatment • Minimal residual disease • Safety Response was assessed after C3 and C6 as per iwCLL 2008 Guidelines. Response was also assessed in the R-Clb arm at C12, with treatment being discontinued for patients showing evidence of CR during C7-C12

Trial name	MABLE
NCT number	NCT01056510
Method of analysis	Efficacy analyses were conducted on the intent-to-treat (ITT) population. 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 twosided continuity-corrected $\chi 2$ test assessed between-arm differences in overall response rates (ORRs) and molecular responses. PFS and OS were summarized by Kaplan–Meier estimates and compared via 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
Subgroup analyses	Groups were divided according to treatment line, and endpoints were evaluated in 1st and 2nd line treatment.

Tabel 2A: Mato et al study

Trial name	-
NCT number	-
Objective	*To study the impact of age and/or del(17p13) status on outcomes and toxicities of ibrutinib in patients with previously untreated CLL*
Publications – title, author, journal, year	*Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial, Anthony R. Mato Lindsey E. Roeker John N. Allan et al. AM Journal of Hematology, 2017*
Study type and design	*A multicenter, retrospective cohort study of CLL patients treated with ibrutinib in the front-line setting at 20 community and academic cancer center, focusing on subsets that would not have been eligible for the RESONATE-2 trial*
Follow-up time	*Median follow-up: 13.8 months*
Population (inclusion and exclusion criteria)	*Criteria for inclusion would be that patients were excluded from the Resonate-2 trial.*
Intervention	*Median starting dose of ibrutinib was 420 mg daily for the entire cohort*
Baseline characteristics	

Characteristic		Number with available data	RESONATE-2 publishe
Median age at CLL diagnosis	63 years (32-96)	391	Not available / reporte
Median age at ibrutinib start	68 years (36–96)	391	73 (65-89)
Median time from CLL diagnosis to ibrutinib start	31 months	388	31 months
Age < 65 years at ibrutinib start	41%	391	0%
Male sex	62.4%	391	65%
Caucasian	92.4%	384	Not available
Rai stage 3-4	49.1%	383	44%
del(17p13) present	29.8%	369	0%
del(11q) present	17.1%	367	21%
TP53 mutation	20.1%	219	Not available/reported
del(17p13) and *TP53* mutation (for patients who had both FISH and NGS testing)	16.0%	219	Not available/reported
Complex karyotype (≥ 3)	23.6%	279	Not available/reported
IGHV unmutated	67.4%	221	43%
β2 microglobulin above ULN	74.9%	146	62%
Elevated lactate dehydrogenase	49%	344	29%
Median follow up	13.8 months (1-76)	383	18.4 months

Primary and secondary endpoints	*The primary endpoint was PFS stratified by age at ibrutinib initiation and del(17p13) status (both categorical variables). PFS was defined as time from ibrutinib initiation to progression or death from any cause as per the Kaplan Meier method. Patients were otherwise censored at the time of last follow-up. Secondary endpoints included ORR, complete remission (CR), OS, toxicity profile, reasons for discontinuation, and subsequent therapies following discontinuation. OS was defined as time from initiation of ibrutinib to death. The International Workshop on Chronic Lymphocytic Leukemia (iwCLL, 2008) criteria were used to define response and progression of disease. Select* *AEs were assessed using the Common Terminology Criteria for Adverse Events (CTCAE)*
Method of analysis	*Comparisons of survival outcomes data were made using the long rank (LR) test. Cox regression analyses were used to estimate hazard ratios in univariate and multivariate analyses. All other comparison analyses were descriptive. All tests were two-sided at the 5% level*
Subgroup analyses	Patients were categorized based on key inclusion criteria for the RESONATE-2 trial: younger than 65 years of age at time of starting ibrutinib (<65) vs ≥65 and chromosome del(17p13)

	present vs del (17p13) absent, and the presence or absence of somatic hypermutation of the B-cell receptor (IGHV mutated vs unmutated).

Table 2A: Ahn et al. study

Trial name	*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*
NCT number	*NCT01500733*
Objective	*To investigate safety and efficacy of long-term therapy with ibrutinib in patients with TP53 aberration or age 65 years or older*
Publications – title, author, journal, year	*Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study, Inhye E. Ahn, Mohammed Z. H. Farooqui, Xin Tian et al. Blood, 2018*
Study type and design	*Phase 2, open-label, single-center study. Ibrutinib was administered orally at the dose of 420 mg once daily until disease progression or the development of unacceptable toxicity. Clinical safety monitoring was performed every other week for the first month, then every 4 weeks until 24 weeks, and every 3 months thereafter.*
Follow-up time	*Median follow-up 57 months*
Population (inclusion and exclusion criteria)	*Eligibility criteria included active CLL or small lymphocytic lymphoma requiring therapy, and del(17p) by fluorescence in situ hybridization in 10% or more of nuclei or TP53 mutation for the TP53 cohort, or age 65 years or older for the elderly cohort, Eastern Cooperative Oncology Group performance status of 2 or less, neutrophil count of 0.5 × 10 /L or higher, and platelet count of at least 30 × 10 /L. Exclusion criteria included any histologic transformation of CLL (Richter's syndrome or prolymphocytic leukemia), autoimmune cytopenia requiring steroids, impaired organ function (total bilirubin ≥1.5 or aspartate aminotransferase/alanine aminotransferase ≥2.5 × upper limit of normal; creatinine ≥2.0 mg/dL or creatinine clearance of 50 mL/min or less), active hepatitis B infection, HIV infection, concomitant prednisone more than 20 mg/day, and/or anticoagulation with warfarin*
Intervention	*Ibrutinib was administered orally at the dose of 420 mg once daily until disease progression or the development of unacceptable toxicity*

<table>
<tr><td>Baseline characteristics</td><td>
Table 1.
Baseline characteristics

<table>
<tr><th></th><th>All (n = 86)</th><th>TP53 cohort (n = 51)</th><th>Elderly cohort (n = 35)</th></tr>
<tr><td>Age, median (range), y</td><td>66 (33-85)</td><td>62 (33-82)</td><td>69 (63*-85)</td></tr>
<tr><td>≥65, N (%)</td><td>55 (64.0)</td><td>21 (41.2)</td><td>34 (97.1)*</td></tr>
<tr><td>Sex, N (%)</td><td></td><td></td><td></td></tr>
<tr><td>Female</td><td>36 (41.9)</td><td>20 (39.2)</td><td>16 (45.7)</td></tr>
<tr><td>Male</td><td>50 (58.1)</td><td>31 (60.8)</td><td>19 (54.3)</td></tr>
<tr><td>Prior treatment status, N (%)</td><td></td><td></td><td></td></tr>
<tr><td>Treatment-naive</td><td>53 (61.6)</td><td>35 (68.6)</td><td>18 (51.4)</td></tr>
<tr><td>Relapsed/refractory†</td><td>33 (38.4)</td><td>16 (31.4)</td><td>17 (48.6)</td></tr>
<tr><td>Rai stage, N (%)</td><td></td><td></td><td></td></tr>
<tr><td>I/II</td><td>28 (32.6)</td><td>19 (37.3)</td><td>9 (25.7)</td></tr>
<tr><td>III/IV</td><td>58 (67.4)</td><td>32 (62.7)</td><td>26 (74.3)</td></tr>
<tr><td>Bulky adenopathy (≥5 cm), N (%)‡</td><td>31 (36.0)</td><td>19 (37.3)</td><td>12 (34.3)</td></tr>
<tr><td>Splenomegaly, N (% evaluable)§</td><td>74 (88.1)</td><td>44 (88.0)</td><td>30 (88.2)</td></tr>
<tr><td>IGHV unmutated, N (%)‖</td><td>57 (66.3)</td><td>34 (66.7)</td><td>23 (65.7)</td></tr>
<tr><td>TP53 aberration, N (%)</td><td>54 (62.8)</td><td>51 (100)</td><td>0 (0)</td></tr>
<tr><td>Deletion 17p</td><td>50 (58.1)</td><td>47 (92.2)</td><td>3 (8.6)¶</td></tr>
<tr><td>TP53 mutation</td><td>4 (4.7)</td><td>4 (7.8)</td><td>0 (0)</td></tr>
<tr><td>β2-microglobulin</td><td></td><td></td><td></td></tr>
<tr><td>Median (range), mg/dL</td><td>4·0 (1.7-12.9)</td><td>3.9 (1.7-12.3)</td><td>4.4 (1.9-12.9)</td></tr>
<tr><td>>4 mg/dL, N (%)</td><td>44 (51.2)</td><td>24 (47.1)</td><td>20 (57.2)</td></tr>
</table>
*One patient not meeting age requirement was removed from study.
†Median number of prior therapies was 3 (range, 1-7).
‡Target lymph nodes and spleen were assessed with CT scans.
§Two patients had splenectomy. Normal spleen volume is less than 315 mL.
‖Unmutated IGHV indicates a less than 2% change in IGHV sequence compared with germ line.
¶Three patients had 7%-9% of nuclei with deletion 17p by fluorescence in situ hybridization; inclusion criteria for the TP53 cohort was more than 10% of nuclei with deletion 17p.
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary endpoint was response after 6 cycles of therapy. Secondary endpoints included safety, tolerability, overall survival (OS), PFS, and best response. At 2, 6, and 12 months, and yearly thereafter, CT, bone marrow biopsies, and flow cytometry were performed. Spleen volume was calculated from CT.
MRD Negativity was tested using flow cytometry</td></tr>
<tr><td>Method of analysis</td><td>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. Wilcoxon signed-rank test was used to assess the change in the quantification of MRD. Spearman’s analysis was used to assess the correlation between blood and bone marrow MRD.</td></tr>
<tr><td>Subgroup analyses</td><td>Among others, Patients were stratified according to IGHV mutation status and del(17p) status.</td></tr>
</table>

8.1.5 Results per trial

Table 3A: CLL14 trial

Trial name:	CLL14										
NCT number:	NCT02242942										
					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 at median follow-up *28.1 months*	VenG	216	0.139								
	GClb	216	0.356								
PFS *24 months*	VenG	216	0.882	0,837-0,927				HR: 0,35	0,23-0,53	<0,001	*Investigator assessed.*
	GClb	216	0.641	0,574-0,708							
PFS *24 months*	VenG	216	0.819					HR: 0.31	0.22-0.44	<0,001	
	GClb	216	0.495								
OS *24 months*	VenG	216	0.918	0,881-0,955				HR: 1.24	0,64-2,40	0.52	
	GClb	216	0.933	0,9-0,967							
OS *36 months*	VenG	216	0.889					HR1.03	0.602-1.753	0.921	
	GClb	216	0.88								
MRD Negative 3 months after treatment. In PB	VenG	216	0.755								*Methods of analysis are described in the manuscript*
	GClb	216	0.352								
Grade 3 or 4 AE	VenG	212	167								
	GClb	214	164								
Overall response	VenG	216	0.847							<0.001	
	GClb	216	0.713								
PFS rate 24 months Subgroup IGHV unmutated	VenG	121	89.4%					HR: 0.22	0.12-0.38		
	GClb	123	51%								

MRD in PB after 3 months – Subgroup IGHV unmutated	VenG GClb	121 123	79.3% 27.6%		HR: 10.05	5.56-18.16	

Table 3A: E1912 trial

Trial name:	**E1912**									
NCT number:	NCT02048813									
				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 36 months	I+R	354	0.894 0,86-0.93				HR: 0.35	0.22-0.56	<0.001	*Methods of analysis are described in the manuscript*
	FCR	175	0.729 0,653-0,813							
OS 36 months	I+R	354	0.988 0,976-1,0				HR: 0.17	0.05-0.54	<0.0001	
	FCR	175	0.915 0,862-0,97							
MRD at 36 months in peripheral blood	I+R	276	0.083 0,054-0,122							
	FCR	103	0.592 0,491-0,688							
Overall response 36 months	I+R	354	0.958 0,931-0,976							
	FCR	175	0.811 0,745-0,866							
AE Grade 3 or higher – 36 months	I+R	352	282			0.91				
	FCR	158	126							
3 Years PFS – Subgroup IGHV unmutated	I+R	210	90.7%				HR: 0.26	0.14-0.50		
	FCR	71	62.5%							

Table 3A: Alliance trial

Trial name:	**Alliance**										
NCT number:	NCT01886872										
					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	B+R	176	0.74	0,66-0,80							*Methods of analysis are described in the manuscript*
	Ibrutinib	178	0.87	0,81-0,92				HR: 0,39*	0,26-0,58	<0,001	
	I+R	170	0.88	0.81-0.92				HR: 0,38*	0,25-0,59	<0,001	
Overall survival	B+R	183	0.95	0,91-0,98							
	Ibrutinib	182	0.90	0,85-0,94						p>0,64	
	I+R	182	0.94	0.89-0.97						p>0,64	
Overall response rate	Ibrutinib	183	0.81	0,75-0,87							
	Ibrutinib	182	0.93	0.88-0.96							
	I+R	182	0.94	0,89-0,97							
MRD	B+R	183	0.08	0.05-0.13							
	Ibrutinib	182	0.01	<0.01-0.03							
	I+R	182	0.04	0.02-0.08							
Hematological AE grade 3-4	B+R	176	102								
	Ibrutinib	180	74				<0.001				
	I+R	181	69								
	B+R	176	88				<0.001*				

Non-Hematological AE grade 3-4	Ibrutinib	180	117				
	I+R	181	119				
PFS Subgroup IGHV Unmutated	B+R	71	31	32 – NE			***Total population of unmutated vs. mutated IGVH*
	Ibrutinib	77	16	NE-NE		HR: 0.51* 0.32-0.81**	
	I+R	70	20	48 - NE			
PFS Subgroup Del(17p)	B+R	14	10				****Signifanct different PFS for Ibrutinib or I+R vs B+R*
	Ibrutinib	9	2			<0.001***	
	I+R	11	3			<0.001***	

Table 3A: CLL10 trial

Trial name:	CLL10									
NCT number:										
					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	BR FCR	279 282	41,7 months 55,2 months	34,9-45,3 NE				HR:1,643	1,308-2,064		*Methods of analysis are described in the manuscript*
PFS at 36 months	BR FCR	279 282	0.47 0.32					HR: 1,626	1,224-2,125		
OS *At 36 motnths*	BR FCR	279 282	0.92 0.91	0,887-0,956 0,87-0,942				HR: 1,034	0,62-1,724	0.897	
MRD Negative *In PB*	BR FCR	170 185	0.63 0.74							p=0,029	
MRD Negative In Bone marrow	BR FCR	98 129	0.32 0.58							<0,0001	
Grade 3 or above AE	BR FCR	278 279	0.84 0.94								
Overall response	BR FCR	279 282	0.96 0.95							p=1,0	
PFS Median *At 60 months*	BR FCR	279 282	42.3 57.6					HR: 1,593	1,271-1,996	<0,0001	*In extension study*
OS 60 months	BR FCR	279 282	0.801 0.809					HR: 1,108	0,755-1,627	0.599	*In extension study*
Median PFS – Subgroup IGHV unmutated	BR FCR	183 152	33.9 43.0					HR: 1.545	1.181-2.02	0.0015	*In extension study*
	BR	183	72.9%								*In extension study*

5 YEAR OS – Subgroup IGHV unmutated	FCR	152	75.55%		HR: 1.203	0.77-1.89	0.42	

Table 3A: Resonate-2

Trial name:	Resonate 2										
NCT number:	NCT01722487										
				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 at 18 months	Ibrutinib	136	Not reached				HR: 0.16	0,09-0,28	<0.001	*Independent review-committee assessed.*
	Chlorambucil	133	18,9 months							
PFS at 18 months	Ibrutinib	136	0.9							*Methods of analysis are described in the manuscript*
	Chlorambucil	133	0.52							
PFS Median at 60 months	Ibrutinib	136	Not reached							
	Chlorambucil	133	15 months	10,2– 19,4						
PFS at 60 months	Ibrutinib	136	0.7				HR: 0.146	0.098-0.218		
	Chlorambucil	133	0.12							
OS at 24 months	Ibrutinib	136	0.98				HR: 0.16	0,05-0,56	<0,001	
	Chlorambucil	133	0.85							
OS at 60 months	Ibrutinib	136	0.83				HR: 0,45	0.266-0.761		*Without censoring for crossover.*
	Chlorambucil	133	0.68							
Median OS at 60 months	Ibrutinib	136	Not reached							*Methods of analysis are described in the manuscript*
	Chlorambucil	133	Not reached							
Overall response 24 months	Ibrutinib	136	0.86						<0.001	
	Chlorambucil	133	0.35							
Overall respone at 60 months	Ibrutinib	136	0.92							
	Chlorambucil	133	0.37							
AE Grade 3 or higher – 24 months	Ibrutinib	135	71							
	Chlorambucil	132	75							
AE grade 3 or higher 60 months	Ibrutinib	135	112							

MRD 24 months	Ibrutinib Chlorambucil	136 133					
FACIT-F CMID at 60 months	Ibrutinib Chlorambucil	136 133	0.63 0.53	Not significant			
Median PFS Subgroup – Del(17p) 60 months	Ibrutinib Chlorambucil	12 3	Not reached -		HR: 0.866*	0,26-2.85	*TP53 Mutation vs. Wild type TP53*
PFS Subgroup – Del(17p) 60 months estimate	Ibrutinib Chlorambucil	12 Non	56% 73%				*TP53 Mutation vs. Wild type TP53*
PFS Subgroup – IgHV unmutated	Ibrutinib Chlorambucil	58 60			HR: 0.083*	0.047-0.145	**Vs population with mutated IGHV*
PFS Subgroup – IgHV unmutated	Ibrutinib Chlorambucil	58 60			HR: 0.105	0.06-0.19	

Table 3A: MaBle trial

Trial name:	Maple										
NCT number:											
					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	
Overall response rate	B+R Clb+R	121 120	0,91 0,86	NA NA						0,304	
Median PFS	B+R Clb+R	121 120	39,6 29,9	NA NA				HR: 0,523	0,339-0,806	0,003	
Median OS	B+R Clb+R	121 120	43,8 NR	NA NA				HR: 0,975	0,505-1,880	0,939	
AE grade 3-4	B+R Clb+R	177 178	132 (75%) 113 (64%)	NA NA	NA	NA	NA	NA	NA	NA	
MRD	B+R Clb+R	121 120	0,41 0,13	NA NA	NA	NA	NA	NA	NA	NA	

Table 3A: Mato et al. study

Trial name:	Mato et al								
NCT number:									
				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	
Median PFS	Ibrutinib	391	Not reached							*Methods of analyses are described in the manuscript*
Median Overall survival	Ibrutinib	391	Not reached							
1 Year PFS	Ibrutinib	391	92%							
1 Year OS	Ibrutinib	391	95%							
1 year PFS – Subgroup with del(17p)	Ibrutinib	108	87%				HR vs without del(17p): 1.9		0.04	

1 year OS – Subgroup with del(17p)	Ibrutinib	108	89%		HR vs without del(17p): 3.9	0.001
1 year PFS Subgroup IGHV unmutated	Ibrutinib	221			No signifant difference vs. mutated population	
AE Grade 3 or 4	Ibrutinib	391	22.5%			

Table 3A: Ahn et al. study

Trial name:	Ahn et al									
NCT number:	NCT01500733									
					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	
5 year estimated PFS	TP53 cohort	51	58%	44.5-74.5						0.026	*Methods of analyses are described in the manuscript*
	Elderly cohort	35	81%	67.1-98.3							
Median OS	TP53 cohort	51	75.7%	64.7-88.7						0.1	
	Elderly cohort	35	83.8%	70-100							
5 year estimated PFS: Subgroup TP53	First-line treatment	34	74.4%	60.2-92.1						0.0002	
	R/R	16	19.4%	6.3-60							
5 year estimated OS: Subgroup TP53	First-line treatment	34	85.3%	74.2-98.1						0.023	
	R/R	16	53.7%	33.4-86.4							
ORR	TP53	51	95.8%	85.7-99.5							
	Elderly	35	93.9%	79.8-99.3							

MRD negativity after 4 years	Peripheral blood Bone marrow	49 25	5 2			
AE grade 3 or 4	Tota population		28%			
PFS Stratified to IGHV	IGHV Unmutated IGHV Mutated	55 29			0.16	
OS Stratified to IGHV	IGHV Unmutated IGHV Mutated	55 29			0.15	

8.2 Results per PICO

Table A4. PICO for VENG vs GClb

Outcome	VenG/GClb HR			Absolute difference (AD) assuming event rate GClb from CLL14 trial			Event rate GClb
	HR	CI_low	CI_high	AD	CI_low	CI_high	
OS, 24 md	1.24	0.64	2.4	-1.50%	n.a.	n.a.	93.30%
OS, 36 md	1.03	0.602	1.753	-1.40%	n.a.	n.a.	88.00%
PFS, 24 md	0.35	0.23	0.53	24.10%	n.a.	n.a.	64.10%
PFS, 36 md	0.31	0.22	0.44	32.40%	n.a.	n.a.	49.50%
AE grade 3-4	1.03	0.93	1.14	-0.61%	1.44%	-2.80%	76.64%
EORTC QLQ-C30, Global Health Status, Difference	- 0.70	n.a.	n.a.	- 0.70	n.a.	n.a.	na

Patient cost analysis and budget impact for venetoclax in combination with obinutuzumab

With model in excel

12th August 2020

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1 Summary

In March 2020, venetoclax in combination with 6 cycles of obinutuzumab received EMA approval as the first time-limited, targeted chemo-free treatment option for first line CLL patients. The approval was based on the CLL14 Phase 3 trial, where 12 cycles of venetoclax in combination with 6 cycles of obinutuzumab reduced the risk of progression or death by 65% compared to 12 cycles of chlorambucil in combination with 6 cycles of obinutuzumab(1).

Based on a model developed by AbbVie in connection with application to UK NICE, a simple model for Progression Free Survival (PFS) and Overall Survival (OS) have been developed for Denmark. The model has been used to construct therapy sequences to analyze costs over the life expectancy of 1st line CLL patients in Denmark. Furthermore, the model is used to estimate the net budget impact of positive recommendation of venetoclax in combination with obinutuzumab.

Results

Patient cost analysis of venetoclax in combination with obinutuzumab was performed vs. 4 comparators in therapy sequences of first, second, and third line treatment.

Table 1: Results of per patient cost analysis over life expectancy for 1st line CLL patients, discounted at 4% p.a., DKK

Treatment sequence	Drug costs	Hospital costs	AE costs	Patient time costs	transportation costs	Total
Non 17p/TP53 population						
VenG->IBR	1,055,785 kr.	115,707 kr.	33,850 kr.	31,518 kr.	3,836 kr.	1,240,696 kr.
GClb6->IBR	1,721,247 kr.	76,383 kr.	33,912 kr.	37,693 kr.	3,346 kr.	1,872,580 kr.
BR->IBR	1,922,365 kr.	67,121 kr.	45,043 kr.	39,903 kr.	3,176 kr.	2,077,607 kr.
FCR->IBR	1,691,858 kr.	73,945 kr.	24,322 kr.	38,246 kr.	3,242 kr.	1,831,613 kr.
17p/TP53 population						
VenG->IBR	779,732 kr.	67,773 kr.	33,079 kr.	19,758 kr.	2,176 kr.	902,518 kr.
IBR->VenR	2,471,055 kr.	65,785 kr.	8,004 kr.	17,181 kr.	2,116 kr.	2,564,142 kr.

Table 2: Per patient cost analysis per therapy line, life expectancy and cost utility, discounted at 4% p.a., DKK

Treatment sequence	Total cost, discounted	Drug costs, discounted	1st line costs, discounted	2nd line costs, discounted	3rd line costs, discounted	Life years	QALY, discounted	ICER vs Arm 1
Non 17p/TP53 population								
VenG->IBR	1,240,696	1,055,785	792,868	438,459	9,369	12.06	7.15	NA
GClb6->IBR	1,872,580	1,721,247	306,327	1,533,488	32,765	8.64	5.49	Dominant
BR->IBR	2,077,607	1,922,365	172,452	1,865,301	39,854	8.06	5.15	Dominant
FCR->IBR	1,831,613	1,691,858	179,629	1,617,425	34,558	8.48	5.39	Dominant
17p/TP53 population								
VenG->IBR	902,518	779,732	729,413	170,732	2,373	6.13	3.96	NA
IBR->VenR	2,564,142	2,471,055	2,474,171	87,598	2,373	6.13	3.96	Dominant

Patient cost analysis showed that life-time costs in therapy sequences where 1st line VenG was followed by 2nd line IBR was cost saving compared to CIT followed by 2nd line IBR for the non del17p/TB53 mutation population. In addition, life expectancy was around 3 years higher in the therapy sequence with 1st line VenG compared to CIT in 1st line. For the patient population with del17/TP53 deletion 1st line VenG followed by 2nd line IBR is highly cost saving compared to 1st line IBR followed by 2nd line VenR at same life expectancy.

Table 3: Budget impact, 1-5 year, in million DKK, un-discounted

Million DKK	Year 1	Year 2	Year 3	Year 4	Year 5
Without Ven+O, running budget	37.4	59.7	90.5	124.9	159.5
With Ven+O, running budget	75.9	86.2	101.5	119.5	138.2
Incremental budget impact, running budget	38.6	26.5	11.0	-5.4	-21.3

The incremental budget impact is positive and decreasing over time in the first 3 years. From the 4th year the incremental budget impact is negative and ending at a saving of 21.3 million DKK in the 5th year. For reference the un-discounted incremental budget impact over 5 years is DKK 49.3 million (DKK 49.2 million discounted), whereas the un-discounted incremental budget impact over 10 years is a cost saving of DKK 235.2 million (DKK 156.2 million discounted).

2 Model

Purpose

The purpose of the model is to enable two different analyses for the Medicine Council application for Venetoclax in combination with obinutuzumab for 1st line therapy for patients with CLL. The two analyses are: Patient cost analysis and budget impact for venetoclax in combination with obinutuzumab (VenG).

Model Structure

To calculate treatment costs per patient during life expectancy a simple cost model with therapy sequences was developed. The model has a fixed time horizon of 30 years in 60 half year cycles to ensure that the entire life expectancy of patients who are 70 years at the start of the model is included in the financial calculations.

The model is based on 1st line treatment and continues through 3rd line treatment. In all Therapy sequences in this report 3rd line treatment is a generic "Best Supportive Care" (BSC). The model is based on survival curves (OS) for 1st, 2nd and 3rd line treatment.

The model is built around therapy sequences in half year cycles over 30 years. Patients start in 1st line therapy, changes to 2nd line therapy and 3rd line therapy determined by Progression Free Survival (PFS) and OS curves in 60 half year cycles.

The model is based on VenG PFS and OS curves for 1st line patients with or without del17/TP53 mutation, respectively and these curves are then manipulated with Hazard Ratios (HR) based on indirect therapy comparison for each therapy option/line. Surviving patients who progress from each therapy line enter the subsequent therapy line in the next half year cycle. From therapy start in the next line, patients follow PFS and OS curves for the specific therapy option chosen.

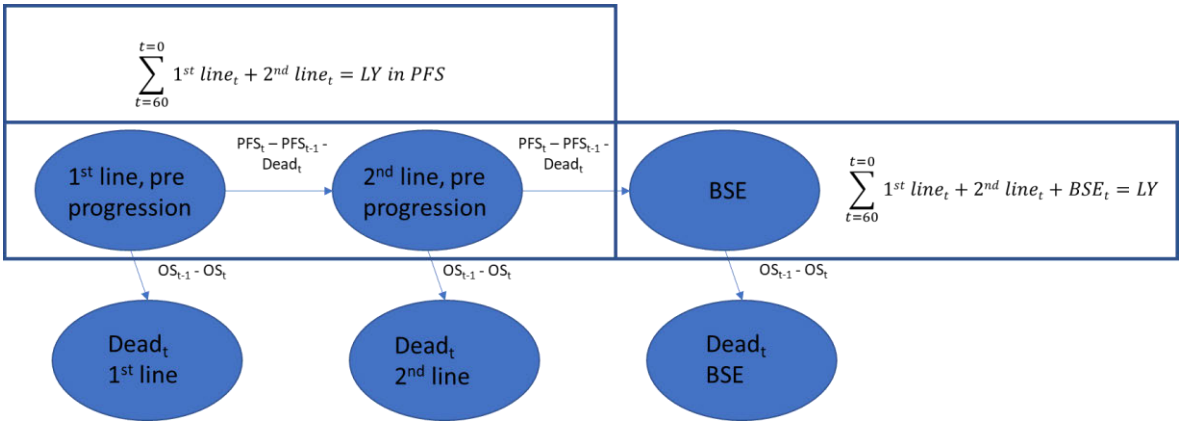
3rd line therapy is assumed to be Best Supportive Care (BSC) and patients cannot progress to further therapy lines and their prognosis is determined by the OS curve for BSC.

As patients progress at different cycles, and as many therapy options for CLL are time limited, the model tracks at what time therapy in each line is started and at what time progression to the next line or death occurs to ensure that costs are distributed correctly in time.

The model estimates life expectancy based on OS curves for each therapy option/line as well as time spent in pre progression in each therapy line.

Based on utility weights for pre- and post-progression survival the model estimates Quality Adjusted Life Years and enables cost utility analyses.

Figure 1: Model structure



Comparators and model arms

The MS excel model contains 4 arms to enable analyses vs. the comparators in the general CLL patient population without del17p/TP53: 6 cycles Chlorambucil in combination with obinutuzumab (GClb6), Bendamustine in combination with rituximab (BR), Fludarabine, cyclophosphamide in combination with rituximab (FCR).

The MS excel model contains 2 arms to enable analyses vs. the comparator in the CLL subpopulation with del17p/TP53: Ibrutinib (IBR).

Each therapy arm consists of a therapy sequence as illustrated in figure 1.

For the general CLL patient population without del17p/TP53: VenG, GClb6, BR and FCR can be chosen in 1st line, whereas 2nd line options are: Venetoclax in combination with rituximab (VenR), GClb6, BR, IBR and BSC. FCR cannot be chosen in 2nd line as no studies on FCR in 2nd line exists.

For the subpopulation with del17p/TP53: VenG and IBR can be chosen in 1st line, whereas 2nd line options are: VenR, IBR and BSC.

PFS and OS curves

For the AbbVie global Cost Effectiveness Model (CEM) PFS- and OS curves were fitted using Exponential, Weibull, Gompertz, Log-logistic, Log-normal, Gamma, Generalized gamma distributions for both VenG and 12 cycles GClb for both the general CLL population and the del17p/TP53 mutation subpopulation based on the data from the CLL14 trial. These PFS- and OS curves have been used from the global AbbVie global CEM (see AbbVie global CEM documentation annexed to this report).

Comparator PFS- and OS curves are estimated based on the PFS- and OS curves for VenG (except for the direct comparator in the CLL14 trial (GClb 12 cycles) where the above mentioned curves are used).

For each cycle, a comparator PFS- and OS rate has been estimated for each comparator using the following formulas:

- PFS_{comp} = MIN(OS_0, PFS_{-1}*(1-(1-EXP(-MAX((1/$HR_{(comp)}$)*(PFS_0-PFS_{-1}), $BM_{(age)}$)))), where PFS is the PFS rate for VenG, $HR_{(comp)}$ is the relevant comparator HR for PFS vs. VenG and BM is Background Mortality for the age group

- OS_{comp} = OS_{-1}*(1-EXP(-MAX((1/$HR_{(comp)}$)*(OS_0-OS_{-1}), $BM_{(age)}$))), where OS is the OS rate for VenG, $HR_{(comp)}$ is the relevant comparator HR for OS vs. VenG and BM is Background Mortality for the age group

Background Mortality is the general population mortality based on two-year life tables for Denmark for 2018-2019 (Table HISB8, https://www.statistikbanken.dk/HISB8).

As the user of the model can choose which distributions are used for PFS and OS amongst the Exponential, Weibull, Gompertz, Log-logistic, Log-normal, Gamma, Generalized gamma distributed curves, there exists combinations where PFS could be higher than OS. Therefore, if the PFS for a specific cycle is higher than OS, PFS is set to OS for that cycle.

2nd line OS and PFS has been estimated using the same formulas but with PFS and OS curves based on HR for 1st vs. 2nd line therapy.

Per patient cost analysis

Per patient cost analysis is performed over 30 years for one patient starting in each of the arms in the MS excel model. The total per patient costs are broken down in: Drug costs, Hospital costs, Adverse event costs (AE costs), Patient time costs and Transportation costs as well as total costs by therapy lines. Total life years (LY) in each arm are the basis for the life time costs an are reported as well as life years spent pre-progression and utility weights for pre-progression and post progression life years are used to report Quality Adjusted Life Years (QALYs) to enable simple cost utility analysis. Both outcomes (LYs and QALYs) as well as all costs are discounted and reported both with and without discounting.

Budget impact model

The Budget Impact Model (BIM) included in the MS excel model uses the first 10 cycles (5 years) of the 6 arms of the patient model, where each arm represents a 1st line therapy option to estimate the budget impact of using VenG in 1st line for CLL patients with and without del17p/tp53 mutation. The market sizes for the patient population with and without del17p/tp53 mutation are set as well as present and future market shares for each of the present 1st line therapy options and VenG. The BIM includes drug-, AE- and hospital costs and does not use discounting as defined in the Medicines Council methodology for economic evaluation(2). The BIM is an open cohort model where new patients, according to the patient numbers set by the user, enter the model each year and follow the prognosis determined by the per patient model until the 5th year. For example in the 3rd year, costs incurred in the 3rd year for surviving patients who started therapy in the 1st year are added to costs incurred in the 2nd year for surviving patients who started therapy in the 2nd year and costs costs incurred in the 1st year for surviving patients who started therapy in the 3rd year.

3 Per patient cost analysis

Per patient cost analysis of venetoclax in combination with obinutuzumab was performed in relation to the 4 comparators as listed below with doses set in the Medicines Council protocol for the evaluation of VenG:

1. Chlorambucil in combination with obinutuzumab dosed as follows for 6 cycles of 28 days:
    a. Chlorambucil p.o. 0.5 mg / kg on days 1 and 15
    b. Obinutuzumab i.v. 100 mg on day 1, 900 mg on day 2 and 1,000 mg on days 8 and 15 in cycle 1, then 1,000 mg on day 1 in cycle 2-6
2. Bendamustine in combination with rituximab dosed as follows for up to 6 cycles of 28 days:
    a. Bendamustin i.v. 70-90 mg / m2 on days 1 and 2
    b. Rituximab i.v. 375 mg / m2 on day 1 of the first cycle, then i.v. 500 mg / m2 on day 1 of subsequent cycle
3. Fludarabine, cyclophosphamide in combination with rituximab (R-FC) dosed as follows for 6 cycles of 28 days:
    a. Fludarabine 25 mg / m2 i.v. day 1-3
    b. Cyclophosphamide 250 mg / m2 i.v. day 1-3
    c. Rituximab 375 mg / m2 i.v. day 1, 1st cycle, cycle 2-6: 500 mg / m2
4. Ibrutinib
    a. 420 mg per day until progression

For venetoclax in combination with obinutuzumab the doses set in the Medicines Council protocol were:

- Venetoclax p.o., cycle 1: 20 mg on days 22-28, cycle 2: 50 mg on days 1-7, 100 mg on days 8-14, 200 mg on days 15-21 and 400 mg on days 22-28. Cycle 3-12: 400 mg on days 1-28 (continuous to end cycle 12).
- Obinutuzumab i.v., cycle 1: 100 mg on day 1, 900 mg on day 2 and 1,000 mg on days 8 and 15, cycle 2-6: 1,000 mg on day 1.

The following dosages and drug prices have been used.

Table 4: Dose over 12 months, as well as PPP

Therapy	Total dose, mg	PPP, per pack	mg per pack	PPP per therapy	Note
6 cycles rituximab (m2 1.89)	5,433.75	6,687.00 kr.	500.00	72,670.97 kr.	Ritemvia®, assumption average surface area 1.89 m2
6 cycles obinutuzumab	8,000.00	26,284.17 kr.	1,000.00	210,273.36 kr.	Gazyvaro®
Ven, 12 cycles	120,470.00	41,036.25 kr.	11,200.00	441,396.16 kr.	Venclyxto®
Ven, 1. year	137,390.00	41,036.25 kr.	11,200.00	503,390.21 kr.	Venclyxto®
Ven, 2. year	146,000.00	41,036.25 kr.	11,200.00	534,936.83 kr.	Venclyxto®
Chlorambucil, 6 cycles	390.00	527.00 kr.	50.00	4,110.60 kr.	Leukeran®, assumption average patient 65 kg
Fludarabin, 6 cycles	850.50	6,550.50 kr.	250.00	23,581.80 kr.	Fludarabinphosphat "Ebewe"
Cyclophosphamid, 6 cycles	8,505.00	153.75 kr.	500.00	2,767.50 kr.	Sendoxan®

Therapy	Total dose, mg	PPP, per pack	mg per pack	PPP per therapy	Note
IBR	153,300.00	42,991.25 kr.	12,600.00	523,060.21 kr.	Imbruvica®
Bendamustine, 6 cycles	1,611.00	3,081.00 kr.	500.00	9,926.98 kr.	Bendamustinhydrochlorid Intas®
BSC	1.00	50,000.00 kr.	1.00	50,000.00 kr.	Assumption

Source: www.medicinpriser.dk dose from Medicines Council protocol for VenG

Best supportive care (BSC) has been added to support a full life expectancy perspective where BSC is used as the last line of treatment for all therapy sequences. A therapy cost of 50,000 DKK has been assumed in the base case. Therapy for these patients can include higher costs including allogenic stem cell transplantation. To qualify this assumption a sensitivity analysis where it is assumed that half the patients reaching BSC receives allogenic stem cell transplantation is added below.

Table 5: Outpatient visits, admissions, Adverse effect cost, patient time, and transportation costs

Therapy option	VenG	GClb	FCR	VenR	IBR	BR	Ven	BSC (3rd line)	Source
Cost inputs									
Admission days at start of therapy	2	2	2	5	1	2	5	30	Assumption based on SmPCs
Admission day cost per day	3,235	3,235	3,235	3,235	3,235	3,235	3,235	3,235	DRG 2020: 17MA98 - MDC17 1-dagsgruppe, pat. mindst 7 år
Number of outpatient visits per year	4	4	4	4	4	4	4	4	Assumption based the present therapy guideline from the CLL group of the Danish Lymphoma Group (November 2019 edition)
Cost per outpatient visit	3,235	3,235	3,235	3,235	3,235	3,235	3,235	3,235	DRG 2020: 17MA98 - MDC17 1-dagsgruppe, pat. mindst 7 år
AE cost	33,764	30,231	19,982	33,764	5,100	40,717	33,764	20,000	See "AE costs", VenR, Ven is set to VenG
Patient time 1st year, hours	60	60	60	132	36	60	132	732	Admission - 24 hrs., outpatient visit - 3 hrs
Patient time following years, hours	12	12	12	12	12	12	12	12	Outpatient visit - 3 hrs
Hourly rate, patient time	179	179	179	179	179	179	179	179	Medicines Council methodology
Patient time cost 1st year	10,740	10,740	10,740	23,628	6,444	10,740	23,628	131,028	Calculation
Patient time cost following years	2,148	2,148	2,148	2,148	2,148	2,148	2,148	2,148	Calculation
Transport, #, 1st year	6	6	6	9	5	6	9	34	Transport to and from per admission /outpatient visit
Transport, #, following year	4	4	4	4	4	4	4	4	Transport to and from per admission /outpatient visit
Unit cost, transportation	100	100	100	100	100	100	100	100	Medicines Council methodology
Transport, cost, 1st year	600	600	600	900	500	600	900	3400	Calculation
Transport, cost, folowing years	400	400	400	400	400	400	400	400	Calculation

Source: DRG http://interaktivdrg.sundhedsdata.dk/, Unit costs https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf PL factors https://www.regioner.dk/aftaler-og-oekonomi/oekonomisk-vejledning/oekonomisk-vejledning-2020

It is assumed that VenG, GClb6, FCR and BR will be started with 2 admission days. While VenR and Ven mono under titration for the first 5 weeks require an admission day per titration, thus 5 admissions are included for these treatments due to the need for 24-hour tests. For BSC, it is assumed that at start of therapy admission will last for 30 days.

For all treatments, outpatient control 4 times per year is assumed.

Adverse event costs (AE costs) are calculated based on the grade 3-4 adverse events with at Least 2% Difference in Rate between Treatment Arms in the CLL14 trial. (see Annex 1).

Cost estimation of patient time and transport costs follow the Medicines Council guidance. It is assumed that patients spend 24 hours per hospitalization day, 3 hours per outpatient visit, and transport costs back and forth for each hospitalization/outpatient visit is set to 100 DKK.

Utility weights for quality adjustment of life years are inputted in the model. The base case utilities per year pre- and post-progression are 0.8 and 0.68 based on Hancock et al 2002(3) and Hornberger et al 2012(4) respectively. The user of the model can easily change these assumptions, for relevant utility weights.

4 Life expectancy and efficacy

Base case PFS and OS curves used for VenG and GClb (12 cycles) were set based on goodness of fit and expert advice for the UK NICE submission (see Annex 2 and AbbVie global CEM documentation annexed to this report).

Table 6: First Line PFS and OS

Endpoint	1L CLL and without del17p/TP53	Del17p/TP53
PFS	VenG: [redacted] Other comparators see HRs in table 7	VenG: [redacted]
OS	[redacted]	VenG: [redacted]

The user of the model can change between the following distributions for PFS and OS; Exponential

- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Gamma
- Generalized gamma

Based on goodness of fit statistics the [redacted] was chosen for PFS and [redacted] for OS. Please see Annex 2 for a through description of estimated PFS and OS curves.

Second line PFS and OS

Second line PFS and OS curves are based on the VenG first line PFS and OS curves. In the base case a HR for both PFS and OS of [redacted] for the non 17p population and [redacted] for the 17p population to 1st line has been assumed. This assumption is subject to sensitivity analysis below.

Treatment effects on PFS and OS

All treatment effects for 1st line comparators (HRs), except for the direct comparator in the CLL14 trial (GClb 12 cycles) where PFS and OS curves were estimated based on the CLL14 trial, are computed based on an Indirect Therapy Comparison (ITC) made by Pharmeit for AbbVie based on substantial literature search and Baysian Network Meta-Analysis (NMA) (see annexed AbbVie ITC).

All treatment effects for 2nd line comparators (HRs), are computed based on a NMA published by Chen et al in 2019(5). The NMA published by Chen and colleagues reported HRs in relation to ofatumumab (OFA) and were subsequently recalculated in relation to VenR to be used in the MS excel model (comparator HR vs OFA/VenR HR vs OFA).

The 3rd line BSE, common to all therapy arms incurs very little cost compared to 1st and 2nd line therapy and the main function is to regulate overall life-expectancy for CLL patients requiring therapy. According to the latest annual report from the Danish Lymphoma data base(6), 10-year survival is 51.8 percent. Life-

expectancy for all CLL patients (including patients not requiring therapy) is thus around 12 years. Approximately 500 patients are diagnosed and around 150 start 1st line therapy annually, which is 30% of the diagnosed patients. It should be noted that the 150 patients starting 1st line therapy could have been diagnosed several years before. The general life-expectancy for a 70-year old Danish male is 14.5 years (www.dst.dk). If patients not requiring therapy have the same prognosis as the general male Danish population (14.5 years) and 70 percent of CLL patients do not require therapy, the life-expectancy with current standard CIT based therapy should be 8.5 years. Setting the HR for OS of BSE at [redacted] means that life-expectancy in the patients receiving 1st line CIT in the model has a life expectancy between 8 and 8.7 years, depending on therapy option.

Table 7: The HRs used to estimate the life-time costs of the therapy options analyzed (HR vs. VenG and in 2nd line VenR)

Therapy option	GClb (6 cycles)*	FCR*	BR (1st line)*	BR (2nd Line)**	FCR (2nd line)***	IBR (2nd line)**	IBR (1st line, 17p)*	IBR (2nd line, 17p)**	BSC, non 17p	BSC, 17p	1st line vs 2nd line, non17p	1st line vs 2nd line, 17p
Hazard ratio PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Hazard ratio OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: *1st line estimates, AbbVie ITC **2nd line estimates, Chen et al 2019(5), ***2nd line FCR set to BR, BSC calibrated based on life-expectancy in the LYFO database

The HR estimates were used to manipulate the 1st line PFS and OS curves estimated based on data from the CLL14 trial as explained in section 2.

[redacted]

[redacted]

As can be seen in figures 2-3, the prognosis for 1st line patients without del17p vs. the del17p subpopulation is substantially different with median PFS around [redacted].

5 Per patient lifetime cost results

Therapy sequences including the 1st line therapy options included in the Medicine Council protocol for evaluation of VenG has been produced. As mentioned earlier, all therapy sequences end with a generic BSC in 3rd line, which is assumed to include 50,000 DKK in therapy costs and 30 days admission to hospital in the first year.

Table 8: Therapy sequences

Therapy sequence (1st line -> 2nd line)	Note
VenG->IBR	Sequence to describe costs if VenG receives positive recommendation in 1st line CLL patients without del17p
GClb->IBR	Comparator sequence for GClb in non del17p 1st line CLL
BR->IBR	Comparator sequence for BR in non del17p 1st line CLL
FCR->IBR	Comparator sequence for FCR in non del17p 1st line CLL
VenG—>IBR, del17p/TP53	Sequence to describe costs if VenG receives positive recommendation in 1st line CLL patients with del17p
IBR—>VenR, del17p/TP53	Comparator sequence for IBR in del17p 1st line CLL

Table 9: Therapy costs including costs for hospitalization, patient time, and transport per therapy sequence over life expectancy, with and without discounting at 4% p.a., DKK

Therapy sequence (1st line -> 2nd line)	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	1,503,176	1,240,696
GClb6->IBR	2,477,936	1,872,580
BR->IBR	2,741,817	2,077,607
FCR->IBR	2,450,892	1,831,613
17p/TP53 population		
VenG->IBR	993,058	902,518
IBR->VenR	3,190,995	2,564,142

Table 9 shows the total cumulated costs over the life expectancy.

VenG treatment of CLL patients, who have not previously received treatment, is associated with substantially lower lifetime costs than GClb, BR and FCR.

It should be noted that treatment with BR and GClb and FCR is associated with significantly poorer survival, see Figure 1. Therapy with VenG followed by IBR is thus dominant compared to therapy with GClb, BR and FCR all followed by IBR in 2nd line.

VenG treatment followed by IBR for del17p/TP53 CLL patients, who have not previously received treatment, has a significantly lower lifetime cost than IBR followed by VenR for the same patient group. As can be seen in Figure 2, there is no difference in life expectancy between the two options implying that VenG is dominant vs. IBR in this patient population.

Discounting changes the relative costs between treatment options due to the cost profile of time limited VenG, where costs fall in the first 2 cycles vs. the chemo immunotherapy (CIT) options where high costs are incurred in 2nd line.

Table 10: Treatment costs broken down on costs for drugs, hospital, patient time and transport, un-discounted over life expectancy, DKK

Therapy sequence	Drug costs	Hospital costs	AE costs	Patient time costs	transportation costs	Total
Non 17p/TP53 population						
VenG->IBR	1,268,120 kr.	154,306 kr.	35,499 kr.	40,098 kr.	5,153 kr.	1,503,176 kr.
GClb6->IBR	2,300,855 kr.	90,827 kr.	36,066 kr.	46,009 kr.	4,180 kr.	2,477,936 kr.
BR->IBR	2,563,977 kr.	78,036 kr.	47,655 kr.	48,206 kr.	3,942 kr.	2,741,817 kr.
FCR->IBR	2,286,794 kr.	87,370 kr.	26,104 kr.	46,571 kr.	4,053 kr.	2,450,892 kr.
17p/TP53 population						
VenG->IBR	849,814 kr.	83,204 kr.	34,448 kr.	22,912 kr.	2,680 kr.	993,058 kr.
IBR->VenR	3,078,339 kr.	81,200 kr.	8,511 kr.	20,325 kr.	2,620 kr.	3,190,995 kr.

Table 10 shows that drug costs are the main driver of total costs. Higher PFS for VenG in the non del17p population means that less drug costs are incurred in the 2nd line compared to CIT therapy options. In the del17p population, due to the low OS substantially fewer patients progress to 2nd line IBR therapy and substantially less drug costs for 2nd line therapy is thus incurred compared to the VenG sequence in the non del17p population.

Table 11: Treatment costs broken down on costs for drugs, hospital, patient time and transport, discounted at 4% p.a. over life expectancy, DKK

Therapy sequence	Drug costs	Hospital costs	AE costs	Patient time costs	transportation costs	Total
Non 17p/TP53 population						
VenG->IBR	1,055,785 kr.	115,707 kr.	33,850 kr.	31,518 kr.	3,836 kr.	1,240,696 kr.
GClb6->IBR	1,721,247 kr.	76,383 kr.	33,912 kr.	37,693 kr.	3,346 kr.	1,872,580 kr.
BR->IBR	1,922,365 kr.	67,121 kr.	45,043 kr.	39,903 kr.	3,176 kr.	2,077,607 kr.
FCR->IBR	1,691,858 kr.	73,945 kr.	24,322 kr.	38,246 kr.	3,242 kr.	1,831,613 kr.
17p/TP53 population						
VenG->IBR	779,732 kr.	67,773 kr.	33,079 kr.	19,758 kr.	2,176 kr.	902,518 kr.
IBR->VenR	2,471,055 kr.	65,785 kr.	8,004 kr.	17,181 kr.	2,116 kr.	2,564,142 kr.

In Table 10-11, the significantly higher cost of hospital treatment for Ven + O patients compared to the other 3 treatments for patients without 17p/TP53 is due to the significantly longer life expectancy (more than 2 years discounted) for Ven + O treated patients. In this extra life expectancy patients receive 4 outpatient visits per year.

Table 12: Incremental cost per patient, VenG vs. 4 comparators, with and without discounting with 4% p.a., DKK

Therapy sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->IBR	974,760	631,884
BR->IBR	1,238,640	836,911
FCR->IBR	947,715	590,917
17p/TP53 population		
VenG->IBR	NA	NA
IBR->VenR	2,197,937	1,661,624

Table 13: Per patient cost analysis per therapy line, life expectancy and cost utility, discounted at 4% p.a., DKK

Therapy sequence	Total cost	Drug costs	1st line costs	2nd line costs	3rd line costs	Life years, un-discounted	QALY, discounted	ICER vs Arm 1
Non 17p/TP53 population								
VenG->IBR	1,240,696	1,055,785	792,868	438,459	9,369	[redacted]	[redacted]	[redacted]
GClb6->IBR	1,872,580	1,721,247	306,327	1,533,488	32,765	[redacted]	[redacted]	[redacted]
BR->IBR	2,077,607	1,922,365	172,452	1,865,301	39,854	[redacted]	[redacted]	[redacted]
FCR->IBR	1,831,613	1,691,858	179,629	1,617,425	34,558	[redacted]	[redacted]	[redacted]
17p/TP53 population								
VenG->IBR	902,518	779,732	729,413	170,732	2,373	[redacted]	[redacted]	[redacted]
IBR->VenR	2,564,142	2,471,055	2,474,171	87,598	2,373	[redacted]	[redacted]	[redacted]

The patient cost analysis demonstrates that life-time costs in therapy sequences where 1st line VenG was followed by 2nd line IBR is cost saving compared to CIT followed by 2nd line IBR for the non del17p/TB53 mutation population. In addition, life expectancy is around 3 years higher in the therapy sequence with 1st line VenG compared to CIT in 1st line. For the patient population with del17/TP53 deletion, 1st line VenG followed by 2nd line IBR is highly cost saving compared to 1st line IBR followed by 2nd line VenR at same life expectancy.

Clinical Question 1:

- Compared to treatment with 6 cycles chlorambucil in combination with obinutuzumab of CLL patients without del17p/TP53, who have not received treatment before, VenG is associated with a cost saving of DKK 631,884 per patient discounted by 4% p.a.
- Compared to treatment with 6 cycles bendamustine in combination with rituximab of CLL patients without del17p/TP53, who have not received treatment before, VenG is associated with a cost saving of DKK 836,911 per patient discounted by 4% p.a.
- Compared to treatment with 6 cycles fludarabine, cyclophosphamide in combination with rituximab of CLL patients without del17p/TP53, who have not received treatment previously, treatment with VenG is associated with a cost saving of DKK 590,917 per patient discounted by 4% p.a.

Clinical Question 2:

- Compared to treatment with ibrutinib of CLL patients with del17p/TP53, who have not received treatment before, VenG is associated with a cost saving of DKK 1,661,624 per patient discounted by 4% p.a.

6 Sensitivity analysis

Therapy sequence

The results presented in the base case above are sensitive to the choice of 2nd line therapy option. In the Danish therapy guidelines CIT in 1st line could be repeated in 2nd line for patients having long response (>3 years) to CIT in 1st line. For patients receiving CIT in first line having shorter responses, choice is between IBR until progression or 2 years VenR.

Table 14: Net cost per patient, VenG followed by IBR vs. 3 comparators with repeated CIT in 2nd line, with and without discounting at 4% p.a., DKK

Therapy sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->BR	-981,479	-767,885
BR->BR	-1,087,863	-865,731
FCR->FCR	-1,108,495	-888,665

For the group of patients where CIT can be repeated in 2nd line VenG has, as expected, substantially higher cost. Discounted costs over life expectancy are thus DKK 750.000-890.000 higher. Life expectancy for the patient group, where 1st line CIT is repeated, is however substantially lower and lost life years are estimated to range between 6 and 6.8 life years. The model also estimates quality adjusted life years (QALYs) and the incremental cost effectiveness ratio (ICER) ranges from [redacted] gained from offering VenG followed by IBR in 2nd line. ICERS below 1 GDP per QALY gained as in this case, is by all standards considered highly cost effective.

Table 15: Net cost per patient, VenG followed by IBR vs 4 comparators with VenR in 2nd line, with and without discounting at 4% p.a., DKK

Therapy sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->VenR	-450,297	-318,988
BR->VenR	-456,161	-319,710
FCR->VenR	-547,528	-412,004

For the group of patients where VenR is used in 2nd line, VenG followed by 2nd line IBR as expected have a higher cost. Discounted costs over life expectancy are thus DKK 320.000-415.000 higher. Life expectancy for the patient group, where 1st line CIT is used, is however lower and lost life years are estimated to range between 3.3 and 3.9 life years. The ICERs range from DKK [redacted] gained from offering VenG followed by IBR compared to CIT followed by VenR in 2nd line. ICERs below 1 GDP per QALY gained, as in this case, is by all standards considered highly cost effective. It is noted that the life years lost in this scenario is lost during 1st line CIT in line with the base case.

In the Medicines Council protocol, one question concerned whether venetoclax could be repeated in 2nd line. Little data exist on patients who have repeated venetoclax in later lines. However, assuming VenR could be offered in 2nd line with same efficacy as in non venetoclax experienced patients cost savings could be realized compared to using IBR in 2nd line.

Table 16: Net cost per patient, VenG followed by IBR vs. hypothetical VenG followed by VenR in 2nd line, with and without discounting at 4% p.a., DKK

Therapy sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
VenG->VenR	-423,877	-271,874

Discounted costs savings over life expectancy are estimated at DKK 271,874. Bearing in mind that efficacy is assumed to be the same as for non venetoclax experienced patients, this therapy option strictly dominates VenG followed by IBR in 2nd line.

Therapy cost BSC

The therapy cost of BSC has been assumed to be DKK 50,000 in the base case. To qualify the assumption and the estimates sensitivity to this assumption, it is assumed that 50% of patients reaching BSC will get allogenic stem cell transplantation. The 2020 DRG for allogenic stem cell transplantation is DKK 688,233 (DRG 26MP22) and the subsequent average cost for BSC is then assumed to be DKK 369,116.5 (50,000+688,233/2).

Table 17: Net cost per patient, VenG followed by IBR vs. 4 comparators, alternative costs assumed for BSC, with and without discounting at 4% p.a., DKK

BSC cost alternative

Treatment sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->IBR	974,760	631,884
BR->IBR	1,238,640	836,911
FCR->IBR	947,715	590,917
17p/TP53 population		
VenG->IBR	NA	NA
IBR->VenR	2,197,937	1,661,624

BSC cost base case

Treatment sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->IBR	1,003,621	654,563
BR->IBR	1,275,276	866,462
FCR->IBR	978,599	615,334
17p/TP53 population		
VenG->IBR	NA	NA
IBR->VenR	2,197,937	1,661,624

Table 17 shows that the effect of changing the cost of BSC is marginal on the estimated lifetime costs. For the del17p/TP53 population there is no effect of the cost of BSC as the OS and PFS curves are identical at the end of lifetime.

Prognosis in in terms of PFS and OS estimates from ITC

The HRs used in the base case are set to the point estimates if the ITC showed that they were significantly different [redacted] see Table 7). If this condition was not meet, the HRs were set to [redacted] Setting the non-significant HRs to their point estimates is performed in this sensitivity analysis.

Table 18: Sensitivity analysis HRs vs. base case HRs used to estimate the life-time costs of the therapy options analyzed (HR vs. VenG and in 2nd line vs. VenR)

Therapy option	GClb (6 cycles)*	FCR*	BR (1st line)*	BR (2nd Line)**	FCR (2nd line)***	IBR (2nd line)**	IBR (1st line, 17p)*	IBR (2nd line, 17p)**	BSC, non 17p	BSC, 17p	1st line vs 2nd line, non17p	1st line vs 2nd line, 17p
Hazard ratio PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Hazard ratio OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: *1st line estimates, AbbVie ITC **2nd line estimates, Chen et al 2019(5), ***2nd line FCR set to BR, BSC calibrated based on life-expectancy in the LYFO database, Non-significant HRs set to their point estimates are marked in bold font

Table 19: Net cost per patient, VenG followed by IBR vs. 4 comparators, alternative HRs assumed for GClb, FCR, BR and IBR, with and without discounting at 4% p.a., DKK

HRs alternative

Treatment sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->IBR	964,605	624,774
BR->IBR	1,072,197	717,358
FCR->IBR	536,889	299,404
17p/TP53 population		
VenG->IBR	NA	NA
IBR->VenR	2,902,276	2,152,401

HRs base case

Treatment sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->IBR	974,760	631,884
BR->IBR	1,238,640	836,911
FCR->IBR	947,715	590,917
17p/TP53 population		
VenG->IBR	NA	NA
IBR->VenR	2,197,937	1,661,624

As can be seen in table 19, the alternative HRs for OS that limits the life expectancy of all patients receiving CIT in 1st line, means that life-time costs are limited accordingly compared to the base case HRs. In the case of FCR, where the point estimate for OS is the lowest of the CIT options, the life-expectancy is limited the most and the cost effect is thus the highest.

For the del17/TP53 mutation population, setting the HRs based on the Mato et al(7) study means that PFS and OS are substantially higher than in the base case. The higher estimated incremental costs are thus explained by longer time spent in IBR therapy and additionally more patients surviving to receive VenR in 2nd line compared to the base case. The difference in life expectancy for this group is 1.12 undiscounted life years for patients starting therapy with IBR compared to VenG. The ICER is however [redacted] gained and is highly unlikely to be cost effective by any standard.

It should be mentioned that the ITC for VenG vs. IBR in the del 17p population based on the single arm, non-randomized, multicenter, retrospective cohort study by Mato et al(7) included 108 and 103 patients for PFS and OS respectively that were compared naïve to 25 patients in the CLL14 study. [redacted].

Prognosis in 2nd line vs 1st line

The 2nd line OS and PFS curves of the model are based on the 1st line OS and PFS for VenG. In the base case 2nd line OS and PFS was assumed to relate to 1st line OS and PFS with HR = [redacted] for the general CLL patient population without del17p/TP53 and HR = [redacted] for the subpopulation with del17p/TP53 mutation.

In this sensitivity analysis both OS and PFS in 2nd line were estimated using HR = [redacted] CLL patients with or without del17p/TP53 mutation.

Table 18: Same OS and PFS in 2nd line as in 1st line, with and without discounting at 4% p.a., DKK

HR = [redacted]

Treatment sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->IBR	1,887,107	1,161,952
BR->IBR	2,399,361	1,528,349
FCR->IBR	1,924,611	1,161,789
17p/TP53 population		
VenG->IBR	NA	NA
IBR->VenR	2,130,507	1,618,567

HR for 2nd line at [redacted]

Treatment sequence	Total cost	Total cost, discounted
Non 17p/TP53 population		
VenG->IBR	NA	NA
GClb6->IBR	974,760	631,884
BR->IBR	1,238,640	836,911
FCR->IBR	947,715	590,917
17p/TP53 population		
VenG->IBR	NA	NA
IBR->VenR	2,197,937	1,661,624

For the non del17p/TP53 mutation population with CLL, the additional survival in 2nd line means that substantially more costs are incurred in 2nd and 3rd line and that the total lifetime cost doubles. In the del17p/TP53 population where the alternative is VenR in 2nd line the time spent in 3rd line is minimized as the therapy free time spent pre progression after stopping VenR is prolonged and costs are slightly lower than in the base case.

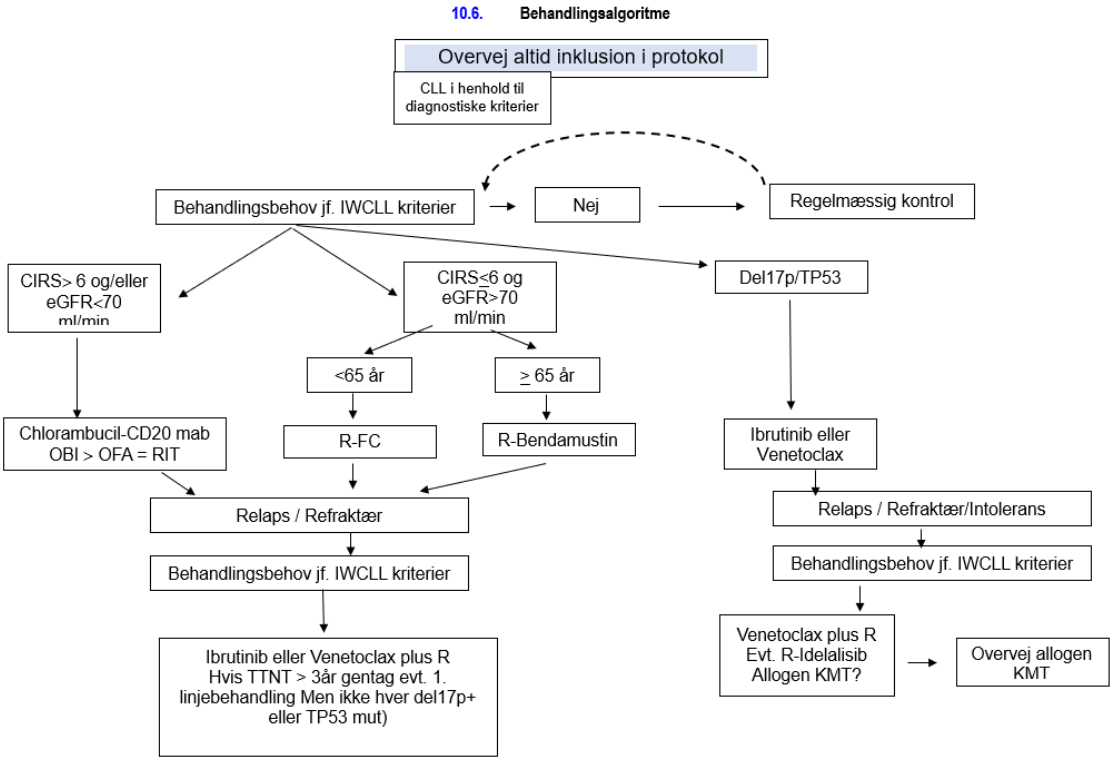
7 Budget impact analysis

Input and assumptions

The assumptions and inputs used in the BIM are equal to those in the patient cost analysis base case. This means that all inputs are identical to the inputs listed in tables 4-7, but that costs for patient time and transportation is omitted.

Clinical practice is rapidly changing in Denmark and the present therapy guideline from the CLL group of the Danish Lymphoma Group (November 2019 edition) already recommend IBR or VenG (or R) as 1st line therapy for CLL patients without del17p/TP53 and unmutated IGHV. To set proportions of patients treated with CIT in CLL without del17p/TP53 mutation thus relies on the previous (March 2019) edition of the therapy guidelines from the CLL group of the Danish Lymphoma Group.

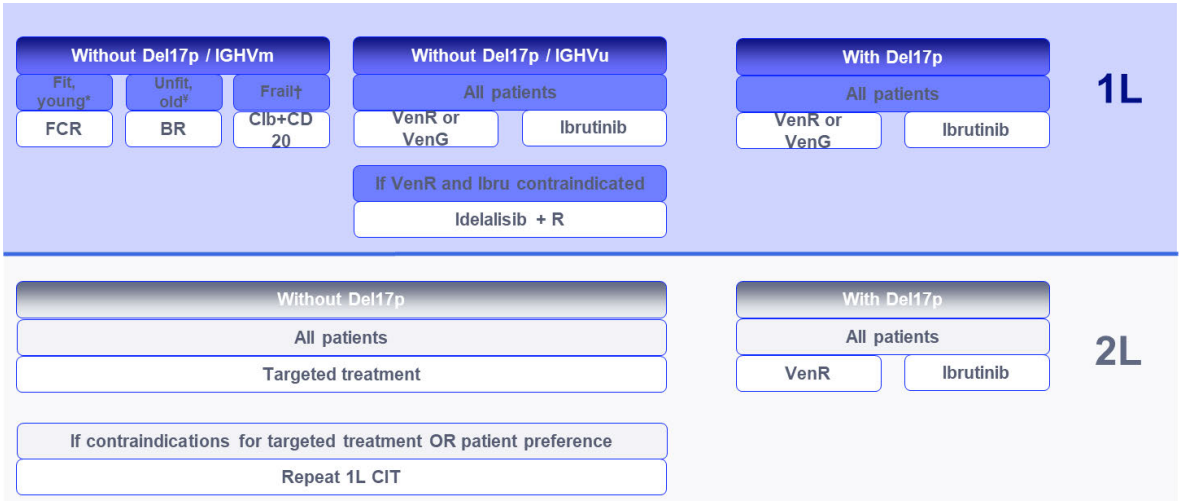
Figure 4: March 2019 therapy guideline from the CLL group of the Danish Lymphoma Group



The Medicines Council has in its protocol for the evaluation of VenG, provided estimates for the number of patients in 1st line CLL (150 in total, with 10% having del17p/TP53). According to the latest annual report from the Danish Lymphoma data base(6) the first quartile of the age distribution of included patients is 64.8 years and the proportion of patients younger than 65 is thus around 25%, whereas the median age is 72.5. Fit patients younger than 65 years are eligible for FCR and this proportion is set to 25%. The proportion of fit patients are set to 50% and BR is thus offered for 25% of patients, whereas unfit elderly patients offered GClb cover the residual 50%.

As earlier mentioned, the present therapy guideline from the CLL group of the Danish Lymphoma Group (November 2019 edition) already recommend IBR or VenG(or R) as 1st line therapy for CLL patients without del17p/TP53 and unmutated IGHV.

Figure 5: November 2019 therapy guideline from the CLL group of the Danish Lymphoma Group



* Eligible for standard dose CIT and below 65 years of age. ¥ Eligible for standard dose CIT and above 65 years of age OR younger than 65 ofyears with CIRS <6 and/or EGFR <70. † Not eligible for standard dose CIT (CIRS>6), but eligible for reduced treatment with Clb + anti CD20
Note: Based on Klinisk retningslinje Kronisk Lymfatisk Leukæmi (CLL), version 1.0
http://www.lymphoma.dk/wp-content/uploads/2019/11/DLG_CLL_Adm.Godk261119.pdf

In the protocol it is stated that 40% and 60% have mutated and unmutated IGHV status and subsequently the future market share of VenG is set to 60%. FCR is set to 25%, BR to 10% and Clb to 5% in the future scenario.

In the del17p/TP53 mutation subpopulation, VenG is set to 80% and IBR 20% in a future scenario where VenG is recommended, whereas a non-recommendation restricts the market to 100% IBR.

Table 19: Patient numbers and market shares

Market			Pt # present market shares								Pt # future market shares				
	Pt. # total	%	Year 1	Year 2	Year 3	Year 4	Year 5		Pt. # total	%	Year 1	Year 2	Year 3	Year 4	Year 5
Non 17p															
VenG->IBR	135	0%	0	0	0	0	0		135	60%	81.00	81.00	81.00	81.00	81.00
GClb6->IBR		50%	67.5	67.5	67.5	67.5	67.5			5%	6.75	6.75	6.75	6.75	6.75
BR->IBR		25%	33.75	33.75	33.75	33.75	33.75			10%	13.50	13.50	13.50	13.50	13.50
FCR->IBR		25%	33.75	33.75	33.75	33.75	33.75			25%	33.75	33.75	33.75	33.75	33.75
17p/TP53															
VenG->IBR	15	0%	0	0	0	0	0		15	80%	12.00	12.00	12.00	12.00	12.00
IBR->VenR		100%	15	15	15	15	15			20%	3.00	3.00	3.00	3.00	3.00
Sum	**150**		**150**	**150**	**150**	**150**	**150**		**150**		**150**	**150**	**150**	**150**	**150**

The budget impact only includes direct regional costs; drug-, hospital-, and adverse event costs.

8 Budget impact analysis results

Tabel 20: Budget without VenG, undiscounted, 1-5 years, DKK million

Market	Year 1	Year 2	Year 3	Year 4	Year 5
	Non 17p				
VenG->IBR	-	-	-	-	-
GClb6->IBR	18.7	25.4	36.5	50.0	64.4
BR->IBR	5.6	10.8	18.9	28.1	37.3
FCR->IBR	5.1	8.9	14.9	22.3	30.0
	17p/TP53				
VenG->IBR	-	-	-	-	-
IBR->VenR	7.9	14.6	20.2	24.5	27.9
Total	**37.4**	**59.7**	**90.5**	**124.9**	**159.5**

With present therapy options it is estimated that the budget for treating 1st line CLL patients will be 37.4 million DKK in the 1st year growing to 159.5 million DKK in the 5th year.

Tabel 21: Budget with VenG, undiscounted, 1-5 years, DKK million

Market	Year 1	Year 2	Year 3	Year 4	Year 5
	Non 17p				
VenG->IBR	56.8	58.9	62.1	66.3	71.3
GClb6->IBR	1.9	2.5	3.6	5.0	6.4
BR->IBR	2.2	4.3	7.6	11.3	14.9
FCR->IBR	5.1	8.9	14.9	22.3	30.0
	17p/TP53				
VenG->IBR	8.3	8.7	9.2	9.7	10.1
IBR->VenR	1.6	2.9	4.0	4.9	5.6
Total	**75.9**	**86.2**	**101.5**	**119.5**	**138.2**

With VenG having the market shares stated in table 18 it is estimated that the budget for treating 1st line CLL patients will be DKK 75.9 million in the 1st year growing to DKK 138.2 million in the 5th year.

Tabel 20: Incremental budget impact with VenG, undiscounted, 1-5 years, DKK million

Market	Year 1	Year 2	Year 3	Year 4	Year 5
	Non 17p				
VenG->IBR	56.8	58.9	62.1	66.3	71.3
GClb6->IBR	-16.8	-22.9	-32.8	-45.0	-57.9
BR->IBR	-3.4	-6.5	-11.4	-16.9	-22.4
FCR->IBR	0.0	0.0	0.0	0.0	0.0
	17p/TP53				
VenG->IBR	8.3	8.7	9.2	9.7	10.1
IBR->VenR	-6.3	-11.7	-16.2	-19.6	-22.3
Total	**38.6**	**26.5**	**11.0**	**-5.4**	**-21.3**

The incremental budget impact is positive and decreasing over time in the first 3 years. From the 4th year the incremental budget impact is negative and ending at an annual saving of DKK 21.3 million in the 5th year.

For reference the un-discounted incremental budget impact over 5 years is DKK 49.3 million (DKK 49.2 million discounted), whereas the un-discounted incremental budget impact over 10 years is a cost saving of DKK 235.2 million (DKK 156.2 million discounted).

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Annex 1: Adverse events costs

Cited from VenG model technical document(8):

"To capture the most relevant adverse events for both treatment arms and based on the CSR read out presentations, the adverse events were split into serious adverse events and grade 3-4 adverse events with at Least 2% Difference in Rate between Treatment Arms.

Neutropenia, Febrile neutropenia, Pneumonia, Sepsis, and thrombocytopenia fell under the serious adverse events and from the CSR the incidence of these events occurring within Grade 3-5 were included from the CLL14 trial. Whereas, for the remaining adverse events the incidence of these events occurring within Grade 3-4 were included from the CSR.

Adverse events are assumed to occur within the first cycle of the model, a simplification which is used in numerous cancer models. Adverse events are associated with one-off costs and negative health related quality of life (HRQoL) impacts.

The most recent publications (including NICE TAs) with the longest follow up data have been used to inform the adverse event probabilities for the external comparators. Table 1 provides the overview of the probabilities alongside the sources used to inform the table.

TABLE 1 ADVERSE EVENT PROBABILITIES

AE incidence	VEN+G	GClb	FCR	BR	Ibr
Asthenia	2.80%	0.50%	0.00%	0.00%	0.00%
Diarrhoea	3.80%	0.50%	0.00%	7.00%	4.00%
Dyspnoea	2.40%	0.50%	0.00%	0.00%	0.00%
Febrile neutropenia	5.20%	3.70%	0.00%	0.00%	1.00%
Infusion related reaction	9.00%	10.30%	0.00%	0.00%	0.00%
Leukopenia	2.40%	4.70%	24.00%	48.00 %	0.00%
Neutropenia	52.80%	47.70%	34.00%	59.00 %	12.00%
Pneumonia	5.70%	4.20%	0.00%	9.00%	0.00%
Sepsis	4.20%	1.40%	0.00%	1.00%	0.00%
Thrombocytopenia	13.70%	15.00%	7.00%	14.00 %	0.00%
Source	CLL14	CLL14	Hallek 2010	Eichhorst 2016	Barr 2018
N (Sample size)	212	214	404	279	136
Reference	Aug 2019 updated (Provided by UK affiliate)	Aug 2019 updated (Provided by UK affiliate)	(9)	(10)	(11)

"

It is noted that data for VenG and Gclb are referenced as CLL14 and were later published by Fisher et al 2019(1).

Costs estimates for the included adverse events were retrieved for Denmark. All DRG rates were found by entering the relevant diagnosis into the interactive DRG grouper for DkDRG: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/gruppering-drg/interaktiv-drg

Table A1.1: AE costs for Denmark, DKK

AE	Cost	Note
Asthenia	4,082.00	DRG 2020 Symptomer og fund, u. kompl. bidiag.
Diarrhoea	5,297.00	DRG 2020 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Dyspnoea	17,830.00	DRG 2020 Symptomer fra luftveje
Febrile neutopenia	37,603.00	DRG 2020: Granulo- og trombocytopeni
Infusion related reaction	36,312.00	DRG 2020 Andre infektioner eller parasitære sygdomme
Leukopenia	22,589.00	DRG 2020 Øvrige sygdomme i blod og bloddannende organer
Neutropenia	37,603.00	DRG 2020: Granulo- og trombocytopeni
Pneumonia	37,050.00	DRG 2020 Lungebetændelse og pleurit, pat. mindst 60 år
Sepsis	43,180.00	DRG 2020 Sepsis
Thrombocytopenia	25,365.00	DRG 2020 Koagulationsforstyrrelser

Costs per event times frequency resulted in the estimated AE costs per therapy option and were incurred in the cost analyses at the start of therapy.

Annex 2: Time to event modeling

Quotes from the Abbvie Global CEM model technical description (see annexed VenG model Technical report(8)) regarding fitted PFS and OS curves used in the simple model build for DK.

“

1.1.1 Assessing the proportional hazards assumption

Introduction

To maximize the predictive power of the CLL14 data, assumptions can be made around how various endpoints might be related to one another. The proportional hazards assumption allows one time-to-event curve to be described in terms of another, by assuming a (homogenous in time) proportional relationship between their underlying hazard functions (i.e. a hazard ratio). The key assumption is that the rate of change of hazards remains constant in time, both in the observed period and throughout the unobserved future. The validity of this assumption can be explored during the observed period, but the extent it remains valid throughout the predictive horizon remains uncertain.

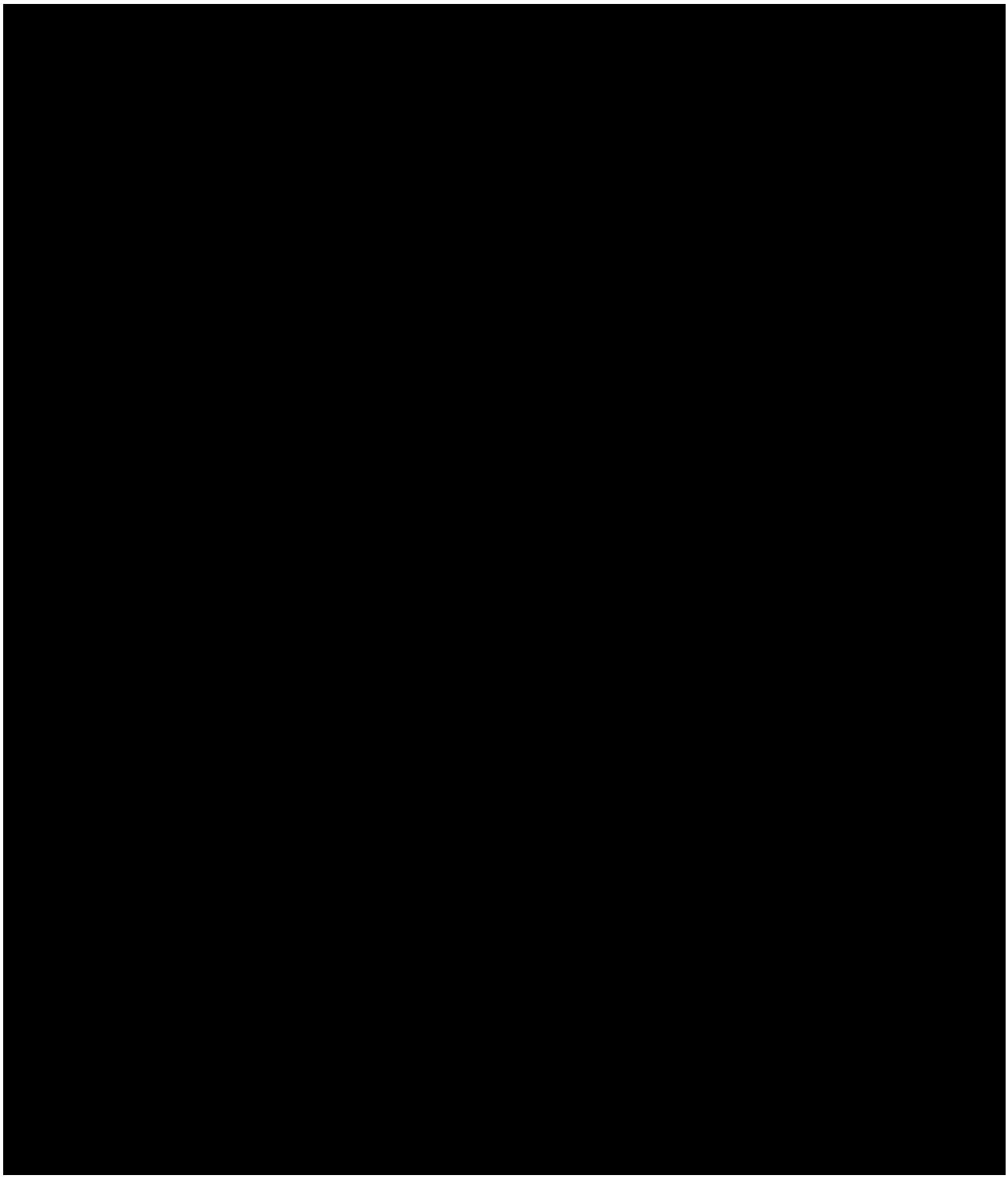
Exploring proportionality of hazards between treatments

The proportionality of hazards between the two treatment arms VEN+G and GClb was explored by fitting a cox proportional hazards model and by evaluating the Schoenfeld residuals. The proportionality of hazards for the two treatments was further assessed by visual inspection of the graph showing the logarithm of the estimated cumulative hazard function. Figure 1 presents the KM curves for OS and PFS (subfigures A and B) and a visual depiction of the assessment of proportional hazards assumption between VEN+G and GClb (subfigures C and D). Subfigures C and D present a plot of the scaled Schoenfeld residuals, along with a smoothed curve and the (logged) hazard ratio for reference. [redacted]

Contrary to the result of the significance test for PFS, the smoothed curve (Figure 1, subfigure C) depicts a violation of proportional hazards due to its ‘U’ shape. As the cox model evaluates the mean slope of this curve, the test for significance in this case can be misleading. The proportionality of hazards for VEN+G and GClb was further explored by visual inspection of the log cumulative hazards plot (Figure 2). [redacted]

For OS, the non-significant proportional hazards test is supported by the Schoenfeld residuals plot where the smoothed hazards curve is a straight line [redacted]
therefore these results were further validated with clinical experts firstly within the ad-board discussion

((See Section 2.10) and also independently with clinical and health economic experts who validated the results of the OS curve [redacted]



[redacted]

”

1.2 Time to event modeling methodology

[redacted]

The individual and dependent models were fitted to the following distributions: exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, generalized-gamma[1]. Additionally, spline 1-3 knot models based on the hazards, odds and probit (or normal) scale were also fitted to the observed time to event data. These extrapolations are presented in appendix 12.6. The goodness of fit for the models were estimated based on model fit statistics (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)), visual fit following the recommendations in the NICE DSU technical support document 14,[34] and clinical plausibility of the long-term extrapolations.

Both the AIC and BIC assess goodness of fit using a loglikelihood function. While the AIC penalizes models only for additional and potentially inefficient parameters, the BIC also considers the sample size (number of observations). Lower AIC and BIC values indicate a better statistical fit.

$$AIC = -2 * loglikelihood + 2 * number\ of\ estimated\ parameters$$

$$BIC = -2 * loglikelihood + \ln(\text{number of observations}) * (number\ of\ estimated\ parameters)$$

To assess the clinical plausibility and external validity, the landmark survival values were discussed with clinical experts and cross-validated with external sources. (Please refer to Section 3.5.1 and Section 3.5.3 for more details.)Progression free survival

Base case model: Independent model Base case distribution: Log-logistic The base case model and distribution for PFS was chosen based on external clinical validation from clinical experts since the results from the internal validity assessment were underpowered. Please refer to Section 2.10.3 and Appendix 12.4 for further details on the clinical validations

1.2.1 [redacted]

[redacted]

[redacted]

$$S(t) = del$$

The exponential and Gompertz models are parameterised as proportional hazards models, whereas the remaining models have an accelerated failure time interpretation. In this case, covariate effects are not interpreted on the hazard scale, but on the time/survival scale. Therefore, the covariate influences the time it takes to reach some arbitrary level of cumulative hazard (i.e. time moves slower or quicker towards the endpoint considered).

Figure 4 provides the extrapolations for PFS for VEN+G and GClb over a 30-year (lifetime) time horizon. Table 123 and Table 124 in appendix 12.6.1 provide the accompanying coefficient estimates. The model fit statistics (AIC and BIC) are presented in Table 2. The exponential model provides the best statistical fit for the VEN+G extrapolations. The log-logistic model provides the best statistical fit for the GClb extrapolations.

The 5-year, 10-year and 20-year landmark survival estimates from the individual modelling of PFS are presented in Table 3. [redacted]

[redacted]

Finally, the hazard functions are explored. Figure 110 in appendix 12.6.1 [redacted]

In conclusion, based on clinical expert advice, the log-logistic model provides the most plausible long-term PFS estimates for GClb. Considering the fact that NICE recommends the same parametric distributions when using independent models,[34] the large(r) degree of uncertainty surrounding long-term PFS for VEN+G compared to GClb, the log-logistic distribution is recommended as the base case. Alternative choices for distributions for PFS will be explored in the scenario analyses.

Time (years)

[redacted]

[redacted]

[redacted]	[redacted]				[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Time (years)

[redacted]

[redacted]

[redacted]	[redacted]				[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.3 Overall survival (all cause death)

1.3.1 Dependent modeling of OS for VEN+G and GClb from CLL14

The dependent model was fitted to OS separately and includes treatment as a covariate (named *tx* in the specification). The model also incorporates the differential effect of del17p/TP53 mutation on the endpoints (named *del* in the specification).

$$S(t) = del + tx$$

Figure 6 presents the estimated OS extrapolations for VEN+G and GClb over a 30-year time horizon. [redacted]

[redacted] However, due to the unrealistic nature of the hazards (Figure 120) for the log-normal model (decreasing over time), it is not suitable to choose this as the base case for the economic model. Various other approaches to determine the most appropriate model were explored and are detailed in the sections below.

Comparison of OS landmark survival from CLL14 with real world evidence

A targeted review was conducted to identify publications providing long term OS estimates for the 1L CLL population. From the targeted review a number of studies were identified which included long-term OS estimates. The study from Brenner et al. (2008)[36] indicates that the absolute survival over 10 years in the 1L CLL population in the US was between 28%-35%, and relative survival estimates ranged between 46%-55%. More recent studies by Pulte et al. (2016),[37] and Bista et al. (2017)[38] indicate the relative OS estimates for 10 years correspond to between 51%-64%. Shvidel et al. (2011)[39] estimated the actuarial long-term survival at 53% over 10 years, and 25% over 20 years. Additionally, for the del17p population for the comparison versus Ibrutinib real world evidence from a retrospective cohort study was identified Mato et al (2018) which was assessed by the NMA team following which a naïve comparison was conducted in the absence recent and relevant evidence in this patient population[25].

The 5-year, 10-year and 20-year survival estimates for CLL14 derived using the dependent modeling approach are presented in Table 7. The long-term survival estimates modeled are similar to the *relative* survival estimates based on real world data instead of the *absolute* long-term survival. However, this can be explained by the fact that these sources are using data from a treatment era where efficacious treatment options were lacking. To explore the impact of relaxing the proportional hazards assumption, individual modeling will be explored in section 0.

Time (years)

[redacted]

[redacted]

1.3.2 Individual modeling of OS for VEN+G and GClb

The observed data for VEN+G and GClb were parametrized individually without assuming proportionality between VEN+G and GClb or OS and PFS (individual model). However, as d17p deletion or TP53 mutation is an important prognostic factor, it was included as a covariate in the model. The inclusion of the covariate del17p/TP53 mutation (named *del* in the specification) allows for the scale parameter to be varied in the estimation of OS.

$$S(t) = del$$

Figure 7 provides the extrapolations for OS for VEN+G and GClb over a 30-year (lifetime) time horizon.

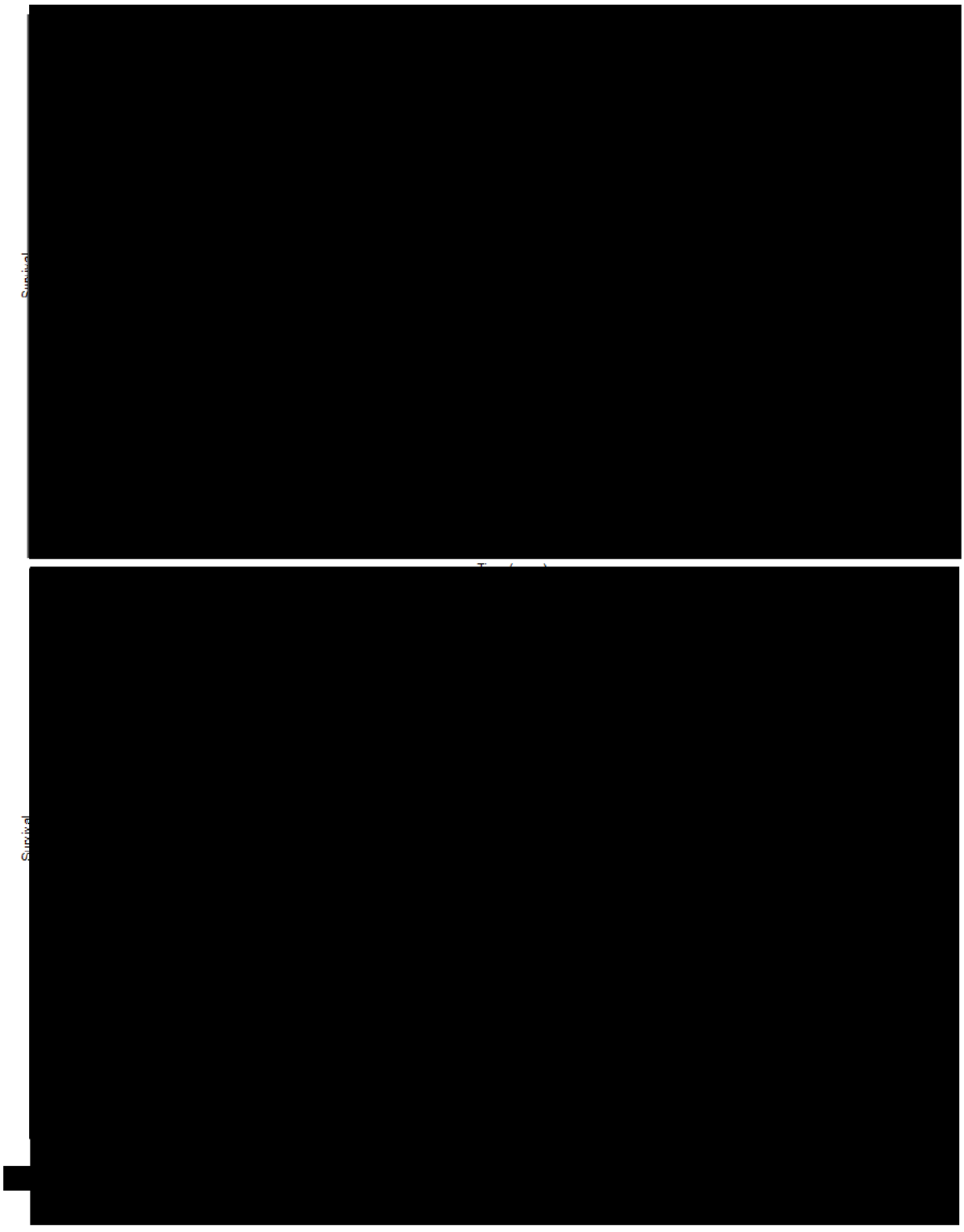
Table 9 provides the accompanying AIC and BIC for the models fit statistics. The exponential model provides the best statistical fit for VEN+G and GClb extrapolations. The accompanying coefficients for the model are presented in appendix 12.6.

[redacted]

[redacted]

[redacted]

[redacted] Thus, other methods for the extrapolation of OS beyond the observed time have been assessed to identify a more conservative approach to modelling OS over time. These are presented in section 3.5.3.



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Medicinrådet

Medicinrådets protokol for vurdering af venetoclax i kombination med obinutuzumab til behandling af tidligere ubehandlede patienter med kronisk lymfatisk leukæmi

Versionsnr.: 1.0

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 deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi 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 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 ansøgende virksomhed få besked.

Godkendt af Medicinrådet, 11. maj 2020
Dokumentnummer: 77455
Versionsnummer: 1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
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1 Begreber og forkortelser

CI	Konfidensinterval
CLL	Kronisk lymfatisk leukæmi
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
ITT	*Intention to treat*
iwCLL	*International Workshop on Chronic Lymphocytic Leukemia*
OR	*Odds ratio*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
SMD	*Standardized Mean Difference*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Abbvie, som ønsker, at Medicinrådet vurderer venetoclax i kombination med obinutuzumab til behandling af patienter med tidligere ubehandlet kronisk lymfatisk leukæmi. Vi modtog den foreløbige ansøgning den 24. januar 2020.

2.1 Kronisk lymfatisk leukæmi

Kronisk lymfatisk leukæmi er en hæmatologisk kræftsygdom, som opstår i kroppens B-lymfocytter og påvirker deres regulering af celledeling og celledød. Det fører til en ophobning af B-lymfocytter bl.a. i knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket. Symptomerne hos patienter med kronisk lymfatisk leukæmi er relaterede hertil og omfatter typisk hævede lymfeknuder, forstørret milt, blodmangel, træthed, uforklarlig feber, vægttab og øget infektionstendens.

Kronisk lymfatisk leukæmi (CLL) er den almindeligste leukæmi 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 i Danmark [2]. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark [3]. Medianalderen er ved diagnose 70 år, og dobbelt så mange mænd som kvinder får diagnosen [1,2].

CLL er ofte asymptomatisk på diagnosetidspunktet og kan blive opdaget tilfældigt efter en blodprøve. Diagnosen stilles ved konstatering af persisterende (vedvarende) lymfocytose, defineret som > 5 mia. monoklonale B-celler pr. liter blod i tre måneder eller derover. På diagnosetidspunktet foretages en vurdering af sygdomsstadie (baseret på sygdomsudbredelse, Binet-stadieinddeling) og sygdommens aggressivitet (risikoprofil på baggrund af cytogenetiske forandringer og *immunoglobulin heavy-chain variable region* (IGHV)-mutationsstatus). Både sygdomsstadie, patientens symptomer og risikoprofil har indflydelse på igangsættelse og valg af behandling, ligesom de har betydning for patienternes prognose. Kronisk lymfatisk leukæmi har ofte et 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 til > 12 år afhængig af sygdomsstadie og risikoprofil.

2.2 Venetoclax i kombination med obinutuzumab

Venetoclax hæmmer funktionen af Bcl-2, som er et protein, der modvirker programmeret celledød. Bcl-2 er overudtrykt i B-lymfocytter, når man har CLL. Når funktionen af Bcl-2 hæmmes, beskyttes cellerne ikke længere mod programmeret celledød, og de vil derfor dø. Derved vil antallet af B-cellelymfocytter falde, og tilstanden forbedres.

Obinutuzumab er et monoklonalt humant antistof rettet mod CD-20, som er udtrykt på overfladen af B-lymfocytter. Når antistoffet binder til B-lymfocytterne, vil kroppens immunforsvar aktiveres, og cellerne nedbrydes.

Lægemidlerne administreres som følger i serier a 28 dage

- 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).

Venetoclax har allerede markedsføringstilladelse i kombination med rituximab til behandling af patienter med CLL, der tidligere har modtaget mindst én behandling. Den behandling blev anbefalet som mulig standardbehandling af Medicinrådet i december 2019.

2.3 Nuværende behandling

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

Behandlingsstrategien afhænger af patientspecifikke faktorer (performancestatus, komorbiditet (cumulative illnes rating scale (CIRS)), alder, præferencer), sygdomskarakteristika (tumorbyrde, stadie, risikoprofil (karakteriseret ved FISH), 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, om de i 1. linje er kandidater til cytostatika i form af enten chlorambucil, fluradabin og cyclofosfamid eller bendamustin i kombination med et anit-CD20-antistof, eller hvorvidt de skal have targeteret behandling.

Patienter med deletion17p/p53-mutation er ikke følsomme for behandling med cytostatika og behandles i stedet med proteinkinasehæmmeren ibrutinib, og idelalisib i kombination med rituximab, når anden behandling ikke er egnet.

For patienter uden deletion17p/p53-mutation afgøres valget af cytostatika og anti-CD20-antistof af patientens alder, performancestatus og mængden af komorbiditet [4]. 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. Desuden har man god, langvarig dokumentation for effekt og bivirkninger ved de velkendte kemoterapier, mens viden om den langsigtede effekt af nyere behandlinger er sparsom. I takt med nye og mere målrettede behandlingsmuligheder er der dog påbegyndt en bevægelse væk fra anvendelse af cytostatika, blandt andet fordi cytostatika er forbundet med langvarig immundepletion.

Ved relaps behandles patienterne uanset deletion17p/p53-mutation med enten venetoclax i kombination med rituximab, som er et anti-CD20-antistof eller ibrutinib [4].

I nuværende dansk klinisk praksis skelnes der i behandlingsøjemed ikke imellem, hvorvidt patienterne har hypermuteret IGHV eller ej, selvom det er af betydning for patienternes prognose. Patienter med umuteret sygdom har en dårligere prognose end patienter med hypermuteret IGHV-status. 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 [5–7] . Denne ændring i behandlingspraksis er reflekteret i den seneste retningslinje for kronisk lymfatisk leukæmi, hvor tidligere ubehandlede patienter uden IGHV-mutation og uden del17p/p53-mutation anbefales behandlet med enten ibrutinib eller venetoclax i kombination med obinutuzumab. Aktuelt er det dog ikke muligt at behandle efter denne retningslinje, da det afventer EMA-godkendelser samt anbefaling fra Medicinrådet.

Der er ca. 150 patienter om året med behandlingsbehov i 1. linje [4], hvoraf ca. 90 % ikke har deletion17p/p53-mutation og behandles med cytostatika i kombination med et anti-CD20-antistof [8]. I denne patientgruppe forventes 40 % at have hypermuteret IGHV og 60 % at være umuteret (hhv. +/- IGHV-status). De resterende 10 % med deletion17p/p53-mutation behandles med ibrutinib.

Fagudvalgets angivelse af antallet af patienter i de forskellige grupper er baseret på estimater fra den landsdækkende LYFO database, viden om tid til første relaps og forekomsten af deletion17p/p53-mutation på forskellige tidspunkter i behandlingsforløbet [9–13].

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 defineret to kliniske spørgsmål, der retter sig mod henholdsvis patienter med eller uden deletion17p/p53-mutation.

3.1 Klinisk spørgsmål 1

Hvilken værdi har venetoclax i kombination med obinutuzumab sammenlignet med cytostatika i kombination med et anti-CD20-antistof 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
Venetoclax i kombination med obinutuzumab doseret som beskrevet i afsnit 2.2.

- 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 slut af cyklus 12).

Komparator
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^2 på dag 1 og 2
- Rituximab i.v. 375 mg/m^2 på dag 1 i første serie, herefter i.v. 500 mg/m^2 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^2 i.v. dag 1-3

Cyclofosfamid 250 mg/m^2 i.v. dag 1-3

Rituximab 375 mg/m^2 i.v. dag 1, 1. serie, serie 2-6: 500 mg/m^2

Anvendelsen af de tre komparatorer afhænger i dansk klinisk praksis af patienternes alder og komorbiditet. Hvis ikke der findes direkte sammenligninger med alle tre komparatorer, bedes ansøger vælge den eller de komparatorer, hvor der findes det bedste evidensgrundlag. Ansøger bedes argumentere for valget af komparator og inkludere en grundig beskrivelse af den eller de patientpopulationer, der indgår i den eller de valgte sammenligninger. Se i øvrigt afsnit 7. Andre overvejelser.

Fagudvalget vil udover den overordnede sammenligning se på subgruppeanalyser baseret på IGHV-status for at belyse, hvorvidt der er en differentieret effekt af venetoclax i kombination med obinutuzumab overfor kemoimmunoterapi. Se i øvrigt afsnit 7. Andre overvejelser.

Effektmål
De valgte effektmål står i tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har venetoclax i kombination med obinutuzumab sammenlignet med ibrutinib for patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation?

Population
Patienter med tidligere ubehandlet kronisk lymfatisk leukæmi med deletion17p/p53-mutation.

Intervention
Som i afsnit 3.1.

Komparator

- Ibrutinib p.o. 420 mg dagligt indtil progression.

Effektmål
De valgte effektmål står i tabel 1.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, den mindste klinisk relevante forskel (retningsgivende) samt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål	Vigtighed	Kategori	Måleenhed	Retningsgivende mindste klinisk relevante forskel
Overlevelse	*Kritisk*	*Dødelighed*	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid	5 %-point
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger**	Forskel i andel der opnår PFS efter 3 år eller længst muligt opfølgningstid	10 %-point
Bivirkninger	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel der oplever grad 3-4 uønskede hændelser (+ kvalitativ gennemgang)	10 %-point
Livskvalitet	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	EORTC QLQ-C30	10 point

* Eftersom PFS er et sammensat effektmål, der indeholder både progression og død, anvendes væsentlighedskriterierne for alvorlige symptomer og bivirkninger.

3.3.1 Overlevelse

Overlevelsesrate (OS-rate)
Det primære mål for behandling af CLL er at forbedre patientens overlevelse. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død, uanset årsag. Overlevelse opgøres typisk som en medianoverlevelse (overall survival, OS) 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. Overlevelsesraten ved 3 år er i omegnen af 80 % for patienter, der behandles i førstelinje [13]. Overlevelsen ønskes derfor opgjort som andelen af patienter, der er i live efter 3 år eller efter længst mulig opfølgningstid. For 3-årsoverlevelsesrate vurderer fagudvalget, at 5 %-point er en klinisk relevant forskel mellem grupperne.

I tilfælde hvor de ønskede overlevelsesdata ikke er tilgængelige, ønsker fagudvalget at ansøger supplerer med information om surrogateffektmålet PFS-rate. Hvis de ønskede overlevelsesdata 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.

Progressionsfri overlevelsesrate (PFS-rate)
Progressionsfri overlevelse er defineret som tiden fra randomisering til sygdomsprogression, jf. iwCLL guidelines [14]. 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, af den mindste klinisk relevante forskel for 3-års PFS-rate er 10 %-point.

3.4 Vigtige effektmål

3.4.1 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 [15]. 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 opgøre disse i den endelige ansøgning.

3.4.2 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 langt størstedelen af patienter (over 80 %) vil opleve en grad 3-4 uønskede hændelser i løbet af 3 år. Da fagudvalget ikke har kendskab til kliniske studier, der direkte sammenligner effekten af venetoclax i kombination med obinutuzumab 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

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor venetoclax i kombination med obinutuzumab er sammenlignet direkte med komparatorerne.

Medicinrådet har fundet følgende fuldtekstartikel, som indeholder en direkte sammenligning mellem venetoclax i kombination med obinutuzumab og den ene komparator, chlorambucil i kombination med obinutuzumab.

- Fischer et al. 2019. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 6;380(23):2225-2236.

Der er ikke tilstrækkeligt datagrundlag til en komplet besvarelse af de kliniske spørgsmål, da der mangler sammenligning med de to øvrige komparatorer.

Ansøger skal derfor undersøge, om der findes andre fuldtekstartikler, som indeholder de angivne mangler. Søgestrengen fremgår nedenfor.

Finder ansøger andre artikler med venetoclax i kombination med obinutuzumab, som indeholder de angivne mangler, skal virksomheden søge efter lignende artikler for komparatorerne. Ansøger skal på baggrund af

artiklerne lave en indirekte sammenligning til at besvare de(n) del(e) af det kliniske spørgsmål, som den direkte sammenligning ikke kan besvare.

I begge tilfælde skal ansøger derudover konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed og CENTRAL udarbejdet i samarbejde med informationsspecialist, kan ses i afsnit 12, bilag 1.

Virksomheden skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

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 skærmklip 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 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 ekskludere først 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 (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal ansøger anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5 Databehandling og -analyse

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 mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

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 (jævnfør 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 (jævnfør Appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise 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’- 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.
- Syntetisér 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 vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

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 vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Fagudvalget ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

Fagudvalget vil overveje, hvorvidt anvendelse af venetoclax i kombination med obinutuzumab i første linje udelukker anvendelse af kemoterapi i senere linjer, og hvorvidt dette er problematisk. Ansøger bedes i øvrigt bidrage med perspektiver herpå i deres endelige ansøgning.

Hvis der ikke er direkte evidens for alle komparatorer i klinisk spørgsmål 1, så bedes ansøger vælge den eller de komparatorer, hvor der findes det bedste evidensgrundlag. I det tilfælde skal ansøger argumentere for, hvorvidt effekten i de kliniske studier kan overføres til den samlede patientpopulation, der behandles med kemoterapi i første linje. Hvis evidensgrundlaget kun dækker en begrænset patientpopulation, vil fagudvalget vurdere, hvorvidt det er acceptabelt at ekstrapolere til en bredere patientpopulation.

For klinisk spørgsmål 1 vil fagudvalget se på separate effektopgørelser baseret på IGHV-status for at belyse, hvorvidt der er en differentieret effekt af venetoclax i kombination med obinutuzumab overfor kemoimmunoterapi. Ansøger bedes bidrage med separate effektopgørelser for patienter hhv. umuteret og hypermuteret IGHV-status for alle effektmål.

Fagudvalget ønsker, at ansøger redegør for, hvorfor venetoclax gives i kombination med rituximab i anden linje og med obinutuzumab i første linje. Ansøger bedes redegøre for, hvorvidt der forventes nogen forskel i den kliniske effekt ved tillæg af de to anti-CD20-antistoffer.

Ansøger bedes redegøre for, hvorvidt der er evidens for, at der kan genbehandles med venetoclax.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget vil derfor ikke tage stilling til en foreløbig placering af lægemidlet.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kronisk lymfatisk leukæmi (CLL)

Formand	**Indstillet af**
Robert Schou Pedersen Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
Medlemmer	**Udpeget af**
Thor Høyer Afdelingslæge	Region Nordjylland
Annika Rewes Afdelingslæge	Region Syddanmark
Rasmus Bo Dahl-Sørensen	Region Sjælland
Kan ikke opfylde Medicinrådets habilitetskrav	Region Hovedstaden
Stine Trolle Poulsen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Samuel Azuz Reservelæge	Dansk Selskab for Klinisk Farmakologi
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

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11 Versionslog

Version	Dato	Ændring
1.0	11. maj. 2020	Godkendt af Medicinrådet.

12 Bilag 1: Søgestrenge

Søgestrenge 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	venetoclax[nm] OR venetoclax[tiab] or Venclyxto*[tiab] or Venclexta*[tiab]	Søgetermer for intervention og komparatorer
10	obinutuzumab[nm] OR obinutuzumab[tiab] or Gazyva*[tiab] or afutuzumab[tiab]	
11	Chlorambucil[mh] OR chlorambucil[tiab] OR amboclorin*[tiab] OR chloraminophene[tiab] OR chlorbutin*[tiab] OR Leukeran*[tiab]	
12	Bendamustine Hydrochloride[mh] OR bendamustin*[tiab] OR Levact*[tiab] OR Treanda*[tiab]	
13	Rituximab[mh] OR rituximab[tiab] OR Rituxan*[tiab] OR Mabthera*[tiab]	
14	fludarabine[nm] OR fludarabine[tiab] OR Fludara*[tiab]	
15	Cyclophosphamide[mh] OR cyclophosphamide[tiab] OR cyclophosphan*[tiab] OR cytophosphan*[tiab] OR Cytoxan*[tiab] OR Endoxan*[tiab] OR Neosar*[tiab]	
16	R-FC[tiab] OR RFC[tiab]	
17	PCI 32765[nm] OR ibrutinib[tiab] OR Imbruvica*[tiab] OR PCI-32765[tiab] OR PCI32765[tiab]	
18	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 (der ekskluderes)
19	**(#8 AND #9 AND #10) NOT #18**	Kombination af indikation og intervention. **Kan screenes først**
20	(#8 AND #10 AND #11) NOT #18	Kombination af indikation og komparator 1
21	(#8 AND #12 AND #13) NOT #18	Kombination af indikation og komparator 2
22	(#8 AND #13 AND #14 AND #15) NOT #18	Kombination af indikation og komparator 3
23	(#8 AND #16) NOT #18	
24	(#8 AND #17)	Kombination af indikation og komparator (sp.2)

25	**(#20 OR #21 OR #22 OR #23 OR #24) NOT #19**	Komparatorer samlet, fratrukket resultater for intervention. **Kan screenes, hvis manglende data er fundet for intervention**

Feltkoder: mh = MeSH Term nm = Supplementary Concept/Substance tiab = title/abstract, inkl. forfatterkeywords pt = publication type

Søgestrenge 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	(venetoclax or Venclyxto* or Venclexta* or "ABT 199" or ABT199 or "GDC 0199" or GDC0199 or "RG 7601" or RG7601):ti,ab,kw	Søgetermer for intervention og komparatorer
#6	(obinutuzumab or Gazyva* or afutuzumab or "GA 101" or GA101 or "RO 5072759" or RO5072759):ti,ab,kw	
#7	(chlorambucil or chlorambucil or amboclorin or chloraminophene or chlorbutin or Leukeran*):ti,ab,kw	
#8	(bendamustin* or Levact* or Treanda*):ti,ab,kw	
#9	(rituximab or Rituxan* or Mabthera*):ti,ab,kw	
#10	(fludarabine or Fludara*):ti,ab,kw	
#11	(cyclophosphamide OR cyclophosphan* or cytophosphan* or Cytoxan* or Endoxan* or Neosar*):ti,ab,kw	
#12	(R-FC or RFC):ti,ab	
#13	(ibrutinib or Imbruvica* or "PCI 32765" or PCI32765):ti,ab,kw	
#14	("conference abstract" or review):pt	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
#15	(clinicaltrials.gov or trialsearch):so	
#16	NCT*:au	
#17	#14 or #15 or #16	
#18	(#4 and #5 and #6) not #17	Kombination af indikation og intervention. **Kan screenes først**
#19	(#4 and #6 and #7) not #17	Kombination af indikation og komparator 1
#20	(#4 and #8 and #9) not #17	Kombination af indikation og komparator 2

#21	((#4 and #9 and #10 and #11) or (#4 and #12)) not #17	Kombination af indikation og komparator 3
#22	(#4 and #13) not #17	Komparatorer samlet, fratrukket resultater for intervention. **Kan screenes, hvis manglende data er fundet for intervention**

Feltkoder: ti: title ab: abstract kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type