Medicinrådet

Bilag til direkte indplacering af acalabrutinib + venetoclax i Medicinrådets evidensgennemgang vedrørende lægemidler til kronisk lymfatisk leukæmi

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. acalabrutinib + venetoclax til kronisk lymfatisk leukæmi
2. Ansøgers endelige ansøgning vedr. acalabrutinib + venetoclax til kronisk lymfatisk leukæmi

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Medicin@amgros.dk
www.amgros.dk

12.01.2026

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.02.2026
Leverandør	AstraZeneca
Lægemiddel	Calquence (acalabrutinib)
Ansøgt indikation	Kombination med Venclyxto (venetoclax) med eller uden Gazyvaro (obinutuzumab) til behandling af voksne patienter med tidligere ubehandlet kronisk lymfatisk leukæmi (CLL).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse – direkte indplacering

Prisinformation

Amgros har følgende aftalepris på Calquence (acalabrutinib):

Tabel 1: Aftalepris.

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Calquence	100 mg (60 stk. tabletter)	40.994,30	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

Konkurrencesituationen

Leverandøren ønsker udelukkende at fokusere på Calquence + Venclyxto uden Gazyvaro jævnfør Medicinrådets vurderingsrapport.

Medicinrådets lægemiddelrekommandation for CLL-patienter har kombinationen Venclyxto + Gazyvaro som 1. valg og Imbruvica + Venclyxto som 2. valg. I nedenstående tabel 2 sammenlignes den årlige lægemiddeludgift for Calquence + Venclyxto uden Gazyvaro med de to anbefalede kombinationsbehandlinger.

Tabel 2: Lægemiddeludgifter per år

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (52 uger) (SAIP, DKK)
Calquence	100 mg, (60 stk.)	200 mg daglig, oral	[redacted]	[redacted]
Venclyxto	100 mg (112 stk.) Ved opstart 10 mg (14 stk.) og 50 mg (7 stk.)	Dagligt fra serie 3 til 14, herunder en 5-ugers optrapningsfase, bestående af 20 mg på dag 1-7, 50 mg på dag 8-14, 100 mg på dag 15-21, 200 mg på dag 22-28. Herefter 400 mg dagligt i serie 4 frem til afslutning af serie 14, oral	[redacted]	[redacted]
Calquence + Venclyxto				[redacted]
Venclyxto	100 mg (112 stk.) Ved opstart 10 mg (14 stk.) og 50 mg (7 stk.)	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 dagligt (kontinuerligt til afslutning af cyklus 12), oral	[redacted]	[redacted]

Gazyvaro	1000 mg (1 stk.)	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, i.v.	[redacted]	[redacted]
Venclyxto + Gazyvaro				[redacted]
Imbruvica	420 mg, (28 stk.)	420 mg daglig, oral	[redacted]	[redacted]
Venclyxto	100mg (112 stk.) Ved opstart 10 mg (14 stk.) og 50 mg (7 stk.)	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 dagligt (kontinuerligt til afslutning af cyklus 12), oral	[redacted]	[redacted]
Imbruvica + Venclyxto				[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Under vurdering	Link til status
Sverige	Delvist anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of acalabrutinib in combination with venetoclax by updating the CLL treatment guidelines

Contact information

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Tables and Figures

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
AV	acalabrutinib + venetoclax
AVO	acalabrutinib + venetoclax + obinutuzumab
Bcl-2	B-cell lymphoma 2
BCR	B-cell antigen receptor
BR	bendamustine + rituximab
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibito
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CIT	chemoimmunotherapy
CLL	chronic lymphocytic leukaemia
CLL-IPI	Chronic Lymphocytic Leukaemia International Prognostic Index
CO	chlorambucil + obinutuzumab
del17	deletion of the short arm of chromosome 17
ECOG-PS	Eastern Cooperative Oncology Group performance status
ESMO	European Society for Medical Oncology
FAS	full analysis set
FCR	fludarabine + cyclophosphamide + rituximab
HR	hazard ratio
HTA	health technology assessment
IGHV	immunoglobulin heavy-chain variable region gene
IPD	individual patient data
IRC	Independent Review Committee-assessed

IQR	interquartile range
ITC	indirect treatment comparison
ITT	intention-to-treat
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
IV	ibrutinib + venetoclax
KM	Kaplan-Meier
MAIC	matching-adjusted indirect comparison
NC	not calculable
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PFS	progression-free survival
PFS-INV	Progression-Free Survival (investigator assessed)
PFS-IRC	Progression-Free Survival (Independent Review Committee-assessed)
PICOS	Population, Intervention, Comparators, Outcomes and Study (design)
QoL	Quality of Life
OS	Overall Survival
RCT	randomised controlled trial
RMST	restricted mean survival time
SAE	serious adverse event
SAT	single-arm trial
SAS	safety analysis set
SLL	small lymphocytic lymphoma
SLR	systematic literature review
STC	Simulated Treatment Comparison
TEAE	treatment-emergent adverse event
TP53	tumour protein p53 gene

TSD	Technical Support Document
VO	venetoclax + obinutuzumab
VOI	venetoclax + obinutuzumab + ibrutinib
VR	venetoclax + rituximab

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Calquence
Generic name	Acalabrutinib
Therapeutic indication as defined by EMA	Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
Marketing authorization holder in Denmark	AstraZeneca
ATC code	L01EL02
Combination therapy and/or co-medication	Combined with venetoclax
(Expected) Date of EC approval	2nd June, 2025
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No

Overview of the pharmaceutical

Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy. Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant. Calquence as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a(BTK)inhibitor.
Other indications that have been evaluated by the DMC (yes/no)	Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy.
Dispensing group	BEGR

Packaging – types, sizes/number of units and concentrations

Lægemiddel	Calquence
Varenummer	099916
Styrke	100 mg
Pakning	60 stk. (blister) filmovertrukne tabl.
Virksomt stof	Acalabrutinib

2. Summary table

[Provide the summary in the table below, maximum 2 pages.]

Summary	
Therapeutic indication relevant for the assessment	Calquence (acalabrutinib) in combination with venetoclax (AV) is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. Only an assessment of acalabrutinib + venetoclax (AV) is relevant for inclusion in the current treatment guidelines.(1)
Dosage regiment and administration:	**Acalabrutinib:** oral 100 mg twice daily every 12 hours starting at cycle 1, fixed duration 14 cycles. **Venetoclax:** oral (capsule or tablet), once daily. From cycle 3, 5-week ramp-up with doses of 20 mg, 50 mg, 100 mg, 200 mg, followed by 400 mg as a fixed daily dose until end of cycle 14. **Cycle length: 28 days.**
Choice of comparators	ibrutinib + venetoclax (IV) and venetoclax + obinutuzumab (VO)
Most important efficacy endpoints (Difference/gain compared to comparator)	Overall survival (OS) and progression-free survival (PFS)
Most important serious adverse events for the intervention and comparator s	

Combination	Serious Adverse Event	N (%)	Cross reference
AV	COVID-19 pneumonia	17 (5.8%)	Table 12
IV	Infections	13 (12.3%)	Table 16
VO (CLL13):	Infusion related reaction	22 (20.4%)	Table 19
VO (CLL14)	Pneumonia	10 (4.7%)	Table 21

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Please refer to the DMC's treatment guidelines: https://filer.medicinraadet.dk/media/boohph5i/medicinradets-evidensgennemgang-vedr-kronisk-lymfatisk-leukaemi-vers-1-1.pdf

3.2 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Calquence in combination with venetoclax is indicated for the treatment of adult patients with previously untreated CLL.
Method of administration	**Acalabrutinib:** oral **Venetoclax:** oral
Dosing	**Acalabrutinib:** oral, 100 mg twice daily every 12 hours starting at cycle 1, fixed duration 14 cycles. **Venetoclax:** oral (capsule or tablet) once daily. From cycle 3, 5-week ramp-up with doses of 20 mg, 50 mg, 100 mg, 200 mg, followed by 400 mg as a fixed daily dose until end of cycle 14. **Cycle length: 28 days.**
Should the pharmaceutical be	No

<table>
<tr><th>Overview of intervention</th><th></th></tr>
<tr><td>administered with other medicines?</td><td></td></tr>
<tr><td>Treatment duration / criteria for end of treatment</td><td>Fixed duration of 14 cycles or start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity.</td></tr>
<tr><td>Necessary monitoring, both during administration and during the treatment period</td><td>No new monitoring required compared to existing practice</td></tr>
<tr><td>Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?</td><td>No new monitoring required compared to existing practice</td></tr>
<tr><td>Package size(s)</td><td>
<table>
<tr><td>Lægemiddel</td><td>Calquence</td></tr>
<tr><td>Varenummer</td><td>099916</td></tr>
<tr><td>Styrke</td><td>100 mg</td></tr>
<tr><td>Pakning</td><td>60 stk. (blister) filmovertrukne tabl.</td></tr>
<tr><td>Virksomt stof</td><td>Acalabrutinib</td></tr>
</table>
Venetoclax:
<table>
<tr><th>Pharmaceutical</th><th>VNR</th><th>Strength,mg</th><th>Size, stk</th></tr>
<tr><td>Venclyxto</td><td>115754</td><td>10</td><td>14</td></tr>
<tr><td>Venclyxto</td><td>537354</td><td>50</td><td>7</td></tr>
<tr><td>Venclyxto</td><td>538776</td><td>100</td><td>7</td></tr>
<tr><td>Venclyxto</td><td>528542</td><td>100</td><td>14</td></tr>
<tr><td>Venclyxto</td><td>532535</td><td>100</td><td>112</td></tr>
</table>
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Overview of intervention	

Mode of action

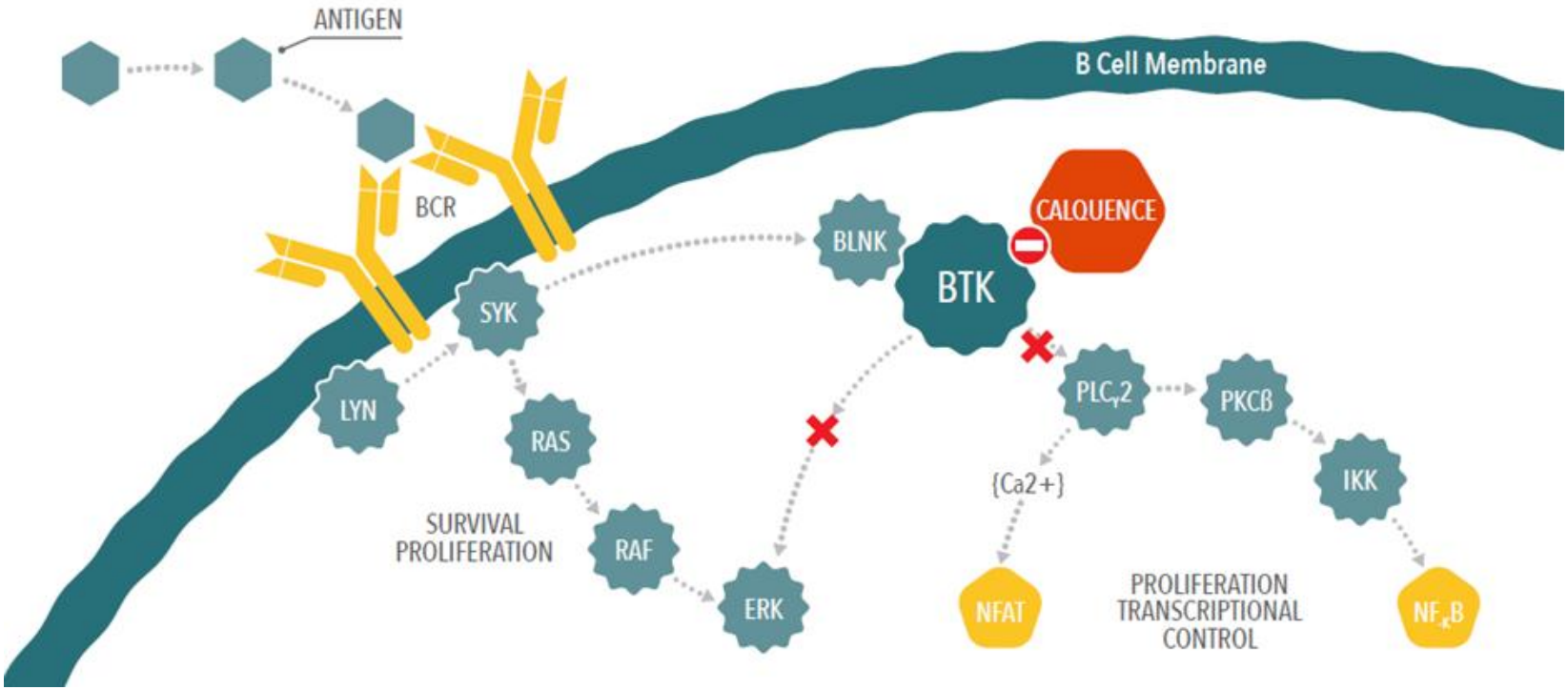
Acalabrutinib

Acalabrutinib is a highly selective, small-molecule BTK inhibitor (2). Bruton's tyrosine kinase (BTK) is an effector protein in the B-cell antigen receptor (BCR) signalling pathway. The enzyme transmits and intensifies signals that are vital for the survival and function of B-cells (3) Independent of antigen stimulation, amplified BCR pathway signalling may contribute to the development and progression of B-cell cancers, such as CLL Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue (Cys481) in the active site of BTK to block its action. This then prevents downstream signalling proteins CD86 and CD69 from being activated, which in turn inhibits the proliferation and tumour growth of malignant (abnormal) B-cells (

Figure 1).

Acalabrutinib has been shown to decrease both the phosphorylation of BTK and its total protein levels. Acalabrutinib also leads to T-cells levels returning to normal (T-cells being an essential part of the immune system that target and eliminate cancer cells), lower levels of chemo-attractants (e.g., the C-C motif chemokine ligand proteins CCL3 and CCL4), and the decreased expression of various cytokines and chemokines (e.g., tumour necrosis factor-α, interleukin-10, and interleukin-16). Together, these effects reduce the ability of CLL cells to migrate towards tissue-homing chemokines, thereby diminishing their capacity to survive . Acalabrutinib has also been linked to decreased expression of markers of T-cell exhaustion compared to baseline in patients undergoing treatment (4-6) .

Figure 1 Acalabrutinib: mechanism of action.



BCR, B-cell receptor; BLNK, B-cell linker; BTK, Bruton tyrosine kinase; Ca^{2+}, calcium ion; ERK, extracellular signal-regulated kinase; IKK, inhibitor of kappa-B kinase; LYN, Lck/Yes novel tyrosine kinase; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PKCβ, protein kinase C beta; PLCγ2, phospholipase-gamma-2; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; SYK, spleen tyrosine kinase. Source: Hendricks *et al.*, 2014.

Venetoclax

Venetoclax is a selective, orally bioavailable, small-molecule inhibitor of Bcl-2. In CLL cells, the Bcl-2 protein frequently is overexpressed on the outer membrane of mitochondria, where it blocks the programmed cell death (apoptosis) of the CLL tumour cells. This promotes their survival as the abnormal B-cells become resistant to chemotherapeutic agents. Venetoclax binds directly to the Bcl-2 protein, thereby displacing pro-apoptotic proteins (e.g., BCL-2 interacting mediator of cell death) to restore apoptosis. This in turn induces permeabilization (i.e., a "puncturing") of the mitochondrial outer membrane to release key molecules involved in apoptosis.(7)

3.2.1 The intervention (acalabrutinib + venetoclax) in Danish clinical practice

The intervention (AV) is expected to be used in patients included in "Anvend" across clinical questions 1–3 (Section 5) in the DMC CLL treatment guidelines.(1) We consider it appropriate to assess the combination as first-line treatment for all patients with CLL, including those with the del17p/*TP53* mutation. This is consistent with the EMA indication that was also considered to be appropriate by the specialized committee for the IV combination according to protocol deviation 4.9:

"Protokolafvigelse 4.9 fra behandlingsvejledningen for KLL(1):
"Medicinrådet har valgt at inkludere interventionen ibru + ven i klinisk spørgsmål 1 og ikke udelukkende for klinisk spørgsmål 2 og 3. Virksomheden, der markedsfører ibru, har under udarbejdelse af protokollen anmodet om, at kombinationen ibru + ven også vurderes til patienter med del17p/TP-53-mutation (klinisk spørgsmål 1). Det er fagudvalgets opfattelse, at det for komplethedens skyld er hensigtsmæssigt at få vurderet kombinationen som førstelinjebehandling til alle patienter med CLL, herunder patienter med del17p/TP-53-mutation, hvilket også er i overenstemmelse med EMAs indikation."(1)

4. Overview of literature

Since the treatment guidelines include a network meta-analysis (NMA), a systematic literature review (SLR) is not presented here.

Comparisons for AV vs. VO and AV vs. IV were made based on the studies already used in the DMC treatment guidelines. Unless otherwise stated, the latest data cuts published after the development of the treatment guidelines have been used. The clinical trials and publications are summarized in Table 1.

Table 1 Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
AMPLIFY NCT 03836261(8) Brown *et al*., 2025. Fixed-duration acalabrutinib combinations in untreated chronic lymphocytic leukemia. N Eng J Med 392: 748–762.	Randomized, global, multicentre, open-label, Phase 3	Treatment (from randomization until study drug discontinuation) and follow-up phase.	**Start (actual)** 25/02/25 **Primary completion (estimated)** 31/01/27 **Completion (estimated)** 31/01/27	• Men and women aged ≥18 years. • CLL diagnosis meeting published diagnostic criteria • Active disease requiring treatment according to iwCLL criteria. • Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–2. • Highly effective birth control used throughout the study.	AV	FCR/ BR	1–3	**Data cut-off: 30/04/24** Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in Arm C (FCR/BR). Median duration of follow-up after end of treatment was 28.3 months in Arm A (AV). **Primary Endpoint** • Independent Review Committee-assessed Progression-Free Survival (IRC-PFS) of AV vs. FCR/BR.

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
	study							**Secondary Endpoints** • Overall Survival (OS). • Safety.
CLL13 NCT:02950051(9-11) Eichhorst *et al*., 2023. First-line venetoclax combinations in chronic lymphocytic leukemia. N Eng J Med 388: 1739–1754. Fürstenau *et al*., 2024. First-line venetoclax combinations versus	Open-label, Phase 3, randomized controlled trial (RCT)	Treatment (from randomization until study drug discontinuation) and follow-up phase.	**Start (actual)** 13/12/16 **Primary completion (actual)** 29/02/24 **Completion (actual)** 29/02/24	• Aged ≥18 years. • Documented CLL requiring treatment according to IWCLL criteria. • ECOG-PS 0–2. • Life expectancy ≥6 months. • Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements. • Adequate bone marrow function indicated by platelet count >30 x10^9/l (unless directly attributable to CLL infiltration of	VO	FCR/ BR	1-3	Median follow-up50.7 months [interquartile range (IQR) 44.6–57.9] **Primary endpoint** Progression-free survival (PFS) for the comparison of GIVe vs. SCIT. **Secondary endpoints** • OS. • Safety parameters: type, frequency, and severity of adverse events (AEs).

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 25: 744–759. Fürstenau *et al.*, 2024. Patient-Reported Quality of Life Outcomes with Venetoclax-Based First-Line Combinations in CLL: An Analysis				the bone marrow, proven by bone marrow biopsy). • Creatinine clearance ≥70 ml/min directly measured with 24 hr-urine collection or calculated according to the modified formula of Cockcroft and Gault: GFR ≈ [(140 – age) x bodyweight) / (72 x creatinine) for men, for women x 0.85)]. Clearance calculation was not necessary for patients with creatinine values within normal. Dehydrated patients with an estimated creatinine clearance <70 ml/min may be eligible if a repeat estimate after adequate hydration was >70 ml/min. • Adequate liver function (indicated by a total bilirubin ≤2 x, AST/ALT				

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
from the Phase 3 GAIA/CLL13 Trial. Blood 144: 3238.				≤2.5 x the institutional ULN value) unless directly attributable to the CLL or to Gilbert's Syndrome. • Negative serological testing for hepatitis B (HBsAg negative and anti-HBc negative; patients positive for anti-HBc included if PCR for HBV DNA was negative and HBV-DNA PCR was performed every month until 12 months after last treatment cycle), negative testing for hepatitis C RNA within 6 weeks prior to registration.				
CLL14 NCT02242942(12-16) Al-Sawaf *et al.*, 2020. Venetoclax plus obinutuzumab	Open-label, Phase 3 RCT	Treatment (from randomization until study drug discontinuation) and	**Start (actual)** 31/12/14	• Documented, previously untreated CLL and requiring treatment according to the iwCLL criteria. • Life expectancy >6 months.	VO	CO	1–3	Median follow-up 76.4 months (IQR: 52.5–80.5). **Primary endpoint** • Progression-Free Survival (investigator assessed; PFS-INV)

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 21: 1188–1200. Fischer *et al.*, 2019. Venetoclax and obinutuzumab in patients with CLL	follow-up phase.	**Primary completion (actual)** 17/08/18 **Completion (estimated)** 31/08/25	• Total Cumulative Illness Rating Scale (CIRS score) >6. • Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as per protocol, unless cytopenia was due to bone marrow involvement of CLL. • Adequate liver function. • Highly effective contraceptive methods used, as per protocol.				based on iwCLL criteria; measured from baseline until disease progression or death (up to ~3.75 years). **Secondary endpoints** • OS: time from randomization to death (up to ~5 years). • Incidence of AEs by NCI CTCAE v4.0: 28 days post last GDC-0199 or 90 days post last dose of obinutuzumab, whichever was longer.

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
and coexisting conditions. N Eng J Med 380: 2225–2236. Al-Sawaf *et al.*, 2021. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study. JCO 39: 4049–4060. Al-Sawaf *et al.*, 2023. Transcriptomic								• Incidence of severe adverse events (SAEs): up to 5 years.

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. Nature Comm. 14: 2147.								
Al-Sawaf *et al.*, 2024. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase								

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
3 CLL14 study. Blood 144: 1924–1935								
GLOW NCT03462719(17-21) Kater *et al.*, 2022. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities.	Open-label, Phase 3 RCT	Treatment (from randomization until study drug discontinuation) and follow-up phase.	**Start (actual)** 17/04/18 **Primary completion (actual)** 26/02/21 **Completion**	• Adults aged ≥65 years or 18–64 years with ≥1 of the following: (i) CIRS score >6; (ii) estimated creatinine clearance <70 mL/min using Cockcroft-Gault equation. • Diagnosis of CLL or small lymphocytic lymphoma and active disease requiring treatment according to IWCLL criteria. • ECOG-PS ≤2.	IV	CO	1–3	Median follow-up: 64 months. **Primary endpoint** • PFS: time from randomization to disease progression or death, whichever occurred first, up to ~6 years (progression

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
NEJM Evid. 1: EVIDoa2200006. Munir *et al.*, 2023. Impact of minimal residual disease on progression-free survival outcomes after fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in the GLOW study. JCO 41: 3689–3699. Niemann *et al.*, 2023. Fixed-duration ibrutinib–venetoclax versus chlorambucil–			**(estimated)** 05/04/29	• Measurable nodal disease (by computed tomography) defined as at least one lymph node >1.5 cm in longest diameter.				based on IWCLL 2008 guidelines). **Secondary endpoints** • OS: time from randomization to death from any cause, over up to 4 years and 10 months. • Safety.

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 24: 1423–1433.								
Moreno *et al*., 2023. First-line fixed-duration ibrutinib plus venetoclax (Ibr+ Ven) versus chlorambucil plus obinutuzumab (Clb+ O): 55-month								

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
follow-up from the Glow Study. Blood 142: 634.								
Niemann et al., 2024. First-line Ibrutinib plus Venetoclax vs chlorambucil plus obinutuzumab in elderly or comorbid patients (pts) with chronic lymphocytic leukemia (CLL): glow study 64-month follow-up (FU) and adverse event (AE)-free progression-free survival (PFS)								

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period

analysis. Blood
144: 1871.

* If there are several publications connected to a trial, include all publications used.

5. Clinical question 1-3

This application addresses three clinical questions from the CLL treatment guidelines(1):

1. Klinisk spørgsmål 1: patienter med del17p/*TP53* mutation.
2. Klinisk spørgsmål 2: patienter uden del17p/*TP53*mutation og med umuteret *IGHV*.
3. Klinisk spørgsmål 3: patienter uden del17p/*TP53*mutation og med muteret *IGHV*.

As already stated in Section 3.2.2, we consider it appropriate to assess the AV combination as first-line treatment for all patients with CLL, including those with the del17p/*TP53* mutation, in line with both the EMA indication and as supported by the specialized committee for the IV combination (protocol deviation 4.9).

Protokolafvigelse 4.9 fra behandlingsvejledningen for KLL:
"Medicinrådet har valgt at inkludere interventionen ibru + ven i klinisk spørgsmål 1 og ikke udelukkende for klinisk spørgsmål 2 og 3. Virksomheden, der markedsfører ibru, har under udarbejdelse af protokollen anmodet om, at kombinationen ibru + ven også vurderes til patienter med del17p/TP-53-mutation (klinisk spørgsmål 1). Det er fagudvalgets opfattelse, at det for komplethedens skyld er hensigtsmæssigt at få vurderet kombinationen som førstelinjebehandling til alle patienter med CLL, herunder patienter med del17p/TP-53-mutation, hvilket også er i overenstemmelse med EMAs indikation"(1)

The available data only allowed for indirect treatment comparison (ITC) analyses of the intention-to-treat (ITT) populations from studies included here. Thus, the results could not be stratified by *IGHV* mutation status. Consequently, the ITC results apply to all three clinical questions considered here.

The ITC was conducted between AMPLIFY and three pivotal comparator trials GLOW (IV), CLL13 (VO), and CLL14 (VO) in previously untreated CLL patients. At almost 5 years of follow-up, the ITCs showed no statistically significant differences in treatment efficacy as regards OS and PFS, and significant reduction in adverse events (≥ grade 3) and serious adverse events. The comparison is based on the same endpoints used in the CLL guideline(1) (Table 2). Quality of Life (QoL) is reported for each trial but was not otherwise compared here. We refer to the DMC treatment guidelines for CLL for the reporting and comparison of QoL results for IV and VO.(1)

Table 2 Endpoints from the DMC CLL guideline

Outcome Measure	Importance	Unit of Measurement	Minimum Clinically Relevant Difference	Result in comparisons to AMPLIFY
Overall survival	Critical	Difference in survival rate at 3 years or longest follow-up	5 percentage points	No significant difference
Progression-free survival	Important	Difference in PFS rate after 3 years or longest follow-up	10 percentage points	No significant difference
Proportion of patients experiencing ≥ grade 3 adverse events	Important	Adverse events	10 percentage points	20% - 30% reduction for AMPLIFY
Review of serious adverse events	Important	Qualitative review	–	20% - 25% reductions for AMPLIFY
Quality of life	Important	Validated generic measure (e.g., EORTC QLQC30)	0.05 (scale 0–1) or 5 points (scale 0-100); alternatively 0.5 SMD	NA

5.1 Efficacy of AV compared to VO and IV in patients with CLL and unmutated- and mutated-*IGHV*

5.1.1 Relevant studies

All relevant studies (AMPLIFY, GLOW, CLL13, and CLL14) are summarised in Table 1.

5.1.2 Comparability of patients across AMPLIFY and the key comparator studies

The available/reported baseline characteristics for AMPLIFY and the key comparator studies are shown in Table 3. Median patient age was higher in CLL14 and GLOW (~70 years) vs. AMPLIFY. The proportion of patients aged ≥65 years ranged from 27% in the AMPLIFY study to 85% in GLOW. Across all four studies, 56% to 75% of patients were male, whilst 87% to 100% had an ECOG-PS score of 0 or 1. The proportion of patients with advanced disease (i.e., Rai stage III–IV or Binet stage C) ranged from 28% to 57%. The baseline CIRS score was influenced by the study inclusion criteria; almost no patients had a high comorbidity burden (CIRS >6) in the AMPLIFY and CLL13 studies in contrast to CLL14 (86%) and GLOW (70%). Moreover, no patients in AMPLIFY and CLL13 expressed the del(17p)/*TP53* mutation due to exclusion criteria vs. 7% to 13% of patients in CLL14 and GLOW.

In summary, the distribution of most characteristics in the comparator studies were similar to those of the AMPLIFY study except for age, creatinine clearance, and the CIRS score. These were notably different in the CLL14 and GLOW studies, where the patients with CLL patients were older, sicker, and less fit than in AMPLIFY.

5.1.3 Comparability of patients in AMPLIFY with Danish patients eligible for treatment

The patient population in the AMPLIFY study is broadly comparable to Danish patients with CLL who are eligible for treatment. Overall, the populations are similar. There is, however, a notable difference in median age; that of AMPLIFY participants was 61 years compared to just over 70 years for Danish patients at diagnosis according to Danish CLL annual reports (22-24). Nevertheless, the AMPLIFY study did include 232 (26.8%) patients aged >65 years (25). The gender distribution in AMPLIFY was comparable to that of the Danish CLL population (64.5% vs. 66.6% (22, 23), males, respectively). The proportion of patients with unmutated *IGHV* in AMPLIFY (58.6%) also closely matches the estimated rate in Denmark of approximately 60% according to the CLL Expert Committee in the DMC (22, 26).

Table 3 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Trial	AMPLIFY				CLL13		CLL14		GLOW	
Arm	AV (291)	FCR/BR (290)	FCR	BR	VO (229)	FCR/BR (229)	VO (216)	CO (216)	IV (106)	CO (105)
N	**291**	290	143	147	**229**	229	**216**	216	**106**	105
Age (median)	**61**	61	56	66	**62**	61	**72**	71	**71**	71.0
Age >65 years (%)	**27.1**	26.6	0	52.4	**35.8**	34.5	**-**	-	**84.9**	89.5
Male sex (%)	**61.2**	63.1	63.6	62.6	**74.7**	71.2	**67.6**	66.0	**55.7**	60.0
ECOG 0–1 (%)	**90.0**	90.3	86.0	94.6	**-**	-	**87.0**	88.0	**87.7**	88.5
ECOG 0 (%)	**55.2**	51.4	-	-	**72.1**	71.6	**41**	48	**33.0**	37.1
ECOG 1 (%)	**35.1**	39.8	-	-	**-**	-	**46**	40	**54.7**	51.4
Rai stage III/IV (%)	**47.1**	43.7	44.1	43.5	**40.8**	47.1	**44***	43*	**57.3**	52.5

Rai stage I/II (%)	**51.9**	54.8	55.9	53.7	**53.5**	49.8	**35***	37*	**47.9***	52.5*
Bulky disease ≥5 cm (%)	**38.8**	42.8	42.7	42.9	**31.1**	29.1	**-**	-	**39.0**	36.2
CIRS >6 (%)	**2.1**	2.0	0.0	2.0	**0.0**	0.0	**86.1**	82.0	**69.8**	58.1
Creatinine clearance mL/min (median)	**82.8**	83.4	-	-	**86.3**	86.3	**67.4**	65.2	**66.5**	63.2
Beta 2-microglobulin >3.5 mg/L (%)	**58.1**	49.3	42.7	55.8	**59.9**	68	**59.4**	62.0	**69.8**	73.3
***TP53* mutation (%)**	**0.0**	0.0	0.0	0.0	**0.0**	0.0	**11.1**		**6.6**	1.9
del(17p) (%)	**0.0**	0.0	0.0	0.0	**0.0**	0.0	**8**	7	**0.0**	0.0
del(11q) (%)	**17.5**	15.9	14.0	17.7	**19.2**		**17.0**	18.0	**18.9**	17.1

Unmutated *IGHV* (%)	**57.4**	59.3	55.2	63.3	**57.0**	57.2	**60.5**	59.0	**51.9**	51.4

*Rai stage was not available, used equivalent Binet stage.

5.2 Comparative analyses of efficacy and safety

The following efficacy and safety reports for AMPLIFY and the comparator studies are based on the latest available data cut for each study, unless otherwise stated. All data cuts are referenced in the study summary tables at the start of each subsection.

Median follow-up differed between the trials.

5.2.1 AMPLIFY: efficacy and safety

The DCO date of the OS interim analysis was 30th April, 2024, with median duration of follow-up from time of randomization was 41.3 months in the AV arm and 38.4 months for FCR/BR.

Table 4 AMPLIFY: study summary

Study [published data cuts]	Study design	Country	Period of conduct	Cytogenetics	Treatment arms	Number of patients
AMPLIFY (8)	Open-label, Phase 3 RCT	27 countries	2019–2024	Without del(17p) or *TP53* mutation	AV	291
					AVO	286
					FCR/BR	290

AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide and rituximab; RCT, randomized controlled trial.

5.2.1.1 Patient population

In total, 867 patients randomized on or before 5th May, 2021, were included in the global cohort for the interim analysis. Around two-thirds of these patients (n=546; 63.0%) were from Europe, 151 (17.4%) from North America (of whom 72 [8.3%] were from the USA), and 170 (19.6%) from other regions. Of the 867 patients randomized in the global cohort, the full analysis set (FAS) included 291 patients in the AV arm, 286 patients in the AVO arm, and 290 patients in the FCR/BR arm.

Of the FAS patients, 291 (100%) in the AV arm, 284 (99.3%) in the AVO arm, and 259 (89.3%) in FCR/BR arm received at least one dose of the study treatment (safety analysis set; SAS). No patients in the AV arm, two in the AVO arm, and 31 in the FCR/BR arm did not receive study treatment. The majority of the 31 patients in the FCR/BR that did not receive any study treatment withdrew consent to participate in the study.

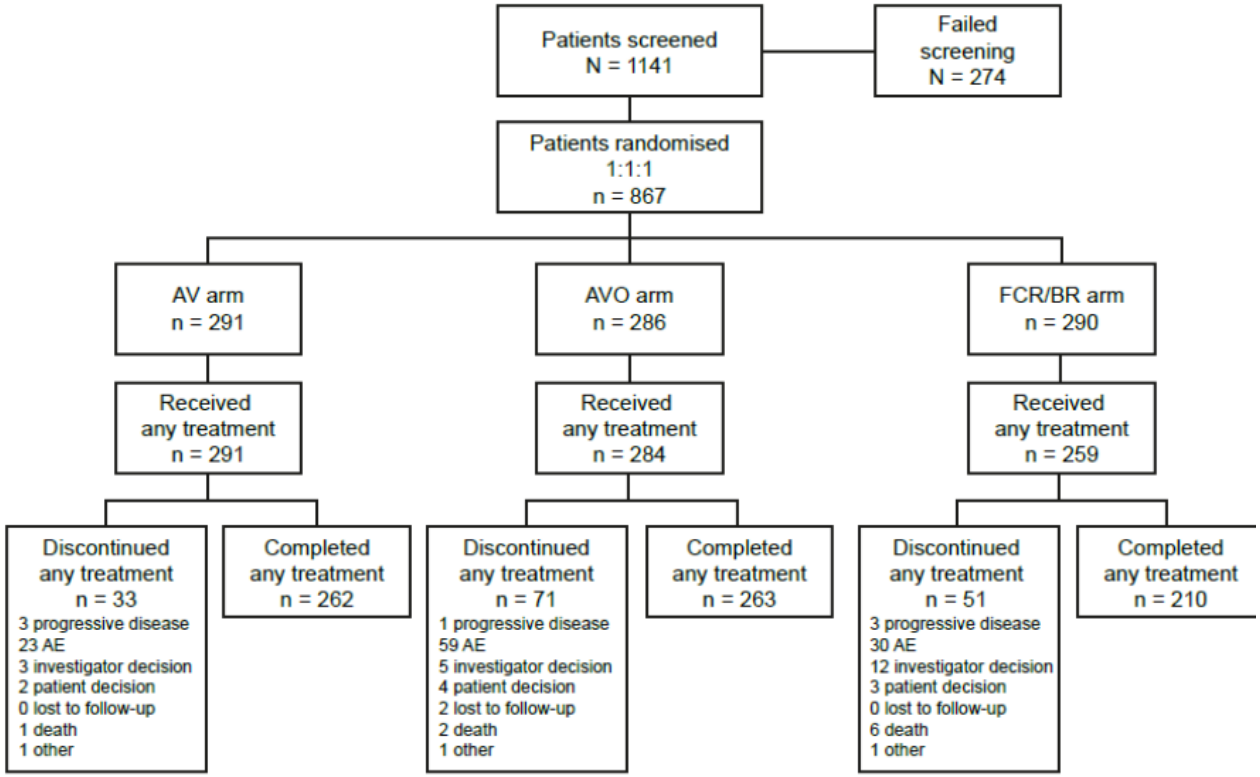
Overall, 155 patients (18.6%) discontinued any study treatment (SAS). The most frequently reported reason for discontinuation of any study treatment was an AE (112 patients; 13.4%) followed by an investigator (20 patients; 2.4%) or a patient decision and death (9 patients; 1.1% each). The most common reason for discontinuing acalabrutinib in the AV arm (n=291) was an AE (22 patients; 7.6%) followed by progressive disease (3

patients; 1.0%) and an investigator or a patient's decision (2 patients; 0.7%). In the AVO arm, the most common reason for discontinuing acalabrutinib (n=284) was an AE (42 patients; 14.8%) followed by an investigator (4 patients; 1.4%) or a patient's decision (3 patients; 1.10%). The most common reason for discontinuing FCR/BR in the FCR/BR arm (n=259) was an AE (30 patients; 11.6%) followed by an investigator decision (12 patients; 4.6%) and death (6 patients; 2.3%).

At the DCO date, none of the global patients were on the study treatment and 725 of the 867 randomized patients (83.6%) were being observed in the study: 269 patients (92.4%) in the AV arm, 245 (85.7%) in the AVO, and 211 (72.8%) in the FCR/BR arm. Overall, 834 patients (96.2%) started any study treatment of whom 678 (81.3%) completed all treatments. The median time on study was 40.8 months (range: 0–59 months). Moreover, 142 patients (16.4%) withdrew from the study: 22 patients (7.6%) in the AV arm, 41 (14.3%) in the AVO arm, and 79 (27.2%) in the FCR/BR arm. The most commonly reported reasons for patient withdrawal across all three treatment arms were death (94 patients; 10.8%) and withdrawal of consent (38 patients; 4.4%).

In total, 321 randomized patients (37.0%) had confirmed or suspected COVID-19 infections, including 109 in the AV arm (37.5%), 131 in the AVO arm (46.1%), and 81 in the FCR/BR arm (31.3%). All but one patient in the AVO arm received any study treatment. Discontinuation of acalabrutinib and venetoclax was higher in the AVO arm than in the AV arm, the primary reason for discontinuation being AE in both cases. The CONSORT diagram for AMPLIFY is shown in Figure 2.

Figure 2 CONSORT diagram for AMPLIFY



CIRS-G, Cumulative Illness Rating Scale-Geriatric; CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group.

Source: AMPLIFY CSR Figure 3.[28]

5.2.1.2 Overall survival

At the DCO date, OS was significantly longer in patients treated with AV than in those treated with FCR/BR, with a 67% reduced risk of death for patients treated with AV vs. FCR/BR HR 0.33; 95% CI: 0.18–0.56; p<0.0001).

Eighteen patients (6.2%) had died in the AV arm and 42 patients (14.5%) in the FCR/BR arm (10% of maturity). A higher proportion of patients died of COVID-19 in the FCR/BR arm than in the AV arm (7.2% vs 3.4%).

The estimated 36-month OS rate was 94.1% with AV and 85.9% with FCR/BR. Median OS for the AV arm was 57.8 months (95% CI: 57.8–not calculable [NC]); however, the median estimate for the AV arm was unstable due to the low number of patients at risk, while the median OS for the FCR/BR was not reached (Table 5). Of the 31 patients who were randomized to the FCR/BR arm and did not receive FCR/BR, none reported an OS event during the study and most were censored at the randomization date.

Importantly, this OS data set is immature with a 10% event rate. Longer follow-up using data from censored patients may change the course of the OS curves. Thus, it is premature to draw any conclusions. This is exemplified by the GLOW OS rate at a median follow-up of 34 months Figure 3 (Figure S6 in (17) vs. at a median follow-up of 46 months Figure 4 (Figure 6 in (19))

Figure 3 GLOW: Kaplan-Meier curves for overall survival (median follow up 34 months)

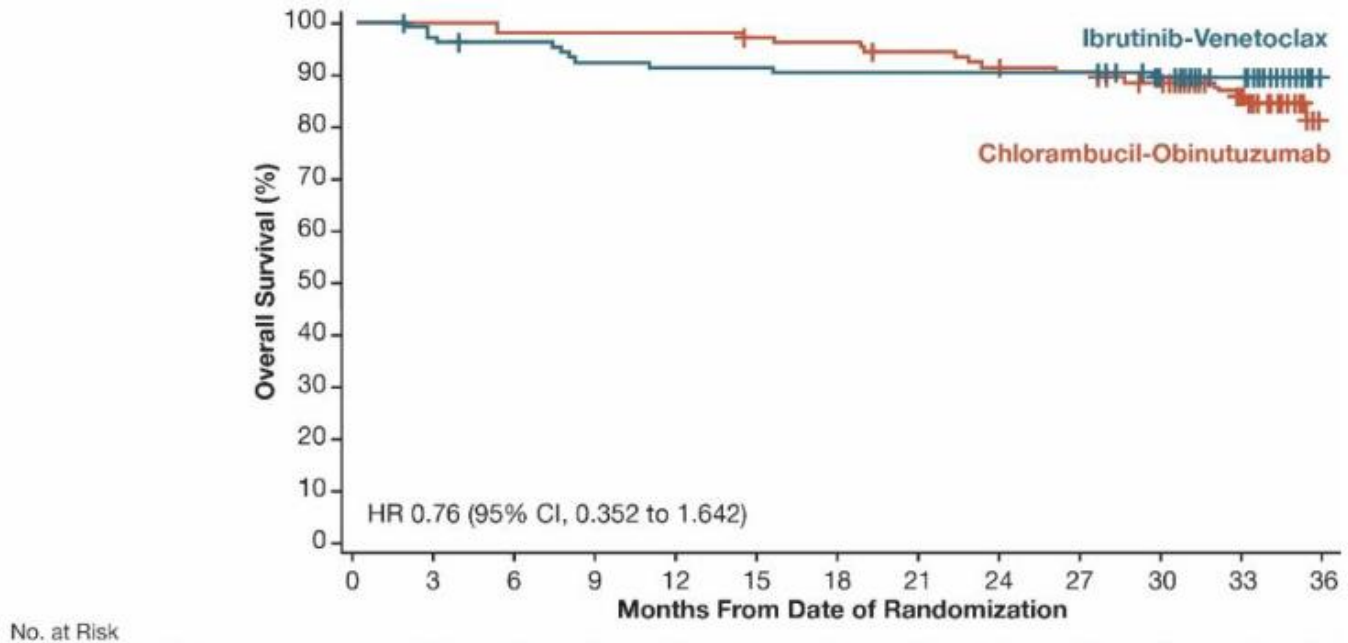
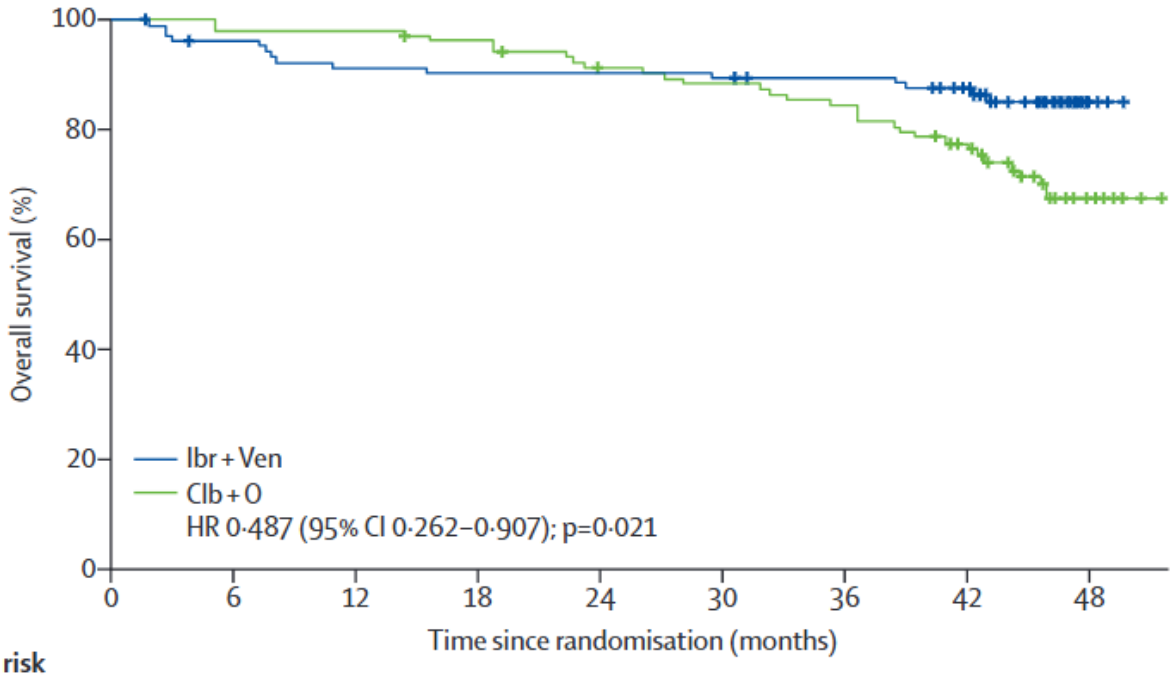


Figure 4 GLOW: Kaplan-Meier curves for overall survival (median follow up 46 months)



Number at risk (number censored)									
Ibr + Ven	106 (0)	100 (2)	95 (2)	94 (2)	94 (2)	93 (2)	91 (4)	83 (10)	12 (79)
Clb + O	105 (0)	103 (0)	103 (0)	100 (1)	93 (3)	90 (3)	86 (3)	74 (8)	15 (60)

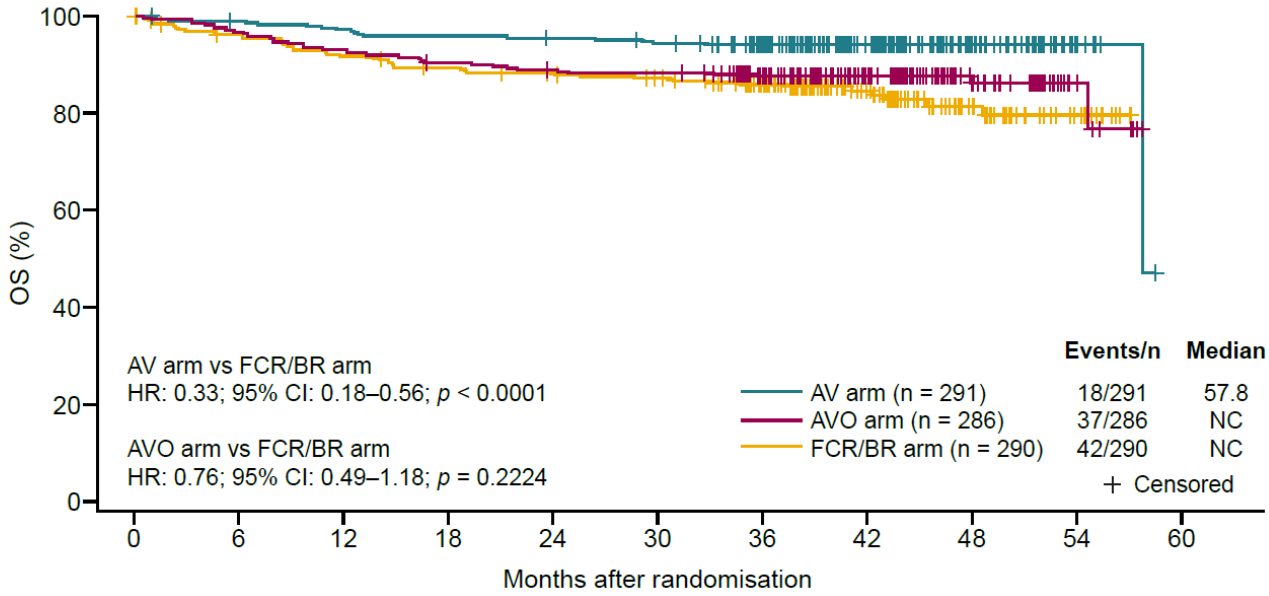
While the median OS is an important outcome, it does not capture the entire distribution of survival times and should be interpreted with caution if it falls well beyond the median follow-up (i.e., in the tail of the KM curve). The hazard ratio and associated p-value for OS consider the entire survival curve, not just the median OS, and provide additional context as to why the AV arm appears to have a longer OS despite a lower median OS. In the AV curve, one of the two patients with the longest follow-up had a PFS event; this changed both the KM survival estimate from 94% to 47% at that time and the median (first timepoint at which OS is <50%) to be reached. This occurred in the tail of the KM curve with only two patients at risk such that additional follow-up is required for a more reliable estimate of median OS.

Table 5 AMPLIFY: overall survival (full analysis set)

OS	AV (n=291)	FCR/BR (n=290)
Event, n (%)		
Death	18 (6.2)	42 (14.5)
OS[a,b] (months)		
Median (95% CI)	57.8[c] (57.8–NC)	NC (NC–NC)
Comparison of treatment groups		
HR (95% CI)[d] *p* value[e]	0.33 (0.18–0.56) < 0.0001	-
OS rate,[a] % (95% CI)		
12 months	97.2 (94.5–98.6)	91.9 (87.8–94.6)
24 months	95.5 (92.4–97.4)	88.3 (83.7–91.7)
36 months	94.1 (90.7–96.3)	85.9 (81.0–89.6)
48 months	94.1 (90.7–96.3)	81.5 (74.9–86.4)

[a]Calculation based on the KM technique.
[b]CI for median OS is derived using the Brookmeyer-Crowley method.
[c]Median estimate for the AV arm is unstable due to the low number of patients at risk.
[d]Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement, and the CI was calculated using the profile likelihood approach. Patients with no observed events were censored at the last known alive date. A HR <1 favours the AV arm or the AVO arm over the FCR/BR arm.
[e]The *p* value is based on the stratified log-rank test.
AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CSR, clinical study report; FCR, fludarabine + cyclophosphamide and rituximab; HR, hazard ratio; KM, Kaplan–Meier; NC, not calculable; OS, overall survival.
Source: AMPLIFY CSR Table 23.(27).

Figure 5 AMPLIFY: Kaplan-Meier curves for overall survival per treatment arm (full analysis set)



Patients at risk											
AV arm	291	286	281	277	275	270	233	142	58	10	0
AVO arm	286	276	265	257	252	250	223	143	64	10	0
FCR/BR arm	290	247	236	228	223	217	182	98	45	13	0

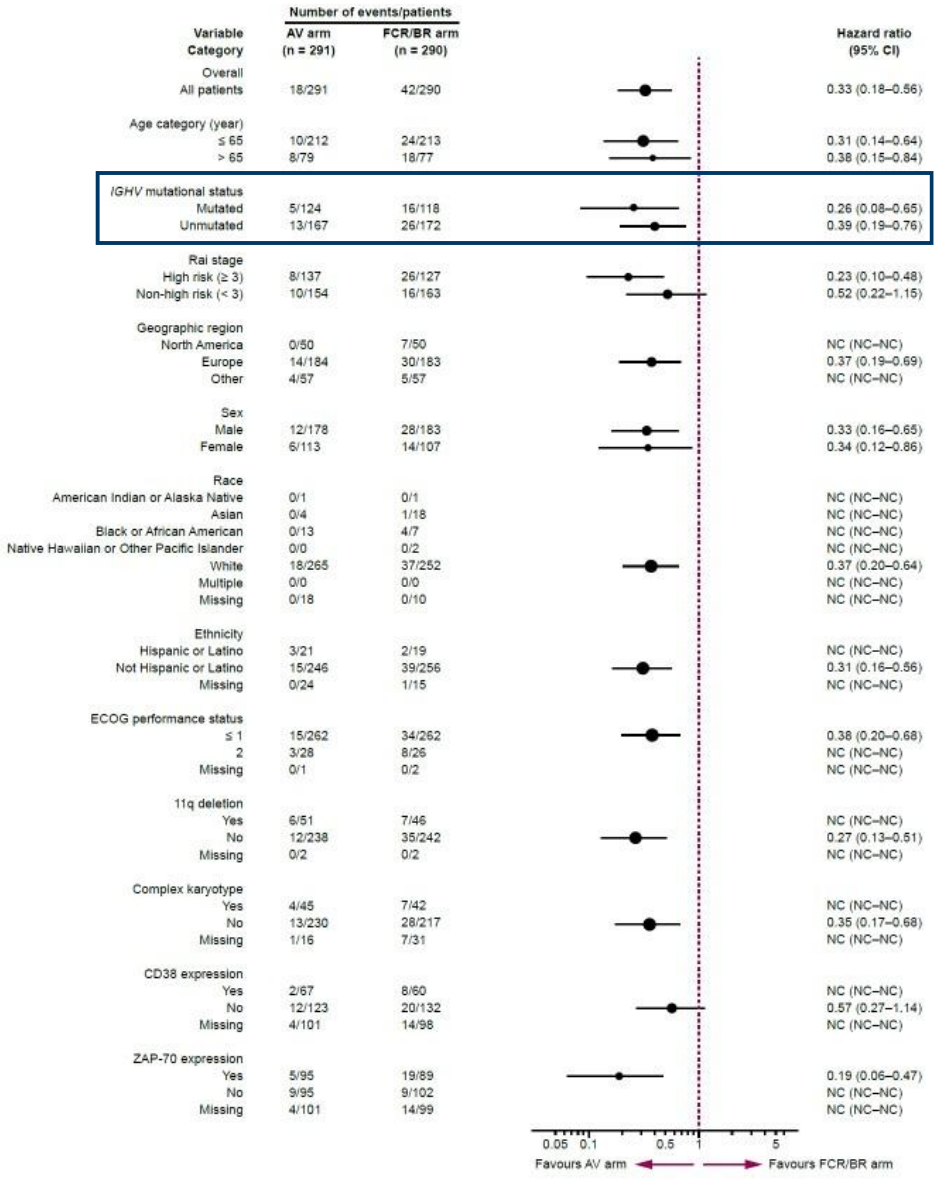
Note: the tail end of the curve of the AV arm is unstable due to the low number of patients at risk.
AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CSR, clinical study report; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; NC, not calculable.
Source: AMPLIFY CSR Figure 8.(27)

5.2.1.2.1 Overall survival: subgroup analysis

The subgroup analysis consistently showed improved OS with AV vs. FCR/BR across most of the pre-specified subgroups, including that defined by *IGHV* status.

The subgroup analysis of OS with AV compared with FCR/BR is show in a Forest plot (Figure 6). All major subgroup OS hazard ratios favoured treatment with AV over FCR/BR, indicating a meaningful reduction in the risk of death. Of particular interest for clinical questions 2 and 3 are the *IGHV* mutational status subgroups. The OS hazard ratio for mutated *IGHV* is 0.26 (95% CI: 0.08–0.65) and for unmutated *IGHV* is 0.39 (95% CI: 0.19–0.76), indicating that AV significantly reduces the risk of death regardless of *IGHV* status vs. FCR/BR. Better resolution of Figure 6 can't be obtained.

Figure 6. AMPLIFY: subgroup analysis for overall survival (full analysis set): AV versus FCR/BR



Note: HR and 95% CI are presented as NC due to too few events in some subgroups across both treatment arms. AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CD38, cyclin D38; CI, confidence interval; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; FCR, fludarabine, cyclophosphamide + rituximab; HR, hazard ratio; *IGHV*, immunoglobulin heavy-chain variable region gene; OS, overall survival; ZAP-70, zeta chain-associated protein kinase 70.
Source: AMPLIFY CSR Figure 9.(27)

5.2.1.2.2 Overall survival: IGHV status

Table 6 and Table 7 report the overall survival by IGHV status. The results are consistent with the ITT population.

Please note that the trial was not powered to assess OS by subgroup, and therefore, not powered to report statistical significance (no p-value is provided for the hazard ratios). The results are further broken down into FCR-only and BR-only, again, the trial was not powered to assess FCR and BR separately.

Table 6 AMPLIFY: overall survival unmutated IGHV status (full analysis set)

OS	AV (n=167)	FCR/BR (n=172)	FCR (n=79)	BR (n=93)
Event, n (%)				
Death	13 (7.8)	26 (15.1)	[redacted]	[redacted]
OS[a,b] (months)				
Median (95% CI)	57.8[c] (57.8–NC)	NC (NC–NC)	[redacted]	[redacted]
Comparison of treatment groups				
HR (95% CI)[d] AV versus column	-	0.39 (0.19-0.76)	[redacted]	[redacted]
OS rate,[a] %				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]

[a]Calculation based on the KM technique.
[b]CI for median OS is derived using the Brookmeyer-Crowley method.
[c]Median estimate for the AV arm is unstable due to the low number of patients at risk.
[d]Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement, and the CI was calculated using the profile likelihood approach. Patients with no observed events were censored at the last known alive date. A HR <1 favours the AV arm or the AVO arm over the FCR/BR arm.
AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CSR, clinical study report; FCR, fludarabine + cyclophosphamide and rituximab; HR, hazard ratio; KM, Kaplan–Meier; NC, not calculable; OS, overall survival.
Source: AMPLIFY CSR.(27).

Table 7 AMPLIFY: overall survival mutated IGHV status (full analysis set)

OS	AV (n=124)	FCR/BR (n=118)	FCR (n=79)	BR (n=93)
Event, n (%)				
Death	5 (4.0)	16 (13.6)	[redacted]	[redacted]
OS[a,b] (months)				
Median (95% CI)	NC (NC–NC)	NC (NC–NC)	NC (NC–NC)	NC (NC–NC)
Comparison of treatment groups				
HR (95% CI)[d] AV versus column	-	0.26 (0.08-0.65)	[redacted]	[redacted]
OS rate,[a] %				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]

[a]Calculation based on the KM technique.
[b]CI for median OS is derived using the Brookmeyer-Crowley method.
[c]Median estimate for the AV arm is unstable due to the low number of patients at risk.
[d]Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement, and the CI was calculated using the profile likelihood approach. Patients with no observed events were censored at the last known alive date. A HR <1 favours the AV arm or the AVO arm over the FCR/BR arm.
AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CSR, clinical study report; FCR, fludarabine + cyclophosphamide and rituximab; HR, hazard ratio; KM, Kaplan–Meier; NC, not calculable; OS, overall survival.
Source: AMPLIFY CSR.(27).

5.2.1.3 Progression-Free Survival

At the DCO date, the study met its primary objective. Treatment with AV statistically significantly reduced the risk of IRC-assessed disease progression or death by 35% (HR: 0.65; 95% CI: 0.49–0.87; p=0.0038) vs. treatment with FCR/BR. The AV combination demonstrated superior efficacy compared to FCR/BR in previously untreated patients with CLL.

Eighty-nine (30.6%) IRC-PFS events were reported in the AV arm and 95 (32.8%) in the FCR/BR arm. The total number of IRC-PFS events from both the AV and FCR/BR arms was 184 (98% information fraction of 188 IRC-PFS events was required for the final analysis). Notably, 31 patients who did not receive FCR/BR treatment were censored at day 1 because they lacked a post baseline assessment.

Median PFS for the AV arm was not reached; it was 47.6 months (95% CI: 43.3–NC) for the FCR/BR arm (Table 8). Median duration of follow-up from the start of randomization was 41.3 months (range: 1–59 months) in the AV arm and 38.4 months (range: 0–57 months) in the FCR/BR arm. Median duration of follow-up after completion of the fixed combination treatment was 28.3 months (range: 0–47 months) in the AV arm.

The KM curve demonstrated separation between treatment arms in favour of AV approximately three months after randomization and throughout the remaining duration of follow-up (Figure 7). The PFS benefit observed in the AV arm was sustained over time, as supported by the higher proportion of patients treated with AV who were alive and progression-free at 24 and 36 months compared with patients receiving FCR/BR (Table 8).

Table 8 AMPLIFY: Independent Review Committee-Assessed Progression-Free Survival (full analysis set): AV vs. FCR/BR

IRC-PFS	AV (n=291)	FCR/BR (n=290)
Event,[a] n (%)		
Any	89 (30.6)	95 (32.8)
Progression	77 (26.5)	66 (22.8)
Death without progression	12 (4.1)	29 (10.0)
PFS,[b,c] months		
Median (95% CI)	NC[d] (51.1–NC)	47.6 (43.3–NC)
Comparison of treatment groups		
HR[e] (95% CI) *p* value[f]	0.65 (0.49, 0.87) 0.0038	-
PFS rate, % (95% CI)		
12 months	94.8 (91.5–96.8)	88.3 (83.6–91.7)
24 months	87.6 (83.1–90.9)	79.0 (73.2–83.6)
36 months	76.5 (71.0–81.1)	66.5 (59.8–72.3)
48 months	63.9 (56.6–70.3)	48.8 (39.5–57.4)

[a]Includes events that occurred within 28 weeks of last evaluable assessment (in the first 3 years after randomization) or within 56 weeks of last evaluable assessment (3 years and later after randomization).
[b]Calculation based on the KM technique.
[c]CI for median PFS was derived based on the Brookmeyer-Crowley method.
[d]Median estimate for the AV arm is unstable due to the low number of patients at risk.
[e]Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the STRATA statement, and the CI was calculated using the profile likelihood approach.

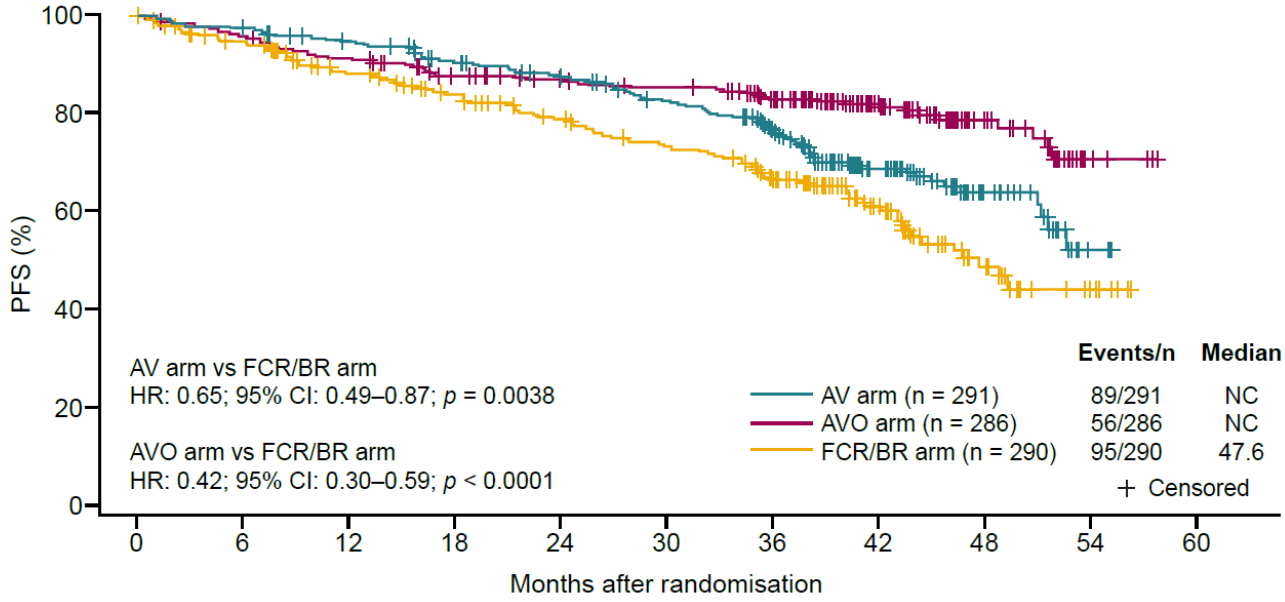
Patients with no observed events were censored at the date of randomisation (if no baseline or post-baseline assessment) or at last response assessment. A HR <1 favours the AV arm or AVO arms over the FCR/BR arm.

[f]Analysis performed using a stratified 2-sided log-rank test and a method that corresponds to the Breslow approach for handling ties (Breslow 1974).

AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CSR, clinical study report; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; IRC, independent review committee-assessed-progression-free survival; KM, Kaplan–Meier; NC, not calculable.

Source: AMPLIFY CSR Table 18.(27)

Figure 7. AMPLIFY: Kaplan-Meier curves for Independent Review Committee-Assessed Progression-Free Survival (full analysis set): AV and AVO vs. FCR/BR



Patients at risk											
AV arm	291	282	269	251	237	219	177	102	35	3	0
AVO arm	286	272	258	237	225	219	191	116	51	7	0
FCR/BR arm	290	236	208	189	170	154	127	66	28	6	0

AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CSR, clinical study report; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; NC, not calculable.

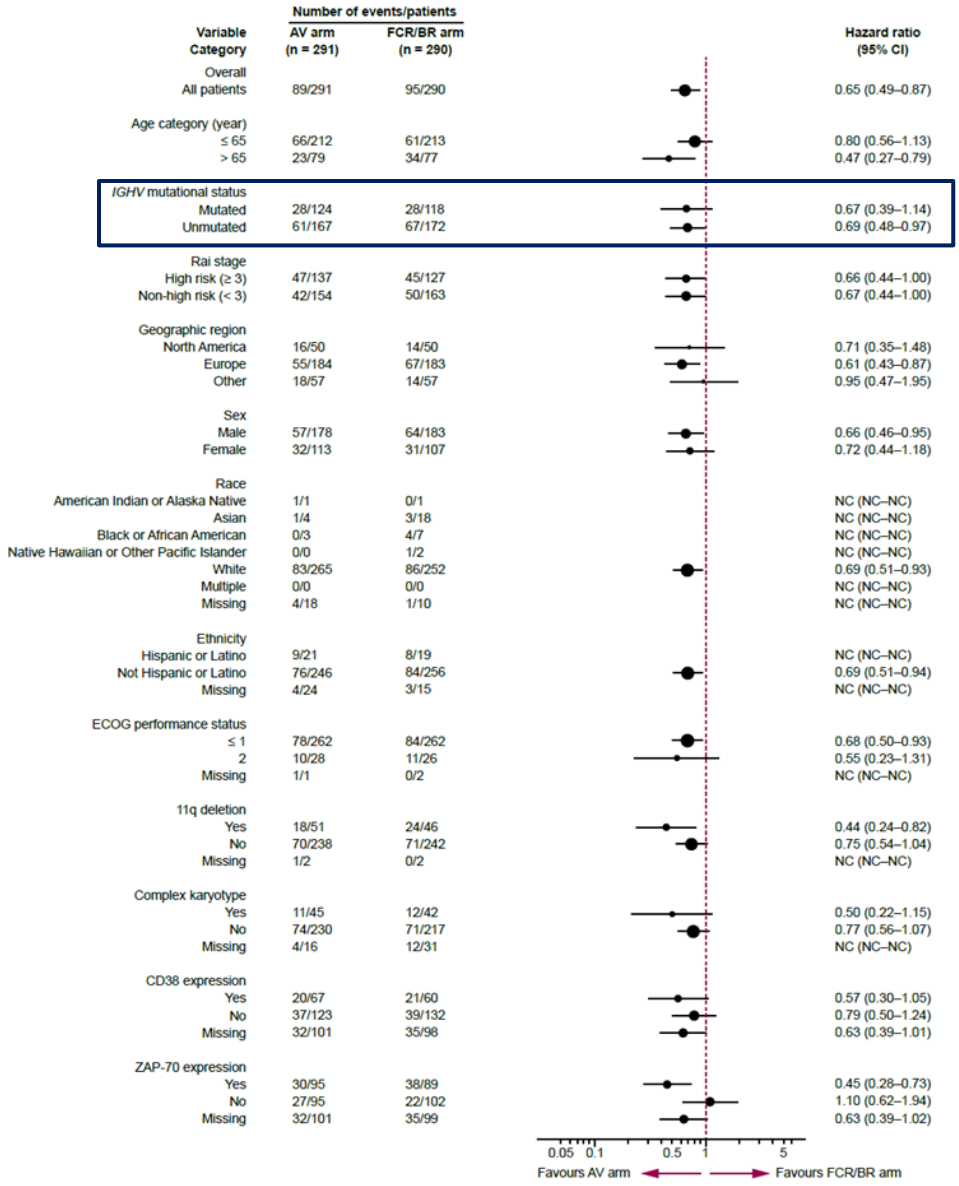
Source: AMPLIFY CSR Figure 4.(27)

5.2.1.3.1 Patient subgroups of the Independent Review Committee-Assessed Progression-Free Survival analyses

The significant improvement in PFS associated with AV treatment vs. FCR/BR was consistent across the majority of pre-specified subgroups, including that defined by *IGHV* status.

The PFS benefit with AV treatment vs. FCR/BR in the ITT population was observed across most of the pre-specified subgroups. The HRs of all subgroups favoured treatment with AV (HR: 0.44–0.95), including that defined by to *IGHV* status. This supports the treatment benefits of AV consistent with the primary analysis. Due to the low sample size of some subgroups, PFS results were variable (Figure 8). Better resolution of Figure 8 can't be obtained.

Figure 8 AMPLIFY: subgroup analysis of the Independent Review Committee-Assessed Progression-Free Survival (full analysis set): AV versus FCR/BR



Note: HR and 95% CI are presented as NC due to too few events in some subgroups across both treatment arms.
AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CD38, cyclin D38; CI, confidence interval; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; *IGHV*, immunoglobulin heavy-chain variable region gene; NC, not calculable; ZAP-70, zeta chain-associated protein kinase 70.
Source: AMPLIFY CSR Figure 5.(27)

5.2.1.3.2 Progression-Free IGHV status

Table 9 and Table 10 report progression-free survival by IGHV status. The results are consistent with the ITT population.

Please note that the trial was not powered to assess OS by subgroup, and therefore, not powered to report statistical significance (no p-value is provided for the hazard ratios).

The results are further broken down into FCR-only and BR-only, again, the trial was not powered to assess FCR and BR separately.

Table 9 AMPLIFY: progression-free survival unmutated IGHV status (full analysis set)

PFS	AV (n=167)	FCR/BR (n=172)	FCR (n=79)	BR (n=93)
Event, n (%)				
Any	61 (36.5)	67 (39.0)	[redacted]	[redacted]
PFS[a,b] (months)				
Median (95% CI)	51.5[c] (46.5–NC)	43.3 (35.2-49.2)	[redacted]	[redacted]
Comparison of treatment groups				
HR (95% CI)[d] AV versus column	-	0.69 (0.48-0.97)	[redacted]	[redacted]
PFS rate,[a] %				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]

[a]Includes events that occurred within 28 weeks of last evaluable assessment (in the first 3 years after randomization) or within 56 weeks of last evaluable assessment (3 years and later after randomization).
[b]Calculation based on the KM technique.
[c]CI for median PFS was derived based on the Brookmeyer-Crowley method.
[d]Median estimate for the AV arm is unstable due to the low number of patients at risk.
[e]Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the STRATA statement, and the CI was calculated using the profile likelihood approach. Patients with no observed events were censored at the date of randomisation (if no baseline or post-baseline assessment) or at last response assessment. A HR <1 favours the AV arm or AVO arms over the FCR/BR arm.
AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CSR, clinical study report; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; IRC, independent review committee-assessed-progression-free survival; KM, Kaplan–Meier; NC, not calculable.
Source: AMPLIFY CSR.(27)

Table 10 AMPLIFY: progression-free survival mutated IGHV status (full analysis set)

PFS	AV (n=124)	FCR/BR (n=118)	FCR (n=64)	BR (n=54)
Event, n (%)				
Any	28 (22.6)	28 (23.7)	[redacted]	[redacted]
PFS[a,b] (months)				
Median (95% CI)	NC (52.6–NC)	NC (46.2–NC)	[redacted]	[redacted]
Comparison of treatment groups				
HR (95% CI)[d] AV versus column	-	0.67 (0.39-1.14)	[redacted]	[redacted]
PFS rate,[a] %				
12 months	[redacted]	[redacted]	[redacted]	[redacted]

PFS	AV (n=124)	FCR/BR (n=118)	FCR (n=64)	BR (n=54)
24 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]

[a]Includes events that occurred within 28 weeks of last evaluable assessment (in the first 3 years after randomization) or within 56 weeks of last evaluable assessment (3 years and later after randomization).
[b]Calculation based on the KM technique.
[c]CI for median PFS was derived based on the Brookmeyer-Crowley method.
[d]Median estimate for the AV arm is unstable due to the low number of patients at risk.
[e]Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the STRATA statement, and the CI was calculated using the profile likelihood approach. Patients with no observed events were censored at the date of randomisation (if no baseline or post-baseline assessment) or at last response assessment. A HR <1 favours the AV arm or AVO arms over the FCR/BR arm.
AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CI, confidence interval; CSR, clinical study report; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; IRC, independent review committee-assessed-progression-free survival; KM, Kaplan–Meier; NC, not calculable.
Source: AMPLIFY CSR.(27)

5.2.1.4 Safety evaluation

Most patients experienced at least one treatment-emergent adverse event (TEAE) during the study (92.8% and 91.1% for the AV and FCR/BR arms, respectively). Grade ≥3 TEAEs occurred in 53.6% and 60.6% of patients and the incidence of serious adverse events (SAEs) was 24.7% and 27.4% in the AV and FCR/BR arms, respectively. Around 8% and 11% of TEAEs led to discontinuation of any study treatment in the AV and FCR/BR arms, respectively. The TEAE incidence leading to acalabrutinib discontinuation was 7.6% in the AV arm. An overview of TEAEs is shown in Table 11.

Table 11 AMPLIFY: overall summary of adverse events (safety analysis set)

n (%)	AV n=291	FCR/BR		
		Total n=259	FCR only n=122	BR only n=137
Any AE	270 (92.8)	236 (91.1)	109 (89.3)	127 (92.7)
Treatment-related	230 (79.0)	215 (83.0)	99 (81.1)	116 (84.7)
Acalabrutinib-related	221 (75.9)	NA	NA	NA
Venetoclax-related	195 (67.0)	NA	NA	NA
Obinutuzumab-related	NA	NA	NA	NA
Bendamustine-related	NA	108 (41.7)	0	108 (78.8)
Rituximab-related	NA	197 (76.1)	87 (71.3)	110 (80.3)
Fludarabine-related	NA	94 (36.3)	94 (77.0)	0
Cyclophosphamide-related	NA	93 (35.9)	93 (76.2)	0

n (%)	AV n=291	FCR/BR		
		Total n=259	FCR only n=122	BR only n=137
Any grade ≥3 AE	156 (53.6)	157 (60.6)	74 (60.7)	83 (60.6)
Treatment-related	117 (40.2)	143 (55.2)	67 (54.9)	76 (55.5)
Acalabrutinib-related	99 (34.0)	NA	NA	NA
Any SAE	72 (24.7)	71 (27.4)	36 (29.5)	35 (25.5)
Treatment-related	27 (9.3)	52 (20.1)	28 (23.0)	24 (17.5)
Acalabrutinib-related	24 (8.2)	NA	NA	NA
AEs leading to death	10 (3.4)	9 (3.5)	5 (4.1)	4 (2.9)
Treatment-related	0	1 (0.4)	0	1 (0.7)
Acalabrutinib-related	0	NA	NA	NA
Treatment	23 (7.9)	28 (10.8)	16 (13.1)	12 (8.8)
Acalabrutinib	22 (7.6)	NA	NA	NA
Venetoclax	18 (6.2)	NA	NA	NA
Obinutuzumab	NA	NA	NA	NA
Bendamustine	NA	10 (3.9)	0	10 (7.3)
Rituximab	NA	27 (10.4)	16 (13.1)	11 (8.0)
Fludarabine	NA	15 (5.8)	15 (12.3)	0
Cyclophosphamide	NA	16 (6.2)	16 (13.1)	0

AE, adverse event; AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CSR, clinical study report; FCR, fludarabine + cyclophosphamide + rituximab; NA, not applicable; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Source: AMPLIFY CSR Table 45.(27)

5.2.1.4.1 Review of serious adverse events

The SAE incidence was 24.7% in the AV arm and 27.4% in the FCR/BR arm. Ten patients (3.4%) in the AV arm and nine (3.5%) in the FCR/BR arm experienced TEAEs that resulted in death. Eight deaths were attributed to COVID-19 in the AV arm and seven for FCR/BR. None of the SAEs that resulted in death in the AV and AVO arms were considered to be causally related to acalabrutinib by the investigator. The treatment-emergent SAEs are summarized in Table 12.

Table 12 AMPLIFY: serious treatment-emergent adverse events reported in ≥1% of patients by preferred term (safety analysis set)

Preferred term	AV (N=291), n (%)	FCR/BR (N=259), n (%)
Patients with ≥1 SAE	**72 (24.7)**	**71 (27.4)**
COVID-19 pneumonia	17 (5.8)	6 (2.3)
Febrile neutropenia	5 (1.7)	21 (8.1)

COVID-19	9 (3.1)	4 (1.5)
Pneumonia	4 (1.4)	8 (3.1)
Anaemia	3 (1.0)	3 (1.2)
Pyrexia	2 (0.7)	8 (3.1)
Acute kidney injury	1 (0.3)	2 (0.8)
Neutropenia	1 (0.3)	2 (0.8)
Pulmonary embolism	1 (0.3)	1 (0.4)
Thrombocytopenia	1 (0.3)	3 (1.2)
Infusion-related reaction	0	5 (1.9)
Neutrophil count decreased	0	3 (1.2)
Tumour lysis syndrome	0	6 (2.3)

AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; SAE, serious adverse event. Source: CSR

5.2.1.4.2 Events of clinical interest

Among TEAEs of clinical interest, cardiac events were reported in 9.3% of patients in the AV arm, including 1.7% with grade ≥3 events, including 2.5% with grade ≥3 events, and 3.5% of patients in the FCR/BR arm, including 1.2% with grade ≥3 events. Most cardiac events were low grade. The most frequently reported (>2% in any arm) cardiac events of any grade in the AV arm included palpitations (2.7%) and atrial fibrillation (0.7%). Notably, the rates of tumour lysis syndrome were low and more frequent in the FCR/BR (3.1%) than the AV (0.3%) arm (Table 13).

Table 13 AMPLIFY: summary of treatment emergent adverse events of clinical interest (safety analysis set)

Event	AV (N=291) n (%)	FCR/BR (N=259) n (%)
Cardiac events		
Any grade	27 (9.3)	9 (3.5)
Grade ≥3	5 (1.7)	3 (1.2)
Atrial fibrillation		
Any grade	2 (0.7)	2 (0.8)
Grade ≥3	1 (0.3)	2 (0.8)
Ventricular arrhythmias/tachyarrhythmias[a]		
Any grade	2 (0.7)	0
Grade ≥3	0	0
Anaemia		
Any grade	20 (6.9)	25 (9.7)
Grade ≥3	11 (3.8)	17 (6.6)
Leukopenia		
Any grade	109 (37.5)	140 (54.1)
Grade ≥3	95 (32.6)	120 (46.3)
Neutropenia		
Any grade	108 (37.1)	132 (51.0)

Event	AV (N=291) n (%)	FCR/BR (N=259) n (%)
Grade ≥3	94 (32.3)	112 (43.2)
Other leukopenia		
Any grade	11 (3.8)	23 (8.9)
Grade ≥3	6 (2.1)	16 (6.2)
Thrombocytopenia		
Any grade	17 (5.8)	39 (15.1)
Grade ≥3	6 (2.1)	28 (10.8)
Haemorrhage		
Any grade	94 (32.3)	11 (4.2)
Grade ≥3	3 (1.0)	1 (0.4)
Major haemorrhage		
Any grade	3 (1.0)	2 (0.8)
Grade ≥3	3 (1.0)	1 (0.4)
Hepatotoxicity		
Any grade	17 (5.8)	9 (3.5)
Grade ≥3	10 (3.4)	4 (1.5)
Hypertension		
Any grade	12 (4.1)	7 (2.7)
Grade ≥3	8 (2.7)	2 (0.8)
Infections		
Any grade	148 (50.9)	82 (31.7)
Grade ≥3	36 (12.4)	26 (10.0)
Interstitial lung disease/pneumonitis		
Any grade	0	1 (0.4)
Grade ≥3	0	1 (0.4)
Tumour lysis syndrome		
Any grade	1 (0.3)	8 (3.1)
Grade ≥3	1 (0.3)	8 (3.1)

[a]AESI category "ventricular arrythmias" was defined using the same group of MedDRA preferred terms as the cardiac event subcategory of "ventricular tachyarrhythmia".
AESI, adverse event of special interest; AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CSR, Clinical Study Report; FCR, fludarabine + cyclophosphamide + rituximab.
Source: AMPLIFY CSR.

5.2.1.4.3 COVID-19

Contingency measures were implemented during the study to maintain patient safety, data integrity, and minimize the impact of the COVID-19 pandemic. All missed laboratory tests/other assessments and visits were documented and, if appropriate, were considered protocol deviations. Nevertheless, confirmed or suspected COVID-19 TEAEs were reported by 22.0% (AV arm) and 3.9% (FCR/BR arm) of patients (Table 14). COVID-19 had a greater impact on treatment-emergent SAEs in the AV arm than the FCR/BR arm, partly due to the longer duration of treatment exposure and thus a longer treatment-emergent observation period. COVID-19 and COVID-19 pneumonia were the only AEs with a fatal outcome in two or more patients in both arms.

Table 14 AMPLIFY: COVID-19 adverse events (safety analysis set)

Preferred term	AV (N=291) n (%)	FCR/BR (N=259) n (%)
Any confirmed or suspected COVID-19 TEAE	64 (22.0)	10 (3.9)
COVID-19	55 (18.9)	6 (2.3)
COVID-19 pneumonia	21 (7.2)	7 (2.7)
Any confirmed or suspected COVID-19 TEAE with outcome death	8 (2.7)	7 (2.7)
COVID-19	2 (0.7)	3 (1.2)
COVID-19 pneumonia	6 (2.1)	4 (1.5)

AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CSR, Clinical Study Report; FCR, fludarabine + cyclophosphamide + rituximab; TEAE, treatment emergent adverse event.
Source: AMPLIFY CSR.

5.2.1.5 AMPLIFY: quality of life

Quality of life was measured using the two-item Global Health Status scale, which is part of the EORTC QLQ-C30. High scores on functional scales indicate a high level of functioning, whereas high scores on symptom scales indicate a high severity of symptoms.

The mean score was moderate (67.95–69.05 out of 100) at baseline for all arms. Overall, the mean change from baseline scores showed a gradual improvement that increased up to a maximum of 12.8 points. This increase indicated a clinically significant improvement in health at time points during the treatment and/or follow-up period for the AV arms. For the FCR/BR arm, the mean change in global health status during treatment cycles ranged from 3.99 to 6.54 (standard deviation [SD]: 18.58–20.24) point score.

5.2.2 CLL13: efficacy and safety

The data cut-off for these exploratory follow-up analyses was 31st January, 2023 with median follow-up of 50.7 months (IQR 44.6–57.9).

Table 15 CLL13: study summary

Study [published data cuts]	Study design	Country	Period of conduct	Cytogenetics	Treatment arms	Number of patients
CLL13 (9-11)	Open-label, Phase 3 RCT	9 EU countries & Israel	2016–19	Without del(17p) or *TP53* mutation	VR	237
					VO	229
					VOI	231
					FCR/BR	229

BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; RCT, randomized controlled trial; VO, venetoclax + obinutuzumab; VOI venetoclax-obinutuzumab-ibrutinib; VR, venetoclax + rituximab.

5.2.2.1 Overall survival

Overall survival did not differ significantly between treatment groups. Median OS was not reached in any of the treatment groups. At data cut-off, 17 (7%) of 229 patients had died in the FCR/BR group, nine (4%) of 237 in the venetoclax + rituximab (VR) group, 11 (5%) of 229 in the venetoclax + obinutuzumab (VO) group, and 11 (5%) of 231 in the venetoclax + obinutuzumab + ibrutinib (VOI) group. Therefore, the estimated 48-month OS rates were 93.5% for the chemotherapy group, 96.2% for VR, 95.1% for VO, and 95.0%% for VOI.(10)

5.2.2.1.1 Overall survival: subgroup analysis

No subgroup analysis for OS in the CLL13 study has been published in the four-year follow up article.

5.2.2.2 Progression-free survival

At data cut-off, the estimated, four-year PFS rates were 85.5% (37 events), 81.8% (55 events), 70.1% (84 events), and 62.0% (84 events) in the VOI, VO, VR, and chemoimmunotherapy groups, respectively. Patients in the VO group had significantly longer PFS than those in the FCR/BR group (HR: 0.47; 97.5% CI 0.32–0.69; p<0.0001). Differences in PFS did not reach the predefined significance level of 0.025 for the comparison between VR and chemoimmunotherapy (FCR/BR) (p=0.10; proportional hazards assumption not satisfied) and between VOI and VO (HR: 0.63; 97.5% CI 0.39–1.02; p=0.031).(10)

5.2.2.2.1 Progression-free survival: subgroup analysis

In an exploratory subgroup analysis, unmutated *IGHV* was associated with shorter PFS across all treatment groups than mutated IGHV. The VO vs. FCR/BR group, the PFS HR was 0.45 (95% CL: 0.31–0.66; p=0.0001) for patients with unmutated *IGHV* and 0.45 (95% CL: 0.20–1.05; p=0.063) for those with mutated *IGHV*. The mutated-*IGHV* subgroup did not reach the 0.025 significance level.(10)

5.2.2.3 Safety evaluation

The most common grade ≥3 TEAEs at data cut-off for the 4-year follow-up were neutropenia (114 [53%] of 216), leukopenia (26 [12%]), and febrile neutropenia (23 [11%]) in the FCR/BR group. In the VO group, these were neutropenia (127 [56%] of 228), thrombocytopenia (42 [18%]), and infusion-related reaction (26 [11%]). Deaths determined to be associated with a study treatment by the investigator occurred in 3 (1%) patients in the FCR/BR group, and none in the VO group. One treatment-emergent fatal COVID-19 case was reported in the VO group. Second primary cancers were reported in 29% of the FCR/BR group and 17% of the VO group.(10)

5.2.2.3.1 Review of serious adverse events

An SAE assessed as related to a study drug was experience in 108 of 228 VO-treated patients and 116 of 216 FCR/BR-treated patients. An infusion-related reaction occurred most often in the FCR/BR group (20.2%), whereas febrile neutropenia was the most common SAE in the VO group (Table 16). (10)

Table 16 CLL13: serious treatment emergent adverse events related to study drug reported by ≥1 of patients

Preferred term	VO (N=228), n (%)	FCR/BR (N=216), n (%)
Total SAE	**108 (47.4)**	**116 (53.7)**
Infusion-related reaction	22 (20.4)	10 (8.6)
Pneumonia	9 (8.3)	10 (8.6)
Tumour lysis syndrome	9 (8.3)	4 (3.4)
Pyrexia	7 (6.5)	11 (9.5)
Thrombocytopenia	7 (6.5)	1 (0.9)
Febrile neutropenia	6 (5.6)	23 (19.8)
Neutropenia	4 (3.7)	2 (1.7)
Atrial fibrillation	2 (1.9)	1 (0.9)
Cytokine release syndrome	2 (1.9)	0
Infection	2 (1.9)	3 (2.6)
Neutropenic infection	2 (1.9)	0
Pancytopenia	2 (1.9)	0
Tooth infection	2 (1.9)	0
Anaemia	1 (0.9)	3 (2.6)
Urinary tract infection	1 (0.9)	2 (1.7)
Febrile infection	0	4 (3.4)
Angina pectoris	0	2 (1.7)
Erythema multiforme	0	2 (1.7)
Influenza	0	2 (1.7)
Nausea	0	2 (1.7)
Respiratory syncytial virus infection	0	2 (1.7)
Sepsis	0	2 (1.7)
Squamous cell carcinoma	0	2 (1.7)

BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; SAE, serious adverse event; VO, venetoclax + obinutuzumab.

5.2.2.3.2 Events of clinical interest

Among TEAEs of clinical interest, neutropenia and/or neutrophil count decrease were reported in 59.2%% of VO-treated patients (including 27.2% with grade 3 and 28.5%

grade 4 events) and 96.0% of patients in the FCR/BR arm (including 18.5% with grade 3 and 34.3% grade 4 events) (Table 17).

Table 17 CLL13: summary of treatment emergent adverse events of clinical interest

Event	VO (N=228) n (%)	FCR/BR (N=216) n (%)
Atrial fibrillation		
Any grade	2 (0.9)	4 (1.9)
Grade ≥3	0	1 (0.5)
Anaemia		
Any grade	19 (8.3)	31 (14.3)
Grade ≥3	11 (4.8)	16 (7.4)
Leukopenia		
Any grade	20 (8.8)	33 (15.3)
Grade ≥3	13 (5.7)	26 (12.0)
Neutropenia and/or neutrophil count decrease		
Any grade	135 (59.2)	121 (96.0)
Grade ≥3	127 (55.7)	114 (52.8)
Thrombocytopenia and/or platelet count decrease		
Any grade	53 (23.2)	41 (19.0)
Grade ≥3	42 (18.4)	22 (10.2)
Hepatotoxicity		
Any grade	2 (0.9)	0
Grade ≥3	2 (0.9)	0
Hypertension		
Any grade	23 (10.1)	6 (2.8)
Grade ≥3	4 (1.8)	3 (1.4)
Infections		
Any grade	11 (4.8)	17 (7.9)
Grade ≥3	4 (1.8)	5 (2.3)
Pneumonitis		
Any grade	1 (0.4)	1 (0.5)
Grade ≥3	1 (0.4)	0
Tumour lysis syndrome		
Any grade	26 (11.4)	10 (4.6)
Grade ≥ 3	20 (8.8)	9 (4.2)

BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; VO, venetoclax + obinutuzumab.

5.2.2.4 Quality of life

Global health status/QoL improved shortly after treatment initiation with VO and the benefit was sustained throughout the study while improvements >MID were reported later with CIT.(11)

5.2.3 CLL14: efficacy and safety

Table 18 CLL14: study summary

Study [published data cuts]	Study design	Country	Period of conduct	Cytogenetics	Treatment arms	Number of patients
CLL14 (12-16)	Open-label Phase 3 RCT	21 countries	2014–18	Not restricted	VO	216
					CO	216

OC, obinutuzumab + chlorambucil; VO, venetoclax + obinutuzumab; RCT, randomized controlled trial.

5.2.3.1 Overall survival

At six years post randomization, the estimated OS rate was 78.7% in the VO arm and 69.2% in the CO arm (HR: 0.69; 95% CI, 0.48–1.01; p=0.052). Of 48 deaths in the VO arm, 9 (18.8%) were related to CLL progression, whereas 26 (37.1%) of 70 deaths in the CO arm were associated with CLL progression.(16)

5.2.3.1.1 Overall survival: subgroup analysis

In the VO arm, patients with unmutated *IGHV* did not have a significantly shorter OS than patients with mutated *IGHV* (6-year OS rates, 77.7% vs. 82.1%, respectively; HR: 1.43; 95% CI, 0.75–2.70). In contrast, patients with unmutated *IGHV* had a significantly shorter OS than those with mutated *IGHV* status in the CO arm (6-year OS rates, 63.0% vs 79.7%, respectively; HR: 2.00; 95% CI, 1.17–3.41). For patients with unmutated *IGHV* status, OS was significantly longer with VO than with CO (HR: 0.58; 95% CI, 0.36–0.92).(16)

5.2.3.2 Progression-free survival

With all patients being off treatment for at least five years, PFS remained significantly superior for VO- than CO-treated patients (median: 76.2 vs 36.4 months, respectively; HR: 0.4; 95% CI: 0.31–0.52; p<0.0001). Overall, 101 and 161 PFS events occurred in the VO and CO arms, respectively. Of these, 67 were disease progressions (66.3% of PFS events) in the VO arm and 141 (87.6% of PFS events) in the CO arm.(16)

5.2.3.2.1 Progression-free survival: subgroup analysis

For patients with unmutated *IGHV*, PFS was significantly longer in the VO arm than in the CO arm (median PFS: 64.8 vs 26.9 months, respectively; HR: 0.30; 95% CI: 0.22–0.42). For patients with mutated *IGHV* and concomitant del(17p) and/or *TP53* mutations, median PFS was not reached (6-year PFS rate, 75.0%).(16)

5.2.3.3 Safety evaluation

During the most recently published observation period (median: 76.8 months in the VO arm, and 75.8 months in the CO arm), SAEs were reported in 133 of 212 (62.7%) VO-treated patients and in 101 of 214 (47.2%) CO-treated patients. The majority of AEs occurred during the treatment phase in both study arms, whereas 9.9% of AEs in the VO arm and 6.9% in the CO arm occurred after treatment.(16)

In the previously published data cut (median follow-up 39.7 months), 79% and 77% of patients experienced grade ≥3 AEs in the VO arm and CO arm, respectively.(13)

5.2.3.3.1 Review of serious adverse events

Reports of SAEs are only available from the published data cut with follow-up of 28.1 months.(12)

Table 19 CLL14: serious adverse events reported by ≥1% of the patients in either treatment group (safety population)

Serious Adverse Event	VO (N=212) n (%)	CO (N=214) n (%)
≥1 serious adverse event	104 (49.1)	90 (42.1)
Infections and infestations		
Pneumonia	10 (4.7)	9 (4.2)
Sepsis	6 (2.8)	2 (0.9)
Cellulitis	3 (1.4)	0
Injury, poisoning, and procedural complications		
Infusion-related reaction	9 (4.2)	13 (6.1)
Blood and lymphatic system disorders		
Febrile neutropenia	11 (5.2)	8 (3.7)
Thrombocytopenia	2 (0.9)	5 (2.3)
Neutropenia	3 (1.4)	1 (0.5)
Neoplasms (benign, malignant, unspecified)		

Serious Adverse Event	VO (N=212) n (%)	CO (N=214) n (%)
Squamous cell carcinoma of skin	2 (0.9)	3 (1.4)
General disorders and administration site conditions		
Pyrexia	8 (3.8)	7 (3.3)
Respiratory, thoracic, and mediastinal disorders		
Chronic obstructive pulmonary disease	3 (1.4)	2 (0.9)
Cardiac disorders		
Atrial fibrillation	1 (0.5)	3 (1.4)
Cardiac failure	3 (1.4)	1 (0.5)
Myocardial infarction	1 (0.5)	3 (1.4)
Metabolism and nutrition disorders		
Tumour lysis syndrome	1 (0.5)	4 (1.9)
Investigations		
Aspartate aminotransferase increased	0	4 (1.9)
Alanine aminotransferase increased	0	3 (1.4)

OC, obinutuzumab + chlorambucil; VO, venetoclax + obinutuzumab.

5.2.3.3.2 Events of clinical interest

Among AEs of clinical interest, neutropenia was reported in 57.5% of patients in the VO arm and 56.5% in the CO arm.(16)

Table 20 CLL14: summary of treatment emergent adverse events of clinical interest

Event	VO (N=212) n (%)	CO (N=214) n (%)
Cardiac failure		
Any grade	4 (1.9)	1 (0.5)

Event	VO (N=212) n (%)	CO (N=214) n (%)
Grade ≥3	4 (1.9)	0
Grade 5	1 (0.5)	0
Atrial fibrillation		
Any grade	6 (2.8)	5 (2.3)
Grade ≥3	4 (1.9)	3 (1.4)
Anaemia		
Any grade	35 (16.5)	40 (18.7)
Grade ≥3	17 (8.0)	14 (6.5)
Leukopenia		
Any grade	12 (5.7)	13 (6.1)
Grade ≥3	5 (2.4)	10 (4.7)
Neutropenia		
Any grade	122 (57.5)	121 (56.5)
Grade ≥3	112 (52.8)	102 (47.7)
Thrombocytopenia		
Any grade	51 (24.1)	50 (23.4)
Grade ≥3	29 (13.7)	32 (15.0)
Hypertension		
Any grade	14 (6.6)	11 (5.1)
Grade ≥3	7 (3.3)	1 (0.5)
Sepsis/septic shock		
Any grade	9 (4.2)	6 (2.8)
Grade ≥3	9 (4.2)	6 (2.8)
Grade 5	6 (2.8)	3 (1.4)
Pneumonia		
Any grade	18 (8.5)	12 (5.6)
Grade ≥3	12 (5.7)	9 (4.2)
Grade 5	1 (0.5)	1 (0.5)
Tumour lysis syndrome		
Any grade	3 (1.4)	7 (3.3)
Grade ≥3	3 (1.4)	7 (3.3)

OC, obinutuzumab + chlorambucil; VO, venetoclax + obinutuzumab.

5.2.3.4 Quality of life

Quality of Life was evaluated in a “PRO population” (N=197 for the VO arm, N=198 for the CO arm). The completion rate for PRO questionnaires was high at 6 years post randomization: 89.3% (VO arm), 92.9% (CO arm). A significantly longer TUDD in global health status/QoL-scale score was observed in the VO arm compared to the CO arm (median TUDD, 82.1 vs. 65.1 months; HR, 0.70; 95% CI, 0.51–0.97), indicating sustained health-related QoL after VO compared to CO therapy.(16)

5.2.4 GLOW: efficacy and safety

The most recent data-cut publication had a median follow-up 64 months, and the survival findings below correspond to this unless otherwise stated.

Table GLOW: study summary

Study [published data cuts]	Study design	Country	Period of conduct	Cytogenetics	Treatment arms	Number of patients
GLOW (17-21)	Open-label, Phase 3 RCT	14 countries	2018-19	Not restricted	IV	106
					CO	105

CO, chlorambucil + obinutuzumab; IV, ibrutinib + venetoclax; RCT, randomized controlled trial.

5.2.4.1 Overall survival

Prolonged OS was seen with IV compared to CO, reducing the relative risk of death by 54% (HR: 0.46; 95% CI: 0.27–0.79; p=0.004). The 60-month OS rates were 81.6% and 60.8% for patients treated with IV and CO, respectively.(21)

An earlier, full-article publication (median follow-up 46 months) reported an OS advantage for the IV arm compared to the CO arm (HR: 0.49, 95% CI: 0.26–0.91; p=0.021). The 42-month OS rates were 87.5% and 77.6% for patients in the IV and CO arms, respectively. There were twice as many deaths in the CO arm (30 of 105 patients) than in the IV arm (15 of 106 patients).(19)

5.2.4.1.1 Overall survival: subgroup analysis

At a median follow-up of 64 months, OS rates were prolonged in patients with mutated *IGHV* (HR; 0.22; 95% CI: 0.06–0.77; p=0.010), with a trend for prolonged survival in those with unmutated *IGHV* (HR: 0.51; 95% CI: 0.26–1.02; p=0.052).(21)

5.2.4.2 Progression-free survival

Prolonged PFS was also seen, with IV, reducing the risk of progression or death by 73% compared to CO (HR: 0.27; 95% CI: 0.18–0.39; p<0.0001). The 60-month PFS rates were 59.9% and 17.8% for IV and CO, respectively.(21)

5.2.4.2.1 Progression-free survival: subgroup analysis

Progression-free survival was prolonged by IV independent of *IGHV* status. The HR was 0.26 (95% CI: 0.17–0.42; p<0.0001) in patients with unmutated *IGHV* and 0.24 (95% CI: 0.10–0.62; p=0.0014) in those with mutated *IGHV*. Estimated 60-months PFS rates in the IV arm were 52.2% and 82.5% for patients with unmutated and mutated *IGHV*, respectively.(21)

5.2.4.3 Safety evaluation

At a median follow-up of 27.7 months, the most common, any-grade AEs were diarrhoea (54 [50.9%]) and neutropenia (44 [41.5%]) in the IV arm, and neutropenia (61 [58.1%]) and infusion-related reactions (31 [29.5%]) in the CO arm. Grade ≥3 AEs occurred in 80 (75.5%) and 73 (69.5%) patients in the IV and CO arms, respectively.(17)

At the 46-month follow-up, all patients were off treatment and the past TEAE period at the time of primary analysis and the only notable safety observation since the is the report of one patient from the CO arm who developed a SAE of myelodysplastic syndrome/myeloproliferative neoplasm. Grade ≥3 AEs remained stable since the primary results occurring in 80 (75.5%) and 73 (69.5%) of patients in the IV and CO arms, respectively. Four patients died suddenly in the IV arm; two deaths were listed as cardiac disorders and two were COVID-19 related.(19)

5.2.4.3.1 Review of serious adverse events

Reports of SAEs are only available in the data cut with a median follow-up of 27.7 months.(17)

A SAE was experienced by 49 of 106 IV-treated patients and 29 of 105 CO-treated patients. Infections occurred frequently in both arms (12.3% and 8.6% in the IV and CO arms, respectively).(17)

Table 21 GLOW: summary of serious adverse events by preferred term reported in ≥2% of patients (safety population)

Serious adverse event	IV (N=106) n (%)	CO (N=105) n (%)
Any	49 (46.2)	29 (27.6)
Infections	13 (12.3)	9 (8.6)
Atrial fibrillation	7 (6.6)	0
Anaemia	3 (2.8)	2 (1.9)
Diarrhoea	3 (2.8)	1 (1.0)
Cardiac failure	3 (2.8)	0

Serious adverse event	IV (N=106) n (%)	CO (N=105) n (%)
Febrile neutropenia	1 (0.9)	3 (2.9)
Infusion-related reaction	0	3 (2.9)
Tumour lysis syndrome	0	3 (2.9)

CO, chlorambucil + obinutuzumab; IV, ibrutinib + venetoclax.

5.2.4.3.2 Events of clinical interest

Among TEAEs (grade ≥3) of clinical interest, cardiac failure was reported in 3.8% of patients in the IV arm, including one with a grade 5 event, and no patients in the CO arm. Most cardiac events were low grade. Notably, one sudden death occurred in the IV arm. In total, 15 deaths occurred in the IV arm during the study, including four related to infections (of which two were related to COVID-19), two cardiac deaths, and four sudden/unknown deaths. In contrast, 30 deaths were reported in the CO arm during the study, including 11 related to infection (of which six were related to COVID-19), four cardiac deaths, and three sudden/unknown deaths. (19)

Table 22 GLOW: summary of treatment emergent adverse events (grade ≥3) of clinical interest (safety set)

Event	IV (N=106) n (%)	CO (N=105) n (%)
Cardiac failure		
Grade ≥3	4 (3.8)	0
Sudden death		
Grade ≥3	2 (1.9)	0
Atrial fibrillation		
Grade ≥3	7 (6.6)	0
Anaemia		
Grade ≥3	3 (2.8)	2 (1.9)
Leukopenia		
Grade ≥3	0	3 (2.9)
Neutropenia		
Grade ≥3	37 (34.9)	52 (49.1)
Thrombocytopenia		
Grade ≥3	6 (5.7)	21 (20.0)
Hypertension		

Event	IV (N=106) n (%)	CO (N=105) n (%)
Grade ≥3	8 (7.5)	2 (1.9)
Infection		
Grade ≥3	2 (1.9)	0
Pneumonia		
Grade ≥3	7 (6.6)	6 (5.7)
Tumour lysis syndrome		
Grade ≥3	0	6 (5.7)

CO, chlorambucil + obinutuzumab; IV, ibrutinib + venetoclax.
Source: (17)

5.2.4.4 Quality of life

The EORTC QLQ-C30 data were presented as time to deterioration defined as a decrease of ≥10 points. Median time to deterioration was 14.95 months [8.38; IN] for IV and 24.18 months [13.86; IN] for CO. Only reported on clinicaltrials.gov with a time frame of up to two years and 10 months of data.

5.2.5 Qualitative description of safety data

This comparison is based on data from the first publication of each respective study (AMPLIFY, CLL13, CLL14, GLOW + ADD REFS).

The proportion of patients experiencing any grade ≥3 AE was markedly lower with AV (54%) compared to both IV (76%) and VO (79% and 80%).

Although neutropenia was the most common serious AE for all regimens, its frequency differed significantly between the regimens: it was most common for VO (53%), less frequent yet still notable for IV (35%), and the lowest of all three for AV (27%). Anaemia and thrombocytopenia were pronounced in the VO arm (8% and 14%, respectively), but essentially absent or below the reporting level for AV and IV.

Infections (and infestations) were most common in the VO and IV arms, and less frequent in AV (12%). Thus, a notable risk of infection risk was associated with all regimens, albeit somewhat less with acalabrutinib.

Atrial fibrillation was seen exclusively with IV (7%); this is a known side effect of ibrutinib. Hypertension was also more frequent in the IV (8%) and VO (7%) arms but absent in the acalabrutinib arm. Hyponatremia appeared only in the IV arm. Diarrhoea was registered only with IV (10%). Infusion-related reactions only occurred with VO due to the mode of administration. The only regimen to report sudden death was IV.

Table 23 Comparison of safety data

Adverse event	AMPLIFY (AV) (41-month follow-up)	CLL13 (VO) (38.8-month follow-up)	CLL14 (VO) (28.1-month follow-up)	GLOW (IV) (27.7-month follow-up)
Any grade ≥3 AE	**53.6%**	**80.3%**	**78.8%**	**75.5%**
Anaemia	0.00%	0.00%	8.00%	0.00%
Atrial fibrillation	0.00%	0.00%	0.00%	6.60%
Diarrhoea	0.00%	0.00%	0.00%	10.38%
Febrile neutropenia	0.00%	0.00%	5.20%	0.00%
Infections and infestations	12.4%	13.2%	17.50%	16.98%
Infusion-related reaction	0.00%	11.4%	9.00%	0.00%
Neutropenia	26.80%	45.2%	52.80%	34.91%
Decreased neutrophil count	5.50%	0.00%	0.00%	0.00%
Thrombocytopenia	0.00%	14.9%	13.70%	5.66%
Hyponatraemia	0.00%	0.00%	0.00%	5.66%
Fatigue/asthenia	0.00%	0.00%	6.60%	0.00%
Hypertension	0.00%	0.00%	6.60%	7.55%
Malignant neoplasm	0.00%	7.4%	6.10%	0.00%
Investigations	0.00%	24.1%	0.00%	0.00%
Metabolism and nutrition disorders	0.00%	13.6%	0.00%	0.00%
Injury, poisoning, procedural complications	0.00%	11.8%	0.00%	0.00%
Tumour lysis syndrome	0.00%	8.4%	0.00%	0.00%
Leukopenia	0.00%	5.7%	0.00%	0.00%
Source	AMPLIFY trial (27)	CLL13 trial Eichhorst 2023 (9)	CLL14 trial Fischer 2019 (12)	GLOW trial Kater et al., 2022 (17)
Assumption	Grade ≥3 AEs that occurred in ≥5% of patients.	Grade 3 or 4 AEs that occurred in ≥5% of patients.	Grade 3 or 4 AEs that occurred in ≥5% of patients.	Grade ≥3 AEs that occurred in 5% of patients.

AV, acalabrutinib + venetoclax; IV, ibrutinib + venetoclax. VO, venetoclax + obinutuzumab.

5.2.6 Comparative analyses of efficacy

5.2.7 Differences in primary outcome definitions between studies

AMPLIFY: PFS-IRC (Section 5.2.1); secondary endpoint: PFS-INV.

CLL13: PFS-INV (co-primary endpoint) (Section 5.2.2).

CLL14: PFS-INV (Section 5.2.3); PFS-IRC (secondary endpoint).

GLOW: PFS-IRC (Section 5.2.4); supplementary PFS-INV performed.

PFS-IRC was used in the comparisons with AMPLIFY against CLL14 and GLOW. PFS-INV was used in the comparison with CLL13, as the study did not report PFS-IRC.

5.2.8 Method of synthesis

The feasibility of performing a valid indirect treatment comparison (ITC) was assessed before comparative analyses were performed. The aim was to determine whether the key assumption for the ITC (i.e., exchangeability) had been met in the four trials included in the analysis see 5.1.1. The assumption was met if the treatment effects observed in the studies informing the ITC would be the same if individuals in each study were substituted to another trial.

To assess exchangeability, we evaluated the similarity and homogeneity of the studies:

- Similarity assumes that there is no difference in known and unknown effect modifiers between the studies.
- Homogeneity refers to the need for sufficient homogeneity as regards clinical (e.g., inclusion criteria) and methodological (e.g., study design) variables, and statistical variation (i.e., are the results sufficiently similar) across studies to justify combining the results.

The similarity and homogeneity assessment considered baseline data that were potentially prognostic and/or treatment effect modifiers in CLL, defined as:

- Covariates (e.g., patient characteristics) that affect or are prognostic of outcomes (prognostic factors);
- Treatment-specific covariates (e.g., patient characteristics) that alter the effect of treatment on outcomes so that the treatment is effective in different subgroups related to the effect modifier (treatment effect modifiers).

The prognostic factors and treatment effect modifiers were identified via a targeted literature search as described in sections 6.1.2.1 and 6.1.2.2.

5.2.8.1 Search methods

Prognostic factors and treatment effect modifiers for the outcomes of interest were identified via a targeted literature search of the following sources:

- CLL guidelines:
    - European Society of Medical Oncology (ESMO)

    - British Society for Haematology (BSH)
    - National Comprehensive Cancer Network (NCCN).
- Prognostic models or scoring systems predicting outcome/severity.
- Publications on prognostic factors identified in PubMed, search string:

  (("chronic lymphocytic leukaemia"[Title] OR "chronic lymphocytic leukemia"[Title]) AND (“prognostic score”[Title] OR “prognostic index"[Title] OR "prognostic model"[Title]) AND 2010/01/01:3000/12/31[Date - Publication])
- Inclusion criteria, stratification factors, and a pre-specified subgroup analysis for studies identified in the SLR.
- Factors used for adjustment in ITCs included in previous health technology assessment (HTA) submissions or peer-reviewed publications.

5.2.8.2 Search results

The main, validated prognostic index for predicting PFS and OS in CLL patients identified in the guidelines and from the PubMed search was CLL-IPI(28). This includes the following factors:

- Age group (>65 years)
- Clinical stage (Binet B/C or Rai I-IV)
- Del(17p) and/or *TP53* mutation
- *IGHV* mutation
- Beta-2 microglobulin level (>3.5 mg/L).

Additional prognostic factors that were reported by three or more sources included:

- Patient sex
- ECOG-PS
- Comorbidities
- Bulky disease
- Creatinine clearance
- Chromosomal abnormalities: trisomy 12 or del(11q) or del(17p) or del(13q).

These factors were reported by studies identified in the PubMed search (n=13), studies included in the feasibility assessment, and previous ITCs (n=6).

To identify potential effect modifiers for treatment in CLL, subgroup analyses reported for the studies included in the feasibility assessment were examined, including ELEVATE-TN and AMPLIFY. Most subgroup analyses were based on the aforementioned prognostic factors; however, no consistent or conclusive evidence of treatment effect modification was identified across these studies. The key covariates identified as potential prognostic factors in CLL are summarised in Table 24.

Table 24 Summary of potential prognostic factors for outcomes in chronic lymphocytic leukaemia

Covariate
Age
Disease stage
Del(17p) deletion
TP53 mutation
Unmutated *IGHV*
Beta-2 microglobulin level
Chronic lymphocytic leukaemia international prognostic index (CLL-IPI) score
Patient sex
Eastern Cooperative Oncology Group performance status (ECOG-PS)
Comorbidities
Bulky disease
Creatinine clearance
Chromosomal abnormality: trisomy 12 or del(11q) or del(17p) or del(13q)

CLL-IPI, International Prognostic Index for Chronic Lymphocytic Leukaemia; ECOG-PS, ECOG Performance Status scale; *IGHV*, immunoglobulin heavy-chain variable region gene; *TP53*, tumour protein p53 gene.

5.2.8.3 Feasibility assessment

Fourteen RCTs and two, single-arm studies were included in the ITC feasibility assessment. Two studies had a high risk of bias (FLAIR and ALLIANCE), otherwise they were well conducted with a low-to-moderate risk of bias.

The feasibility assessment revealed significant heterogeneity in design, population inclusion criteria, and treatment administration across the studies, as seen in the study characteristics summarised in Table 25. The era during which the studies were conducted also differed; here, the differential impact of COVID-19 on how each study was conducted and associated processes and outcomes could represent a potential source of bias in an NMA.

Table 25 Study characteristics and key inclusion criteria of the 16 studies included in the feasibility assessment for ITC

Study [published data cuts]	Study design	Country	Period of conduct	Cytogenetics	Age (years)	ECOG-PS	CIRS	Creatinine clearance (mL/min)	Follow-up (months; latest data cut)	Treatment arm	Treatment duration	Number of patients
AMPLIFY	Open-label, Phase 3 RCT	27 countries	2019–24	Without del(17p) or m*TP53*	≥18	≤2	<6	≥50	36	AV	Fixed	291
										AVO	Fixed	286
										FCR/BR	Fixed	290
ELEVATE-TN	Open-label, Phase 3 RCT	18 countries	2015–17	Not restricted	≥65 or ≥18 with comorbidities	≤2	>6	30–69	72	AO	TTP	179
										A	TTP	179
										OC	Fixed	177
CLL11	Open-label, Phase 3 RCT	26 countries	2010–12	Not restricted	≥18	–	>6	<70	36	OC	Fixed	333
										RC	Fixed	330
										C	Fixed	118
CLL13	Open-label, Phase 3 RCT	9 EU countries & Israel	2016–19	Without del(17p) or m*TP53*	≥18	≤2	<6	≥70	48	FCR/BR	Fixed	229
										VR	Fixed	237
										VO	Fixed	229
										VOI	TTP	231
CLL14	Open-label, Phase 3 RCT	21 countries	2014–18	Not restricted	≥18	–	>6	<70	72	VO	Fixed	216
										OC	Fixed	216
GLOW	Open-label, Phase 3 RCT	14 countries	2018–19	Not restricted	≥65 or ≥18 with comorbidities	≤2	>6	<70	64	IV	Fixed	106
										OC	Fixed	105
ALLIANCE			2013–16	Not restricted	≥65	≤2	–	≥ 40	55	BR	Fixed	183

	Phase 3 RCT	USA & Canada								I	TTP	182
										IR	TTP	182
iLLUMINATE	Open-label, Phase 3 RCT	16 countries	2014–18	Not restricted	≥65 or ≥18 with comorbidities	≤2	>6	<70	45	IO	TTP	113
										OC	Fixed	116
ChangE	Open-label, Phase 3 RCT	5 Asian countries	2020–24	Without del(17p) or m*TP53*	≥65 or ≥18 with comorbidities	–	>6	30–69	–	A	TTP	77
										RC	Fixed	78
RESONATE-2	Open-label, Phase 3 RCT	16 countries	2013–15	Without del(17p) or m*TP53*	≥65	≤2	–	Adequate renal function	60	I	TTP	136
										C	Fixed	133
CRISTALLO	Open-label, Phase 3 RCT	5 countries	2020–23	Without del(17p) or m*TP53*	≥18	–	≤6	≥ 70	–	VO	Fixed	80
										FCR/BR	Fixed	86
FLAIR	Open-label, Phase 3 RCT	UK	2014–18	Without del(17p)	≥18 to ≤75	WHO ≤2	–	–	48	IR	TTP	386
										FCR	Fixed	385
SEQUOIA	Open-label, Phase 3 RCT	14 countries	2017–19	Without del(17p)	≥65 or ≥18 with comorbidities	≤2	>6	<70	60	Z	TTP	241
										BR	Fixed	238
E1912	Open-label, Phase 3 RCT	USA	2014–16	Without del(17p) or m*TP53*	<70	≤2	–	–	36	IR	TTP	354
										FCR/BR	Fixed	175

CAPTIVATE FD (29-31)	Open-label, Phase 2 SAT	5 countries	2016–20	Not restricted	≥18 to <70	≤2	–	Adequate renal function	36	IV	Fixed	159
Jain *et al*., 2019	Open-label, Phase 2 SAT	USA	2016–18	Not restricted	≥65, or ≥18 with >1 high-risk genetic feature	≤2	–	>50	36	IV	Fixed	80

–, not reported. A, acalabrutinib; AV, acalabrutinib + venetoclax; AVO, acalabrutinib + venetoclax + obinutuzumab; BR, bendamustine + rituximab; CIRS, Cumulative Illness Rating Scale; C, chlorambucil; ECOG-PS, Eastern Cooperative Oncology Group Performance Status score; FCR, fludarabine + cyclophosphamide + rituximab; I, ibrutinib; IO, ibrutinib-obinutuzumab; IR, ibrutinib-rituximab; IV, ibrutinib-venetoclax; OC, obinutuzumab-chlorambucil; m*TP53*, mutated tumour protein p53 gene; RCT, randomized controlled trial; RC, rituximab + chlorambucil; SAT, single-arm trial; TTP, Treat to progression; VO, venetoclax + obinutuzumab; Z, zanubrutinib.

5.2.9 Statistical methods

There was substantial heterogeneity across the network of studies considered for an NMA. Due to the differences in baseline characteristics, assumptions about the equivalence of comparator therapies and proportional hazards mean that a NMA will lack clinical validity. Such concerns would be compounded by the impact of the COVID-19 pandemic and treatment switching based on unadjusted treatment effect estimates in several key trials included in the network. This would make it difficult to justify combining these data. Therefore, a population-adjusted ITC using a smaller subset of studies that includes the comparator treatment of interest should be used. Since the GLOW, CAPTIVATE, CLL13, and CLL14 studies included IV or VO as a comparator arm, these were considered for an unanchored comparison with AMPLIFY.

There was significant non-overlap in patient characteristics in the studies, particularly regarding age, CIRS, and cytogenetic abnormalities. This would, therefore, undermine the positivity assumption required for a matching-adjusted indirect comparison (MAIC), i.e., that all patients in target population are represented by patients in the matching cohort. Moreover, as the distribution of matching covariates differed markedly, MAICs would result in extreme weights being assigned to a small subset of patients, in turn severely reducing the effective sample size and potentially resulting in estimates that are neither credible nor statistically robust.

Based on the lack of overlap between key population characteristics and the related limitations of using a MAIC, the preferred option was a regression-based, simulated treatment comparison (STC) approach. Regression-based approaches, such as STC, are not restricted to scenarios with sufficient overlap, provided that extrapolation beyond the range of individual patient data (IPD) is valid.(30)

In summary, a STC was used for the ITCs with GLOW (IV comparator) and CLL14 (VO comparator). However, since CLL13 had relatively comparable baseline characteristics to AMPLIFY (Table 3 and Table 25), an anchored ITC was possible for this study via the common comparator (FCR/BR) using the method of Bucher *et al*.(32)

5.2.10 Simulated treatment comparison

The STCs were performed according to methodology described by Fawsitt *et al*.(33) The STC approach utilizes IPD from one study and aggregate data from a comparator trial to compare the relative efficacy of two treatments indirectly.(34, 35) Predictive equations are developed by modelling the association between outcomes and baseline covariates in the IPD population. These are used to predict the outcomes of AV that would have been observed in the aggregate comparator population.

Firstly, a parametric survival model was fitted using IPD from the AMPLIFY study:

$$g(s(t)) = \beta_0 + \beta_1 X$$

where β_0 is an intercept term, β_1 a vector of coefficients for prognostic variables and effect modifiers, and X a subvector of the full covariate vector that is transformed onto a linear predictor scale with link function $g(\cdot)$.

From this model, the predicted survival curve at the average characteristics $\mu(x)$ of the comparator arm was calculated:

$$g(s(t,\mu(x))) = \beta_0 + \beta_1\mu(x)$$

This equation was then used to predict the effect of AV on an "average" patient in the comparator cohort ($RMST_{CEM(comp)}$), where RMST is the restricted mean survival time.

For an unanchored ITC, the treatment difference is estimated as:

$$RMST_{comp} - RMST_{CEM(comp)}$$

where $RMST_{comp}$ is the effect of the comparator treatment in the comparator study.

The standard error (and associated 95% CIs) for the treatment differences was estimated using the standard errors for the RMST of each treatment. Since the treatment groups are independent, the variance of the difference is the sum of the individual variances; the square-root of this is the standard error of the difference.

Confidence limits were then calculated assuming normality of the sampling distribution:

$$RMST\ diff\ CLs = RMST\ diff\ estimate \pm (1.96 \times RMST\ diff\ std.error)$$

5.2.11 Parametric survival models

For each endpoint (PFS-IRC and OS) for AV in AMPLIFY, parametric survival models were fitted to the survival data using the flexsurv package in R.(36) Parametric models recommended by the National Institute for Health Care Excellence Technical Support Document (NICE TSD14) were used (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic).(37) These models make explicit assumptions regarding the shape of the hazard by imposing a specific statistical model on the event times. For instance, an exponential distribution assumes a constant hazard of the event, while Weibull or Gompertz assume monotonic hazards.(37) The choice of distribution in modeling the outcome determines how the relative effect of AV versus comparator treatments are expressed.

The best-fitting models were selected using the Akaike information criterion (AIC). This assesses the goodness-of-fit of the model to the data using the likelihood function, whilst penalising models with a greater number of estimated parameters to avoid overfitting. A lower AIC suggests a more parsimonious model.

The RMST was estimated from the best-fitting parametric model for AMPLIFY and from digitized KM data for the comparator studies using the minimum of the longest follow-up time between the two studies for each endpoint. The standard error and 95% CIs for the RMST in AMPLIFY were estimated via sampling from the normal asymptotic distribution of the estimated parameters for each model.

5.2.12 Covariate selection

Baseline characteristics reported by both AMPLIFY and the comparator studies, and therefore available for inclusion in the predictive model, were compared across studies. For comparator studies evaluating the same treatment (i.e., IV or VO), aggregate baseline data were combined to enable a pooled comparison. This was possible since all

the covariates were binary variables. Additionally, separate analyses were conducted for GLOW and CLL14 because these studies reported more complete baseline data, including the CIRS score.

For the unanchored STCs, the difference in RMST was calculated for three different models, namely the:

- Full model: all available covariates were reported by both studies.
- Unadjusted model: no covariates were reported.
- AIC-optimised model: a subset of covariates selected by backward, stepwise selection resulting in the best (lowest) AIC. The selection process was conducted using the parametric distribution from the best-fitting model using all covariates.

As an additional sensitivity analysis, these three models were also run using the three best-fitting parametric distributions for each endpoint or treatment combination (based on the model with all covariates).

5.2.13 Restricted mean survival time for comparator studies

For each endpoint (PFS-IRC and OS) and each treatment arm (IV and VO) in CLL14 and GLOW, the RMST was estimated non-parametrically using KM curves. The curves were fitted to the reconstructed survival data from digitally published KM curves using the survival package in R. The standard error and 95% CIs for the RMST were estimated as described in the vignette for the survival package in R.(36)

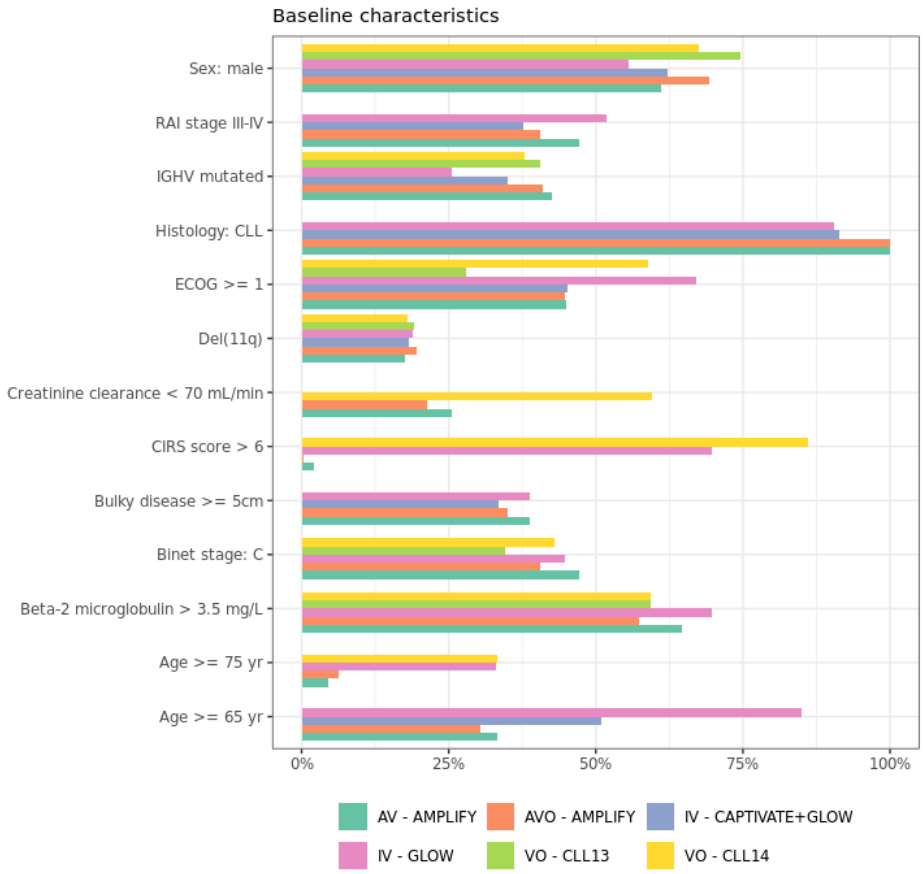
5.2.14 Comparative analysis results

The results of the STCs for PFS and OS using IPD from the AV arm in AMPLIFY, and aggregate data from CLL14 and GLOW, as well as the anchored Bucher ITC for CLL13, are described in this section.

5.2.15 Covariate selection for outcome prediction models

The baseline characteristics available for both AMPLIFY and comparator studies CLL14 and GLOW are shown in Figure 9.

Figure 9 Distribution of baseline characteristics, by treatment comparator



CIRS, Cumulative Illness Rating Scale; ECOG-PS, ECOG Performance Status scale; *IGHV*, immunoglobulin heavy-chain variable region gene.

The subset of baseline characteristics retained following the AIC-based procedure using backwards stepwise selection on the best-fitting model for the AV arm are listed in Table 26. ECOG PS, creatinine clearance and sex were dropped from all models.

Table 26 Subset of variables selected using AIC-based backwards stepwise regression for AV treatment arm, by endpoint and study

Treatment	Endpoint	Parameter	GLOW	CLL14
AV	OS	Age ≥65 years	Y	
AV	OS	Age ≥75 years		Y
AV	OS	Beta-2 microglobulin >3.5 mg/L	Y	Y
AV	OS	Del(11q)	Y	Y
AV	PFS	Beta-2 microglobulin >3.5 mg/L	Y	Y
AV	PFS	Binet stage C		Y
AV	PFS	Bulky disease ≥ 5 cm	Y	
AV	PFS	*IGHV* mutated	Y	Y
AV	PFS	RAI stage III-IV	Y	

AV, acalabrutinib + venetoclax; CIRS, Cumulative Illness Rating Scale; ECOG-PS, ECOG Performance Status scale; *IGHV*, immunoglobulin heavy-chain variable region gene; OS, Overall Survival; PFS, Progression-Free Survival.

5.2.16 Simulated treatment comparison results from best-fitting parametric model with all covariates included (full model)

5.2.16.1 Overall survival

The RMST difference with 95% CIs for OS (Table 27) for the ITCs for AV with IV and VO from the best-fitting parametric models are shown in a Forest plot (Figure 10). The STC-adjusted survival curves for each comparison are shown in Figure 11.

At 57.7 months of follow-up, there was no significant difference in RMST for AV compared to GLOW [redacted] Similarly, there was no significant difference in RMST for the comparative analysis with CLL14 for the VO comparator [redacted]

Therefore, these results show no statistically significant differences in treatment efficacy in AV, IV and VO regarding OS.

Table 27 Restricted mean survival time difference for overall survival (57.7-month follow-up) from the simulated treatment comparison using all covariates

Study	Distribution	RMST difference (AV; comparator) months (95% CI)
AV reference		
GLOW (IV)	Gompertz	xxxx
CLL14 (VO)	Gompertz	xxxx

AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; OS, overall survival; RMST, restricted mean survival time; VO, venetoclax + obinutuzumab.

Figure 10 xxxxxxxxxxxxx

AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; OS, overall survival; RMST, restricted mean survival time; VO, venetoclax + obinutuzumab.

Figure 11 xxxxxxxxxxx

5.2.16.2 Progression-free survival

The RMST differences with 95% CIs for PFS-IRC for the ITCs for AV with IV and VO from the best-fitting parametric models are shown in a Forest plot (Figure 12). The STC-adjusted survival curves for each comparison are shown in Figure 13.

At 55.1 months of follow-up, there was no significant difference in RMST for AV compared to IV in GLOW (xxxxxxxxxxxxxxxxxxxxxxxx Similarly, the RMST was not significantly different in the separate analysis for CLL14 xxxxxxxxxxxxxxx

Therefore, these results show no statistically significant differences in treatment efficacy in AV, IV and VO regarding PFS.

Table 28 Restricted mean survival time differences for progression-free survival (55.1-month follow-up) from s simulated treatment comparisons using all covariates

Study	Distribution	RMST difference (AV; comparator) months (95% CI)
AV reference		
GLOW (IV)	Gompertz	xxxx
CLL14 (VO)	Gompertz	xxxx

AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; RMST, restricted mean survival time; VO, venetoclax + obinutuzumab.

Figure 12 xxxxxxxxxxxxxxxxxxxxxx

Figure 13 xxxxxxxxxxxxxxxxxxxxxxxxxxxxx

5.2.16.3 Simulated treatment comparison sensitivity analyses

5.2.16.4 Using different covariate options

The RMST differences for the sensitivity analysis comparing STC results for the best-fitting parametric model using the different covariate options (full model, unadjusted model and AIC-optimised model) are shown in Forest plots for OS (Figure 14) and PFS (Figure 15). The full set of results for RMST differences for OS and PFS are shown in Table 29.

For the separate STC analyses of GLOW (IV) and CLL14 (VO), the unadjusted and AIC-optimised models had improved point estimates for OS and less favourable point estimates for PFS, and narrower CIs compared to the full models that included all available covariates.

Therefore, these results show no statistically significant differences in treatment efficacy in AV, IV and VO regarding OS and PFS.

Figure 14 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

AIC, Akaike Information Criterion; AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; OS, overall survival; RMST, restricted mean survival time; VO, venetoclax + obinutuzumab.

Figure 15: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

AIC, Akaike Information Criterion; AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; PFS, progression-free survival; RMST, restricted mean survival time; VO, venetoclax + obinutuzumab.

Table 29 Restricted mean survival time differences for overall survival and progression-free survival from simulated treatment comparisons using different covariate options

Treatment		Distribution	Covariates	RMST difference (AV; comparator) months (95% CI)
GLOW (IV)				
OS	AV	Gompertz	All	[redacted]
OS	AV	Gompertz	No covariates	[redacted]
OS	AV	Gompertz	AIC-based selection	[redacted]
PFS	AV	Gompertz	All	[redacted]
PFS	AV	Gompertz	No covariates	[redacted]
PFS	AV	Gompertz	AIC-based selection	-0.9 (-4.7–3.0)
CLL14 (VO)				
OS	AV	Gompertz	All	[redacted]
OS	AV	Gompertz	No covariates	[redacted]
OS	AV	Gompertz	AIC-based selection	[redacted]
PFS	AV	Gompertz	All	[redacted]
PFS	AV	Gompertz	No covariates	[redacted]
PFS	AV	Gompertz	AIC-based selection	[redacted]

AIC, Akaike Information Criterion; AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time; VO, venetoclax + obinutuzumab.

5.2.16.5 Using the three, best-fitting parametric survival distributions

The STCs were also re-run using the different covariate options to compare results of the three, best-fitting parametric survival distributions to the AMPLIFY data. The resultant Forest plots for this sensitivity analysis are shown in Figure 16 Figure 17. The RMST differences (95% CIs) were almost identical across the distributions, indicating stability in the base case results presented in Section 5.2.16.1 and Section 5.2.16.2.

Figure 16 [redacted]

AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time.

Figure 17 [redacted]

5.2.17 Anchored Bucher indirect treatment comparison with CLL13

5.2.17.1 Overall survival

The hazard ratios with 95% CIs for OS (Table) for the Bucher ITC using CLL13(10) are shown in a Forest plot (Figure 18). There was no significant difference in OS for AV vs. VO ([redacted]

Therefore, these results show no statistically significant differences in treatment efficacy in AV and VO regarding OS.

Figure 18 [redacted]

Table Hazard ratios for overall survival from the Bucher indirect treatment comparison of AMPLIFY with CLL13

Treatment comparison	HR (95% CI)
Study results	
VO vs. FCR/BR	0.56 (0.25–1.22)
AV vs. FCR/BR	0.33 (0.18–0.56)
Bucher ITC	
AV vs. VO	[redacted]

AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CI, confidence interval; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; ITC, indirect treatment comparison; VO, venetoclax + obinutuzumab.

5.2.17.2 Progression-free survival

The hazard ratios with 95% CIs for OS (Table 30) for the Bucher ITC utilising the PFS-INV results of CLL13 and AMPLIFY(10) are shown in a Forest plot (Figure 19). There was no significant difference in PFS-INV for AV vs. VO [redacted]

Therefore, these results show no statistically significant differences in treatment efficacy in AV and VO regarding PFS.

Figure 19 [redacted]

AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CI, confidence interval; FCR, fludarabine + cyclophosphamide + rituximab; ITC, indirect treatment comparison; PFS-INV, progression-free survival (investigator-assessed); VO, venetoclax + obinutuzumab.

Table 30 Hazard ratios for investigator-assessed, progression-free survival from the Bucher indirect treatment comparison of AMPLIFY with CLL13

Treatment comparison	HR (95% CI)
Study results	
VO vs. FCR/BR	0.47 (0.34–0.66)
AV vs. FCR/BR	0.58 (0.43–0.78)
Bucher ITC	
AV vs. VO	[redacted]

AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CI, confidence interval; FCR, fludarabine + cyclophosphamide + rituximab; HR, hazard ratio; ITC, indirect treatment comparison; VO, venetoclax + obinutuzumab.

5.2.18 Summary

To produce clinically and scientifically valid efficacy comparisons between the AV, IV, and VO regimens we performed an ITC feasibility assessment, which revealed significant heterogeneity in design, population inclusion criteria, and treatment administration across the studies. There was substantial heterogeneity across the network of studies considered for an NMA, and a lack of overlap between key population characteristics and the related limitations of using a MAIC. Therefore, we produced a STC utilizing GLOW and CLL14, and an anchored Bucher ITC utilizing CLL13.

At almost 5 years of follow-up, the STC for AV vs. IV and AV vs. VO showed no statistically significant differences in treatment efficacy as regards OS and PFS (Table 31). More covariates were included in the separate STCs using CLL14 and GLOW, such as CIRS score and creatinine clearance that overlapped the least with AMPLIFY. This resulted in wider confidence intervals, as expected. The additional uncertainty arising from including these two covariates was also reflected in the sensitivity analyses. The sensitivity analyses using alternative parametric survival distributions were almost identical to the best-fitting model. This implies that the results from the base-case analysis were robust as regards the parametric function used in the model specification.

The results of the anchored ITC comparison with CLL13 (AV vs. VO) also showed no statistically significant differences in treatment efficacy as regards survival outcomes (Table 32).

Table 31 Summary: comparative analysis results for AMPLIFY vs. GLOW, and vs. CLL14

Outcome measure	AMPLIFY (AV) vs.	Distribution	RMST difference (AV; comparator) months (95% CI)
Overall survival			
	GLOW (IV)	Gompertz	[redacted]

Outcome measure	AMPLIFY (AV) vs.	Distribution	RMST difference (AV; comparator) months (95% CI)
At 57.7 months follow-up	CLL14 (VO)	Gompertz	[redacted]
Progression-free survival			
At 55.1 months follow-up	GLOW (IV)	Gompertz	[redacted]
	CLL14 (VO)	Gompertz	[redacted]

AV, acalabrutinib + venetoclax; CI, confidence interval; IV, ibrutinib-venetoclax; VO, venetoclax + obinutuzumab.

Table 32 Summary: comparative analysis results for AMPLIFY vs. CLL13

Outcome measure	Treatment comparison	HR (95% CI)
Overall survival	**Study results**	
	VO vs. FCR/BR	0.56 (0.25–1.22)
	AV vs. FCR/BR	0.33 (0.18–0.56)
	Bucher ITC	
	AV vs. VO	[redacted]
Progression-free survival (investigator-assessed)	**Study results**	
	VO vs. FCR/BR	0.47 (0.34–0.66)
	AV vs. FCR/BR	0.58 (0.43–0.78)
	Bucher ITC	

Outcome measure	Treatment comparison	HR (95% CI)
	AV vs. VO	[redacted]

AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CI, confidence interval; FCR, fludarabine + cyclophosphamide + rituximab; HR, Hazard ratio; ITC, indirect treatment comparison; PFS-INV, progression-free survival (investigator-assessed); VO, venetoclax + obinutuzumab.

5.3 Conclusion

We conducted an ITC of AV vs. IV and vs. VO in previously untreated CLL patients. Active comparator arms from two clinical trials (CLL14 and GLOW) were included in unanchored, pairwise comparisons with the AV treatment arm from AMPLIFY using STC methodology. To reinforce the findings of the STC of AV versus VO, and anchored ITC using Bucher methodology was produced due to the common comparator arm in the AMPLIFY and CLL13 studies. Table 33 displays the results of these comparisons for each outcome measure.

In the efficacy comparisons, there was no significant difference in terms of OS and PFS between the AV and IV regimens and the AV and VO regimens. This was confirmed in the Bucher results for the AV and VO comparison.

In the safety comparisons, it was evident that the regimen containing acalabrutinib results in a significant reduction of AE (≥ grade 3) and SAE. The minimum clinically relevant difference as defined by the DMC is 10 percentage points for AE. The AV regimen shows 20% fewer grade 3 and above AE compared to IV, and 30% fewer compared to VO. Additionally, AMPLIFY reports 20% and 25% fewer SAE compared to IV and VO, respectively.

To conclude, the ITCs showed no significant difference in the efficacy, and improved safety of the AV regimen compared to the IV and VO regimens (Table 33).

Table 33 The minimum clinically relevant difference in survival outcome results vs. those of the simulated treatment and Bucher indirect treatment comparisons

Outcome measure	Importance	Unit of measurement	Minimum Clinically Relevant Difference	Result in comparison
Overall survival	Critical	Difference in survival rate at 3 years or longest follow-up	5 percentage points	**STC:** no significant difference **BUCHERS vs. CLL13:** no significant difference

Progression-free survival	Important	Difference in PFS rate after 3 years or longest follow-up	10 percentage points	**STC:** no significant difference **BUCHERS vs. CLL13:** no significant difference
Proportion experiencing grade ≥3 adverse events	Important	Adverse events	10 percentage points	**Any grade ≥3 AE** **AV:** 53.6% at median follow-up of 41.3 months **IV:** 75.5% at median follow-up of 27.7 months **VO (CLL14):** 78.8% at median follow-up of 39·7 months **VO (CLL13):** 80.3% at median follow-up 50·7 months
Review of serious adverse events	Important	Qualitative review	–	**Any SAE** **AV:** 72(24.7%) at median follow-up of 41.3 months **IV:** 49 (46.2%) at a median follow-up of 27.7 months **VO (CLL14):** 104 (49.1%) at a median follow-up of 28.1 months

				VO (CLL13): 108 (47.4%) at a median follow-up time of 38.8 months
Quality of Life	Important	Validated generic measure (e.g., EORTC QLQC30)	0.05 (scale 0–1) or 5 points (scale 0–100); alternatively 0.5 SMD	**NA**

AE, adverse event; AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; CI, confidence interval; FCR, fludarabine + cyclophosphamide + rituximab; HR, Hazard ratio; ITC, indirect treatment comparison; NA, not applicable; SAE, serious adverse event; STE, simulated treatment comparisons; VO, venetoclax + obinutuzumab.

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Appendix A. Main characteristics of studies included

Table AMPLIFY: 34 main study characteristics

Trial name: AMPLIFY	**NCT03836261**
Objective	To evaluate the efficacy and safety of (i) acalabrutinib in combination with venetoclax, and (ii) acalabrutinib in combination with venetoclax, with and without obinutuzumab (AV, AVO) compared to chemoimmunotherapy (FCR/BR) in subjects with previously untreated chronic lymphocytic leukaemia (CLL).
Publications – title, author, journal, year	Brown *et al.*, 2025. Fixed-duration acalabrutinib combinations in untreated chronic lymphocytic leukemia. N Eng J Med 392: 748–762.
Study type and design	Randomized, global, multicentre, open-label, Phase 3 study of the efficacy and safety of AV and AVO vs. chemoimmunotherapy (FCR/BR) in subjects with previously untreated CLL without del(17p) or *TP53*. Subjects were randomized (1:1:1 ratio) into three study arms via a block-stratified randomization procedure. The study included screening (35 days), treatment (from randomization until study drug discontinuation), and a follow-up phase. AV, acalabrutinib + venetoclax; BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; *TP53*, tumour protein p53 gene.
Sample size (n)	984
Main inclusion criteria	• Men and women aged ≥18 years. • Eastern Cooperative Oncology Group performance score (ECOG-PS) 0–2. • Diagnosis of CLL meeting published diagnostic criteria. (Hallek et al. 2018) • Active disease according to iwCLL 2018 criteria requiring treatment. • Use of highly effective birth control during the study.

Trial name: AMPLIFY	NCT03836261
Main exclusion criteria	• Any prior CLL-specific therapies. • Detected del(17p) or *TP53* mutation. • Transformation of CLL to aggressive non-Hodgkin lymphoma (e.g., Richter's transformation, prolymphocytic leukaemia, or diffuse large B cell lymphoma) or central nervous system involvement by leukaemia. • History of confirmed progressive multifocal leukoencephalopathy (PML). • Received any investigational drug within 30 days before first dose of study drug. • Major surgical procedure within 30 days before the first dose of study drug. • Significant cardiovascular disease, such as symptomatic arrhythmias, congestive heart failure or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease. Note: subjects with controlled, asymptomatic atrial fibrillation were allowed to enrol. • Malabsorption syndrome; disease significantly affecting gastrointestinal function; stomach resection or extensive small bowel resection that was likely to affect absorption; symptomatic inflammatory bowel disease; partial or complete bowel obstruction; or, gastric restrictions and bariatric surgery (e.g., gastric bypass). • Received a live virus vaccination within 28 days of first dose of study drug. • Known history of infection with human immunodeficiency virus (HIV). • Serologic status reflecting active hepatitis B or C infection. • History of known hypersensitivity or anaphylactic reactions to study drugs or excipients. • History of stroke or intracranial haemorrhage within 6 months before first dose of study drug. • Known bleeding disorders. • Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists. • Breastfeeding or pregnant female participants.

Trial name: AMPLIFY	NCT03836261
	• Concurrent participation in another therapeutic clinical trial.
Intervention	Acalabrutinib: a Bruton's tyrosine kinase inhibitor (BTKi; a targeted therapy); oral tablet (100 mg) taken twice daily every 12 hours, starting at cycle 1; fixed duration; 14 cycles (100 mg) Venetoclax: a B-cell lymphoma 2 (Bcl-2) inhibitor; oral (capsule or tablet) taken once daily from cycle 3, a 5-week ramp-up with doses of 20 mg, 50 mg, 100 mg, 200 mg, then 400 mg as a fixed daily dose until end of cycle 14, start of new anti-CLL therapy or CLL progression or unacceptable toxicity.
Comparator(s)	All patients randomised to standard CIT received up to six cycles[a] of either FCR or BR as intravenous (IV) infusions, according to standard institutional practice. Patients aged ≤65 years with a creatinine clearance of ≥70 mL/min were restricted to FCR.
Follow-up time	Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in Arm C (FCR/BR). Median duration of follow-up after end of treatment was 28.3 months in Arm A (AV).
Primary, secondary and exploratory endpoints	**Primary endpoint** • **PFS-IRC of AV vs. FCR/BR:** Progression-free survival (PFS), defined as the time from randomisation until disease progression (as per IWCLL 2018 criteria) or death from any cause, whichever occurs first, was calculated as the date of first disease progression or death (or censoring date for censored patients) minus the randomisation date, plus one day. **Secondary endpoints** • **PFS-IRC of AVO vs FCR/BR:** PFS-IRC definition and calculation as for PFS-IRC. • **Overall survival (OS):** Time from randomisation to death from any cause calculated as the death date (or censoring date) minus the randomisation date, plus one day. Patients not known to have died before the DCO date were censored. • **Minimal residual disease (MRD) Negativity Rate:** MRD, measured by flow cytometry in blood and bone marrow, was assessed at the start of cycle 9 (AV Arm), cycle 10 (AVO Arm), and 12 weeks post cycle 6 initiation (FCR/BR Arm). The MRD negativity rate was the proportion of

patients with blood or bone marrow containing <1 CLL cell per 10,000 leukocytes.

- **PFS-INV of AV vs. FCR/BR:**
  PF-INV definition and calculation as for IRC-PFS.

- **IRC-EFS and PFS-INV:**
  EFS (event-free survival), as the time from randomisation to the first instance of disease progression, death, or the start of subsequent anti-CLL therapy, was calculated as the date of the first event (or censoring date for censored patients) minus the randomisation date, plus one day. This endpoint is reported in the Appendix (Secondary Endpoints: IRC-EFS).

- **IRC-ORR and INV-ORR:**
  Overall response rate (ORR) was the proportion of patients who achieved a best overall response (BOR) of CR, CRi, nPR, or PR; only patients with measurable disease at baseline were included in this analysis.

- **IRC-BOR and INV-BOR:**
  BOR, defined as the best response among CR, CRi, nPR, PR, stable disease, or PD, was assessed by IRC or investigator according to iwCLL 2018 criteria. This was at or before the first subsequent anti-CLL therapy or disease progression, whichever came first.

- **IRC-DOR and INV-DOR:**
  Duration of response (DOR), as the period from the first response of CR, CRi, nPR, or PR to the first documented disease progression or death, was calculated as the event or censoring date minus the date of first CR, CRi, nPR, or PR, plus one day.

- **IRC-TTNT and INV-TTNT:**
  Time-to-next treatment (TTNT) was the time from randomisation to the initiation of non-protocol-specified CLL treatment or death. Non-protocol-specified treatment included commercial acalabrutinib therapy. Patients who had not started such treatment before the DCO date were censored at their last visit. TTNT was calculated as the earlier of the start date of such treatment or date of death (or last visit for censored patients) minus randomisation date, plus one day.

Safety endpoints

- **Adverse events (AEs):**
  Graded according to NCI CTCAE v5.0 for both haematological and non-haematological AEs. Each AE was coded using MedDRA terminology.

- **Treatment emergent adverse events (TEAEs):**
  Any events with onset on or after the first dose of study drug, or ongoing events that worsened in severity after the first dose and before 30 days post-last dose or before new anti-CLL therapy. If both start and end dates were missing or fell after dosing, the AE was considered to be a TEAE.

- **Adverse events of special interest (AESIs):**
  Identified based on preclinical findings, emerging clinical data on acalabrutinib, and pharmacological effects of approved BTK inhibitors, AESIs required close monitoring and prompt communication with the Sponsor, and might be serious or non-serious. AESIs included ventricular arrhythmias and suspected transmission of infectious agents via biological products.

- **Events of clinical interest (ECIs):**
  Selected based on preclinical and clinical study data for acalabrutinib and on pharmacological effects of BTK inhibitors. Dedicated analyses used Standardised MedDRA Queries, system organ classes, or sponsor-defined groupings. A detailed ECI list formed part of the SAP for all acalabrutinib studies and was used internally.

Exploratory endpoints

- **Patient-reported outcomes (PROs):**
  Included assessment of disease-related symptoms and health-related quality of life by EORTC QLQ-C30; symptoms from the IL27; fatigue by the FACIT-Fatigue Scale; overall impression of health status changes via the PGI-C scale; and, overall impression of cancer symptom severity by the PGI-S scale.

- **Medical resource utilisation data (MRU):**
  Included hospitalisations, emergency department visits, transfusions, and use of haematopoietic growth factors; collected for each treatment arm.

Endpoints included in this application:

Primary endpoint

- IRC-PFS of AV compared with FCR/BR.

Secondary endpoints

- OS
- AEs
- TEAEs.

AE, adverse event; OS, overall survival; PFS, progression-free survival; PFS-IRC, Progression-Free Survival (Independent Review Committee-assessed); PFS-INV, Progression-Free Survival (Investigator-assessed); TEAE, treatment emergent adverse event

Method of analysis

- **Statistical analyses and data summaries conducted using SAS® Version 9.4 or higher.**
- **Descriptive statistics provided for all variables as appropriate.**
    - Continuous variables: summarized by number of observations, mean, standard deviation (SD), median, upper and lower quartiles, minimum, and maximum.
    - Categorical variables: summarized by frequency counts and percentages for each category.
- Percentages were calculated out of the total for the corresponding treatment group, unless otherwise stated. Overall totals were calculated for baseline summaries only.
- Confidence intervals (CIs) were generally presented at the 2-sided 95% level; for binomial variables, exact methods were used unless otherwise specified.
- Calculation of time-to-event or duration endpoints was based on the study day of the event or censoring date, not visit number or label.
- Missing efficacy or safety data were not imputed unless otherwise specified.
- Conversion rules for days to cycle/months/years:
    - 1 cycle = 28 days = 4 weeks
    - 1 month = 30.4375 days
    - 1 year = 365.25 days
- All summaries were presented by treatment arm unless otherwise specified. Data listings were sorted by treatment arm and patient number.

Multiplicity

- Overall Type I error was controlled at the 0.05 level using the Lan-DeMets alpha-spending function based on O'Brien-Fleming boundaries, splitting α into nominal α1 (interim) and α2 (final) according to the information fraction.
- An alpha-exhaustive recycling strategy was used to adjust for multiplicity due to multiple endpoints.
- If PFS assessed by IRC in Arm A (AV) versus Arm C (FCR/BR) was statistically significant, secondary endpoints were tested in a fixed sequential hierarchical manner as detailed in the SAP.

Analysis of efficacy endpoints

- All efficacy analyses were performed on the Full Analysis Set (FAS) and analysed as randomized.
- PFS, EFS, TTNT, and OS analyses used a stratified 2-sided log-rank test.
- Hazard ratios (HR) and 95% CIs were estimated using a stratified Cox proportional hazards model.
- Stratification factors for all stratified analyses:
    - Age: >65 or ≤65 years
    - *IGHV* mutational status: mutated vs. unmutated
    - Rai stage: high-risk (≥3) vs. non-high-risk (<3)
    - Geographic region: North America vs. Europe vs. Other.

Subgroup analyses

Subgroup analyses were performed using potential prognostic variables at screening or baseline (listed below) to investigate the consistency and robustness of PFS as assessed by IRC between Arms A (AV) versus C (FCR/BR) and Arms B (AVG) versus C (FCR/BR):

• Randomization stratification factors per EDC/lab data recording:

- Age: >65 or ≤65

- *IGHV* mutational status: mutated vs. unmutated (including unproductive *IGHV* rearrangement)

- Rai stage: high risk (≥3) vs. non-high risk (<3)

- Geographic region: North America vs. Europe vs. Other

• Sex: male vs. female

• Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White

• Ethnicity: Hispanic or Latino, Not Hispanic or Latino

• ECOG-PS: 2, ≤1

Trial name: AMPLIFY	NCT03836261
	• Complex karyotype: Yes/No (Y/N) • CD38 expression: Y/N • ZAP-70 expression: Y/N • 11q deletion mutation: Y/N No adjustments to the significance level for testing were made since all these subgroup analyses were considered exploratory and were only supportive of the primary analysis of PFS. For each subgroup level of a factor, the HR and 95% CI (2-sided 95% profile likelihood CIs) were calculated using an unstratified Cox proportional hazards model. These were summarized and presented as a Forest plot with the overall primary analysis results.
Other relevant information	NA

Table 35 GLOW: main study characteristics

Trial name: GLOW	NCT03462719
Objective	To assess PFS from treatment with IV compared with CO as assessed by an Independent Review Committee (IRC). IV, ibrutinib + venetoclax; OC, obinutuzumab + chlorambucil.
Publications – title, author, journal, year	Kater *et al.*, 2022. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. NEJM Evid. 1(7): EVIDoa2200006. Munir *et al.*, 2023. "Impact of minimal residual disease on progression-free survival outcomes after fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in the GLOW study. JCO 41: 3689–3699. Niemann *et al.*, 2023. Fixed-duration ibrutinib–venetoclax versus chlorambucil–obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 24: 1423–1433. Moreno *et al.*, 2023. First-line fixed-duration ibrutinib plus venetoclax (Ibr+ Ven) versus chlorambucil plus obinutuzumab (Clb+ O): 55-month follow-up from the Glow Study. Blood 142: 634. Niemann *et al.*, 2024. First-line Ibrutinib plus Venetoclax vs chlorambucil plus obinutuzumab in elderly or comorbid patients

Trial name: GLOW	NCT03462719
	(pts) with chronic lymphocytic leukemia (CLL): glow study 64-month follow-up (FU) and adverse event (AE)-free progression-free survival (PFS) analysis. Blood 144: 1871.
Study type and design	Randomized, open-label, Phase 3 study of the combination of IV vs. CO for the first-line treatment of subjects with CLL/small lymphocytic lymphoma (SLL).
Sample size (n)	211
Main inclusion criteria	• Adult participants aged (a) ≥65 years or (b) 18–64 years with ≥1 of the following: 1. Cumulative Illness Rating Scale (CIRS) score >6. 2. Creatinine clearance estimated <70 mL/min using Cockcroft-Gault equation. • Diagnosis of CLL/SLL according to iwCLL criteria. • Measurable nodal disease (by computed tomography), defined as at least one lymph node >1.5 cm in longest diameter. • ECOG-PS ≤2 • Active CLL/SLL requiring treatment per the iwCLL criteria.
Main exclusion criteria	• Prior anti-leukaemic therapy for CLL or SLL. • Presence of del17p or known *TP53* mutation detected at a threshold of >10 percent (%) variable allele frequency. • Major surgery within 4 weeks of first dose of study treatment. • Known bleeding disorders (e.g., von Willebrand's disease or haemophilia). • Central nervous system involvement or suspected Richter's syndrome.
Intervention	N= 106 • Drug: ibrutinib (I) ○ Participants received ibrutinib 420 mg orally once daily for up to 15 cycles. • Drug: venetoclax (V)

Trial name: GLOW	NCT03462719
	○ Participants received venetoclax in combination with ibrutinib (IV) for a total of 12 cycles, beginning at Cycle 4. For the first 5 weeks of venetoclax treatment, the treatment dose was ramped up from 20 to 400 mg.
Comparator(s)	N= 105 • Drug: chlorambucil (C) ○ Participants received chlorambucil at a dose of 0.5 mg/kg body weight on Days 1 and 15 of Cycles 1 to 6. • Drug: obinutuzumab ○ Participants received obinutuzumab 1000 mg intravenously on Days 1, 8, and 15 of Cycle 1, and Day 1 of Cycles 2 to 6.
Follow-up time	Median follow-up of 64 months
Primary, secondary and exploratory endpoints	**Primary endpoint (Current Submission 2022-02-25)** • PFS: time from randomization to either disease progression determined by an IRC or death from any cause, whichever occurred first and assessed over up to 2 years and 10 months. The PFS was based on the iwCLL 2008 criteria, including new or enlarging lymph nodes (>15 mm); new hepatomegaly or splenomegaly; organ infiltrates; new bone lesions; ascites or pleural effusion due to CLL; ≥50% increase from nadir in lymph node size or sum diameters of multiple nodes; ≥50% increase from nadir in liver/spleen size; ≥50% rise in lymphocyte count (to ≥5×10^9/L); or rapid doubling of acetyl-L-carnitine (ALC) over two serial assessments if ALC was ≥30,000×10^9/L (unless treatment-related lymphocytosis); new cytopenia from CLL or transformation to a more aggressive histology. **Primary endpoint (Original Submission 2018-03-06)** • PFS: time from randomization to disease progression or death, whichever occured first, up to about 6 years. Progression was based on iwCLL 2008 guidelines. **Secondary endpoints (Current Submission 2023-08-07)**

- MRD Negative Rate: percentage of participants with bone marrow MRD <1 CLL cell per 10,000 leukocytes (or <0.01%) by next-generation sequencing. Missing MRD data treated as MRD-positive.
- Complete Response Rate (CRR): percentage of participants achieving complete response (CR) or complete response with incomplete marrow recovery (CRi) before starting further therapy, per IRC assessment. CR involved no lymphadenopathy/hepatosplenomegaly; no symptoms; neutrophils >1.5×10^9/L; platelets >100×10^9/L; haemoglobin >11 g/dL; ALC <4,000/µL; normocellular marrow with <30% lymphocytes and no nodules; CRi was CR with incomplete marrow recovery.
- ORR: percentage of participants with best overall response of CR, CRi, nodular partial response (nPR), or partial response (PR) according to iwCLL 2008. PR was a ≥50% decrease in relevant lymphoid parameters plus improvement in haematological parameters.
- OS: time from randomization to death from any cause, over up to 4 years and 10 months.
- DOR: interval from first documentation of response (including partial response with lymphocytosis) to first progression or death, according to IRC and iwCLL 2008 progression criteria.
- TTNT: time from randomization to the start of any subsequent anti-leukaemic therapy.
- Time to Worsening by EQ-5D-5L: interval from randomization to first observation of decline measured by EQ-5D-5L health status (≥7-point drop on the 0-100 VAS or ≥0.08 decline in utility score). The EQ-5D-5L describes health state in five dimensions resulting in a single utility score (from -1 to 1, lower means worse health).
- Time to Worsening by EORTC QLQ-C30: time from randomization to first observed functional deterioration, as measured by EORTC QLQ-C30 (≥10-point decline for function/global health, or ≥10-point worsening in symptoms on 0-100 scales).
- Time to Worsening and Improvement by FACIT-Fatigue: time from randomization to first ≥3-point decrease or

increase in the FACIT-Fatigue 13-item scale (0 = worst, 52 = best score).

- Number of participants with AE): tally of participants with AEs as a measure of safety and tolerability, assessed up to 4 years and 10 months.
- Number of participants with abnormal clinical laboratory findings: number of participants experiencing abnormal laboratory values (haematology/chemistry).
- Percentage with sustained haemoglobin improvement: percentage of participants with ≥2 g/dL rise in haemoglobin maintained for ≥56 days without blood transfusion or growth factors.
- Percentage with sustained platelet improvement: percentage of participants with ≥50% platelet rise from baseline for ≥56 days without transfusion or growth factors.
- Plasma concentration of IV: IV plasma concentrations determined at specific timepoints using validated LC-MS/MS to assess pharmacokinetics.

Secondary endpoints (Original Submission 2018-03-06)

- Percentage MRD Negative: proportion of participants with bone marrow MRD <1 CLL cell per 10,000 leukocytes or <0.01% determined by flow cytometry, up to 6 years.
- ORR: percentage with a best overall response of CR, CRi, PR, or nPR for ≥2 months. CR required no lymph nodes >1.5 cm; normal marrow; blood lymphocytes <4,000/µL; platelets >100,000/µL; hemoglobin >11 g/dL; neutrophils >1,500/µL.
- Complete Response (CR) Rate: proportion with no lymph nodes >1.5 cm, no hepatosplenomegaly, normal/normocellular bone marrow and blood parameters.
- DOR: time from initial documentation of response to first documented progression or death according to iwCLL 2008 criteria.
- OS: time from randomization to death from any cause.
- TTNT: from randomization to start of any post-study anti-leukaemic therapy.

- Time to Worsening by EORTC QLQ-C30: interval to a clinically important negative change; ≥10-point change considered meaningful.
- Time to Worsening by FACIT-Fatigue: interval to ≥3-point decrease in fatigue score, considered clinically important change.
- Time to Worsening by EQ-5D-5L: interval to at least 0.07-point decline in the utility score or ≥7-point drop in VAS, considered meaningful.
- Number of participants with AEs: number experiencing AEs, as a measure of safety/tolerability, up to 18 months.
- Number of participants with abnormal laboratory findings: tally of participants with abnormal lab results, up to 18 months.
- Percentage with sustained haemoglobin Improvement: percentage with persistent haemoglobin improvement over baseline, up to around 6 years.
- Percentage with sustained platelet improvement: percentage with persistent clinically significant platelet increase over baseline, up to around 6 years.
- Trough (Ctrough,ss) plasma concentration: ibrutinib concentration at steady-state collected at end of dosing interval (24 hours) on specified days/cycles, in the absence and presence of venetoclax.

Endpoints included in this application:

- PFS measured time from randomization to disease progression or death, whichever occured first, up to about 6 years, with progression based on iwCLL 2008 guidelines.
- OS: defined as time from randomization to death from any cause, over up to 4 years and 10 months.
- Safety.

Method of analysis Kaplan–Meier estimates were provided for time-to-event variables. Comparisons between arms were performed using the Cochran-Mantel-Haenszel chi-square test for discrete variables and log-rank test for time-to-event variables. All tests were conducted at a two-sided alpha level of 0.05 with 95% CIs, unless stated otherwise.

Subgroup analyses Only the intention-to-treat (ITT) and safety population were used.

Trial name: GLOW	NCT03462719
Other relevant information	NA

Table 36 CLL13: main study characteristics

Trial name: CLL13	NCT02950051
Objective	To evaluate whether standard chemoimmunotherapy (FCR, BR) in frontline treatment of physically fit patients with CLL and without del17p/*TP53* mutations can be replaced by combinations of targeted drugs (venetoclax, ibrutinib) with anti-CD20-antibodies (rituximab, rbinutuzumab), which may induce extremely long-lasting remissions. BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab.
Publications – title, author, journal, year	Eichhorst *et al*., 2023. First-line venetoclax combinations in chronic lymphocytic leukemia. N Eng J Med 388: 1739–1754. Fürstenau *et al*., 2024. First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 25: 744–759. Fürstenau, Moritz*, et al*., 2024. Patient-Reported Quality of Life Outcomes with Venetoclax-Based First-Line Combinations in CLL: An Analysis from the Phase 3 GAIA/CLL13 Trial. Blood 144: 3238.
Study type and design	An open-label, randomised, phase 3 study (GAIA/CLL13) conducted at 159 sites in ten countries in Europe and the Middle East. Eligible patients were aged ≥18 years with a life expectancy of ≥6 months, an ECOG-PS of 0–2, a CIRS of ≤6 or a single score of ≤4, and no *TP53* aberrations. Patients were randomly assigned (1:1:1:1), with a computer-generated list stratified by age, Binet stage, and regional study group, to either chemoimmunotherapy (FCR, BR), VR, VO or VOI. All treatments were administered in 28-day cycles. VR, venetoclax + rituximab; VO, venetoclax + obinutuzumab; VOI, venetoclax+ obinutuzumab + ibrutinib
Sample size (n)	926 (n=229 FCR/BR group; n=237 VR group; n=229 VO; and n=231 VOI group)

Trial name: CLL13	NCT02950051
Main inclusion criteria	1. Documented CLL requiring treatment according to iwCLL criteria. 2. Aged ≥18 years. 3. Life expectancy ≥ 6 months. 4. Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements. 5. Adequate bone marrow function indicated by a platelet count >30 x10^9/l (unless directly attributable to CLL infiltration of the bone marrow, proven by bone marrow biopsy). 6. Creatinine clearance ≥70ml/min directly measured with 24-hr urine collection or calculated according to the modified formula of Cockcroft and Gault (for men: GFR ≈ ((140 - age) x bodyweight) / (72 x creatinine), for women x 0, 85). For patients with creatinine values within the normal range the calculation of the clearance is not necessary. Dehydrated patients with an estimated creatinine clearance <70 mL/min might be eligible if a repeat estimate after adequate hydration is >70 mL/min. 7. Adequate liver function as indicated by a total bilirubin ≤ 2 x, AST/ALT ≤ 2.5 x the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome. 8. Negative serological testing for hepatitis B (HBsAg negative and anti-HBc negative; patients positive for anti-HBc may be included if PCR for HBV DNA was negative and HBV-DNA PCR was performed every month until 12 months after last treatment cycle), negative testing for hepatitis C RNA within 6 weeks prior to registration. 9. ECOG-PS 0–2
Main exclusion criteria	1. Any prior CLL-specific therapies (except corticosteroid treatment administered due to necessary immediate intervention; within the last 10 days before start of study treatment, only dose equivalents of 20 mg prednisolone were permitted). 2. Transformation of CLL (Richter transformation).

3. Decompensated haemolysis, defined as ongoing haemoglobin drop in spite of three more concurrent treatments being administered for haemolysis.
4. Detected del(17p) or *TP53* mutation.
5. Patients with a history of PML.
6. Any comorbidity or organ system impairment rated with a single CIRS (cumulative illness rating scale) score of 4 (excluding the eyes/ears/nose/throat/larynx organ system), a total CIRS score of >6 or any other life-threatening illness, medical condition or organ system dysfunction that, in the investigator´s opinion, could have comprised patient safety or interfered with the absorption or metabolism of study drugs (e.g., inability to swallow tablets or impaired resorption in the gastrointestinal tract).
7. Urinary outflow obstruction.
8. Malignancies other than CLL requiring systemic therapies, not being treated in curative intention before (unless the malignant disease was in a stable remission due to the discretion of the treating physician) or showing signs of progression after curative treatment.
9. Uncontrolled or active infection.
10. Patients with known infection with HIV.
11. Requirement of therapy with strong CYP3A4 and CYP3A5 inhibitors/inducers.
12. Anticoagulant therapy with warfarin or phenoprocoumon, (rotation to alternative anticoagulation was allowed, but notabley, patients being treated with NOAKs could be included, but had to be properly informed about the potential risk of bleeding under treatment with ibrutinib).
13. History of stroke or intracranial haemorrhage within 6 months prior to registration.
14. Use of investigational agents that might interfere with the study drug within 28 days prior to registration.
15. Vaccination with live vaccines 28 days prior to registration.
16. Major surgery <30 days before start of treatment.

Trial name: CLL13	NCT02950051
	17. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, known sensitivity or allergy to murine products. 18. Known hypersensitivity to any active substance or to any of the excipients of one of the drugs used in the trial. 19. Pregnant women and nursing mothers (a negative pregnancy test was required for all women of childbearing potential within 7 days before start of treatment; further pregnancy testing performed regularly). 20. Fertile men or women of childbearing potential unless: (i) surgically sterile or ≥2 years post menopause onset; or (ii) willing to use two methods of reliable contraception including one highly effective contraceptive method (Pearl Index <1) and one additional effective (barrier) method during study treatment and for 18 months post end of study treatment. 21. Legal incapacity. 22. Prisoners or subjects who were institutionalized by regulatory or court order. 23. Persons who werein dependence to the sponsor or an investigator.
ntervention	n=229. Patients received daily venetoclax (400 mg orally) for ten cycles after a 5-week ramp-up phase starting on day 22 of cycle 1. Obinutuzumab was added (cycle 1: 100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15; cycles 2–6: 1000 mg on day 1).
Comparator(s)	n= 229. Patients in the FCR/BR group received six cycles of treatment, with patients aged >65 years receiving intravenous bendamustine (90 mg/m^2, days 1–2), whereas patients aged ≤65 years received intravenous fludarabine (25 mg/m^2, days 1–3) and intravenous cyclophosphamide (250 mg/m^2, days 1–3). Intravenous rituximab (375 mg/m^2, day 1 of cycle 1; 500 mg/m^2, day 1 of cycles 2–6) was added to chemotherapy.
Follow-up time	50.7 months (IQR 44.6–57.9).

Trial name: CLL13	NCT02950051
Primary, secondary and exploratory endpoints	**All study endpoints** **Co-primary endpoints:** • MRD in peripheral blood (PB), measured by flow cytometry at month 15, for the comparison of GVe vs. standard chemoimmunotherapy (SCIT) (per F. Hoffmann-LaRoche CLL13 trial protocol, University of Cologne CLL13/GCLLSG-GAIA trial). • PFS for the comparison of GIVe versus SCIT. **Secondary endpoints:** • MRD levels in peripheral blood at month 15 for all comparisons except GVe versus SCIT. • MRD levels in PB at different time points (months 2, 9, and 13; later time points might be evaluated at the discretion of the treating physician at local laboratories). • MRD levels measured in bone marrow at final restaging (2 months after the end of last treatment cycle). • PFS for all other comparisons except GIVe vs. SCIT. • ORR assessed at months 3, 9, 13, and 15. • Clinical complete response (CR)/CR with incomplete marrow recovery (CRi) rate, assessed at interim staging, cycle 9 day 1 (or final restaging for SCIT arm), IR (or three months after RE in SCIT arm), and month 15 with regard to best response achieved. • EFS. • OS. • DOR in patients with: (i) complete response (CR) or CR with incomplete recovery of bone marrow (CRi); partial response (PR). • Time to next CLL treatment. • Safety parameters: type, frequency, and severity of AEs and AESI, and their relationship to study treatment. • Health-related quality of life and compliance, evaluated by MARS and EORTC QLQ-C30 and QLQ-CLL16 questionnaires.

- Exploratory evaluations of potential associations between biomarkers and subject characteristics or outcome measures.

Exploratory endpoints:

- Evaluation of the relationship between various baseline markers and clinical outcome parameters.
- Correlation between MRD in bone marrow and peripheral blood.
- Correlation between MRD in bone marrow and PFS/EFS/OS.
- Correlation between MRD in peripheral blood and PFS/EFS/OS.
- Comparison of outcome between FCR and BR regimens.

Criteria for evaluation:

Efficacy:

Lymph nodes, spleen, and liver measurements by physical examination.

CT or MRI scans at final restaging and additionally if clinically indicated.

Abdominal ultrasound for measurement of enlarged lymph nodes (if clinically indicated).

Complete blood count (CBC).

Assessment of MRD in peripheral blood at months 1, 2, 9, 13, and 15 using flow cytometry.

Bone marrow aspirate/biopsy for standard histopathology and MRD assessment at final restaging by flow cytometry.

Survival status.

Survey of start and type of next CLL treatment.

Safety:

- Clinical laboratory evaluations.
- Concomitant medications.
- AEs monitored according to NCI CTCAE Version 4.

Trial name: CLL13	NCT02950051
	• HBV-DNA PCR every month in patients with positive anti-HBc test at screening, until at least 12 months after the last treatment cycle. • Pregnancy testing for all women of childbearing potential. **Endpoints included in this application:** • PF) for the comparison of GIVe vs. SCIT. • OS. • Safety.
Method of analysis	Treatment comparison was performed using a two-sided stratified log-rank test (at 0.025 significance level, adjusted for the interim analysis and considering the stratification factors age and Binet stage). If the null hypothesis was rejected and the observed HR was favourable for the GIVe study arm, it was concluded that GIVe significantly lowered the risk of PFS events as compared to SCIT. A two-sided non-stratified log-rank test was performed to support the primary analysis. Median PFS and the 97.5% confidence limits were estimated using Kaplan-Meier survival methodology (Kaplan-Meier survival curve presented as a visual description). PFS rates for 1, 2 and 3 years etc. after randomization were reported. Estimates of the treatment effect were expressed as HRs, including 97.5% CIs estimated via a stratified Cox proportional-hazards analysis. Statistical analysis of other efficacy endpoints: secondary time-to-event and rate-based endpoints analysed using the same statistical methods described for the primary analyses.
Subgroup analyses	Only the ITT and safety population was used.
Other relevant information	*NA*

Table 37 CLL14: main study characteristics

Trial name: CLL14	NCT02242942
Objective	To compare the efficacy and safety of a combined regimen of OV vs. CO in participants with CLL and coexisting medical conditions. The time on study treatment was approximately one year and the follow-up period was up to 9 years. OV, obinutuzumab + venetoclax; OC, obinutuzumab + chlorambucil.

Trial name: CLL14	NCT02242942
Publications – title, author, journal, year	Al-Sawaf et al., 2020. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 21: 1188–1200. Fischer et al, 2019. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. New Eng J Med 380: 2225–2236. Al-Sawaf et al, 2021. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study. JCO 39: 4049–4060. Al-Sawaf et al., 2023. Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. Nature Comm 14: 2147. Al-Sawaf et al., 2024. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. Blood 144: 1924–1935.
Study type and design	An open-label, multicentre, randomized Phase III study done at 196 sites in 21 countries. Eligible patients were aged ≥18 years, had untreated CLL and coexisting conditions with CIRS >6, a creatinine clearance of 30–69 mL/min, or both. Patients were randomly assigned (1:1) via a web and voicemail system with allocation concealment and based on a computer-generated randomisation schedule with a block size of six and stratified by Binet stage and geographical region.
Sample size (n)	445
Main inclusion criteria	• Documented, previously untreated CLL according to the iwCLL criteria. • CLL requiring treatment according to iwCLL criteria. • Total CIRS score >6. • Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as per protocol, unless cytopenia was due to marrow involvement of CLL. • Adequate liver function. • Life expectancy >6 months.

Trial name: CLL14	NCT02242942
	• Agreement to use highly effective contraceptive methods per protocol.
Main exclusion criteria	• Transformation of CLL to aggressive Non-Hodgkin's lymphoma (Richter's transformation or pro-lymphocytic leukaemia). • Known central nervous system involvement. • Participants with a history of confirmed 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 haemolytic anaemia or immune thrombocytopenia. • Inadequate renal function. • History of prior malignancy, except for conditions listed in the protocol if participants had 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 HIV or human T-cell leukaemia virus-1 (HTLV-1). • Required warfarin, marcumar or phenprocoumon.

Trial name: CLL14	NCT02242942
	• Received agents known to be strong and moderate Cytochrome P450-3A inhibitors or inducers within 7 days prior to the first dose of study drug.
Intervention	Oral VO initiated on day 22 of cycle 1 (28-day cycles) with a 5-week dose ramp-up (20 mg, 50 mg, 100 mg, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of cycle 12 combined with intravenous obinutuzumab for six cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on days 8 and day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6.
Comparator(s)	Oral CO at 0·5 mg/kg bodyweight on days 1 and 15 of each cycle for 12 cycles combined with intravenous obinutuzumab for six cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on days 8 and day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6.
Follow-up time	76.4 months; IQR: 52.5–80.5.

Primary, secondary and exploratory endpoints	• **Primary (Current) Endpoint (Submitted: 2019-09-10)**
	  ○ PFS based on investigator assessment using iwCLL criteria, measured from baseline until disease progression or death (up to ~3.75 years).
	  ○ PFS according to iwCLL 2008 criteria: time from randomization to first occurrence of progressive disease (PD) or death from any cause.
	  ▪ Disease progression defined by any one of the following:
	  ▪ ≥50% increase in absolute circulating lymphocytes to at least 5×10^9/L
	  ▪ Appearance of new palpable lymph nodes (>15 mm in the longest diameter) or any new extra-nodal lesion
	  ▪ ≥50% increase in the longest diameter of a previous site of lymphadenopathy

- ≥50% increase in enlargement of the liver and/or spleen
- Transformation to a more aggressive histology.

- **Secondary (Current) Endpoints (Submitted: 2020-12-19)**
  - PFS based on IRC assessments according to iwCLL criteria (baseline until disease progression or death, up to ~3.75 years).
  - Percentage of participants with an Overall Response (OR) at Completion of Treatment (at ~15 months)
    - OR defined as complete response (CR), CR with incomplete bone marrow recovery (CRi), or partial response (PR) according to iwCLL 2008 criteria.
    - CR requires: peripheral blood lymphocytes <4 × 10^9/L; absence of lymphadenopathy (by physical exam/CT); no hepatomegaly/splenomegaly, absence of disease or constitutional symptoms; neutrophils >1.5 × 10^9/L, platelets >100 × 10^9/L; haemoglobin >110 g/L; bone marrow at least normocellular for age without clonal infiltrate (except CRi).
    - PR, any two for ≥2 months: ≥50% decrease in peripheral blood lymphocyte count; ≥50% reduction in lymphadenopathy; ≥50% reduction of liver/spleen enlargement; and at least one of: neutrophils >1.5 × 10^9/L, platelets >100 × 10^9/L, haemoglobin >110 g/L.
  - Percentage of participants with a Complete Response Rate (CRR) at the completion of treatment (at ~15 months):

        - CRR = rate of response of CR or CRi per iwCLL 2008 criteria (see above for CR criteria).
    - Percentage of participants with MRD negativity in peripheral blood at completion of treatment (~15 months)
        - MRD negativity: <1 CLL cell per 10,000 leukocytes in peripheral blood (ASO-PCR).
    - Percentage of participants with MRD negativity in bone marrow at completion of treatment (~15 months)
        - MRD negativity: <1 CLL cell per 10,000 leukocytes in bone marrow (ASO-PCR).
    - OS measured from baseline until death (up to ~10.75 years)
        - OS defined as time from randomization to death due to any cause.
- **Other selected secondary endpoints**
    - Percentage of participants with MRD negativity (in peripheral blood and bone marrow) at completion of combination treatment assessment (~9 months)
        - As measured by ASO-PCR at Day 1 Cycle 9 or 3 months after last IV infusion.
    - Percentage of participants with OR at end of combination treatment (~6 months)
        - Assessed at Day 1 Cycle 7 or 28 days after last IV infusion.
        - OR, CR, PR definitions as stated above.
    - DOR:
        - Time from first documented response to progression or death (up to ~10.75 years)
        - PD defined as lymphadenopathy, ≥50% increase in liver/spleen, ≥50% increase

in lymphocyte count, transformation, or cytopenia.

- Percentage of participants by best response achieved (CR, CRi, PR, stable disease [SD], or PD):
  - Assessment up to 3 months after treatment completion (~15 months).
  - CR/PR/PD/SD definitions as stated above; SD means no CR/PR/PD.
- EFS:
  - Time from randomization to progression/relapse, death, or start of new anti-leukaemic therapy (up to ~10.75 years).
- Time-to-next anti-leukaemic treatment:
  - Time from randomization to first intake of new anti-leukaemic therapy (up to ~10.75 years).
- Number of participants with AEs (up to ~10.75 years)
  - AE: any unfavourable, unintended medical occurrence, regardless of treatment-relationship; includes signs, symptoms, or disease, and worsening of pre-existing conditions.
- Percentage with CD19+/CD5+ B cells or CD14+ monocytes (up to ~10.75 years).
- Percentage with human-anti-human antibodies (up to ~10.75 years).
- Percentage recorded as premature study withdrawals (up to ~10.75 years).
- Plasma concentrations of venetoclax (pre-dose and 4 hr post-dose Day 1 Cycle 4).
- Serum concentrations of obinutuzumab (pre-infusion and end of infusion Day 1 Cycle 4).
- Change from baseline in MDASI-CLL score (up to ~10.75 years):

        - 25-item CLL-symptoms questionnaire, rated 0–10 for severity and interference with life.
    - Change from baseline in EORTC QLQ-C30 (up to ~10.75 years):
        - Patient-reported outcome: 5 functional, 3 symptom, and 1 global health/quality-of-life scale; scored 0–100.
    - Change from baseline in EQ-5D-3L (up to ~10.75 years):
        - Assesses 5 health states; includes a visual analogue scale (VAS) for overall health (scored 0–100).

- **Secondary (Original) Endpoints (Submitted: 2014-09-16)**
    - PFS based on IRC assessment: time from randomization to progression, relapse, or death (up to 5 years).
    - ORR: CR, CRi, or PR according to iwCLL criteria (at completion of treatment, ~1 year).
    - MRD response rate by ASO-PCR (at completion/combination response, ~1 year and ~9 months).
    - OS: time from randomization to death (up to ~5 years).
    - DOR: from first documented to PD or death (up to ~5 years).
    - Best response achieved (CR, CRi, PR, SD, PD), assessment at completion, within ~1 year.
    - EFS: up to ~5 years.
    - Time to next anti-leukaemic treatment: up to ~5 years.
    - Incidence of AEs by NCI CTCAE v4.0: 28 days post last GDC-0199 or 90 days post last obinutuzumab, whichever is longer.
    - Incidence of SAEs: up to 5 years.

Trial name: CLL14	NCT02242942
	○ Incidence of AESIs: up to 2 years after last study drug dose. **Endpoints included in this application:** ○ PFS based on investigator assessment using iwCLL criteria, measured from baseline until disease progression or death (up to ~3.75 years). ○ OS: time from randomization to death (up to ~5 years). ○ Incidence of AEs by NCI CTCAE v4.0: 28 days post last GDC-0199 or 90 days post last obinutuzumab, whichever is longer. ○ Incidence of SAEs: up to 5 years.
Method of analysis	Treatment comparisons were made using a two-sided log-rank test (at 0.05 significance-level, adjusted for the interim analyses), stratified by Binet stage. If the null hypothesis was rejected and the observed HR was favourable for the OV arm, it was concluded that OV significantly lowered the risk of PFS events more than GClb. Obinutuzumab and Venetoclax (GDC-0199)F. Hoffman-La Roche Ltd 124/Protocol BO25323, Version 7. A two-sided non-stratified log-rank test was performed to support the primary analysis. Median PFS and the 95% CIs were estimated using Kaplan-Meier survival methodology (Kaplan-Meier survival curves presented for a visual description). PFS rates for 1, 2, and 3 years after randomization with 95% CIs were reported. Estimates of the treatment effect were expressed as HR including 95% confidence limits estimated through a Cox proportional-hazards analysis stratified by Binet stage. Primary analysis for FDA submission based on assessment of PFS by an Independent Review Committee (IRC).
Subgroup analyses	Only ITT and Safety population was used.
Other relevant information	NA

Appendix B. Efficacy results per study

Table 38 AMPLIFY: efficacy results

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in	AV FCR /BR	291 290	57.8 months (57.8; NC) NC months (NC [NC–NC])	NC	NA	NA	HR: 0.33	(0.18–0.56)	<0.0001	Calculation based on the Kaplan-Meier (KM) method. CI for median OS derived based on the Brookmeyer-Crowley method. Median estimate for the AV arm unstable due to the low number of patients at risk. Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification	(8)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Arm C (FCR/BR).										variables included in the strata statement; CI calculated using the profile likelihood approach.	
36-Month OS Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in Arm C (FCR/BR).	AV FCR/BR	291 290	94.1 (90.7–96.3) 85.9 (81.0–89.6)	NC	NA	NA	HR: NA				(8)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
48-Month OS Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in Arm C (FCR/BR).	AV	291	94.1 (90.7–96.3)	NC	NA	NA	HR: 0.33	(0.18–0.56)	<0.0001		(8)
	FCR/BR	290	81.5 (74.9–86.4)								

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median PFS Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in Arm C (FCR/BR).	AV FCR /BR	291 290	NC months (51.1–NC) 47.6 months (43.3–NC)	NC	2.39–19.01	0.01	HR: 0.65	(0.49–0.87)	0.0038	Calculation based on the KM method. Calculation based on the KM method. CI for median PFS derived based on the Brookmeyer-Crowley method. Median estimate for the AV arm unstable due to the low number of patients at risk. Analysis performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the STRATA statement; CI	(8)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										calculated using the profile likelihood approach.	
36-month PFS Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in Arm C (FCR/BR).	AV FCR/BR	290 291	76.5 (71.0–81.1) 66.5 (59.8–72.3)				NA	NA	NA	Absolute difference in effect estimated using a two-sided t-test.	(8)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
48-Month PFS Median duration of follow-up from time of randomization was 41.3 months in Arm A (AV) and 38.4 months in Arm C (FCR/BR).	AV	290	63.9 (56.6–70.3)								(8)
	FCR/BR	291	48.8 (39.5–57.4)								

Table 39 CLL13: efficacy results

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**97.5% CI**	***P* value**		
Median OS Median follow-up 50.7 months.	VO	229	NR	NA	NA	NA	NA	NA	NA	Median survival based on the KM method. HR based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	(10)
	FCR/BR	229	NR								
48-Month OS Median follow-up 50.7 months.	VO	229	95.1% (97.5% CI 91.9–98.3)	NA	NA	NA	NA	NA	NA	Survival rates based on the KM method. HR based on a Cox proportional hazards model with adjustment for stratification, and study arm.	(10)
	FCR/BR	229	93.5% (97.5% CI 89.6–97.4)								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**97.5% CI**	***P* value**		
Median PFS Median follow-up 50.7 months.	VO	229	NR	NA	NA	NA	HR: 0.47	0.32–0.69	log rank p<0.0001	Absolute difference in effect estimated using a two-sided t-test.	(10)
	FCR/BR	229	NR								
48-Month PFS Median follow-up 50.7 months.	VO	229	81.8% (97.5%CI: 75.8–87,8)								(10)
	FCR/BR	229	62.0% (97.5%CI: 54.4;69.7)								

Table 40 CLL14: efficacy results

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS Median observation time was 76.4 months (IQR: 52.5–80.5)	VO	216	NR	NA	NA	NA	HR: 0.69	0.48–1.01	0.052	Median survival based on the KM method. HR based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	(16)
	CO	216	NR								
	VO	216	85.4%	NA	NA	NA	NA	NA	NA		(14)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
48-Month OS	CO	216	83.1%								
Median observation time of 52.4 months (IQR: 49.5–56.2											
Median PFS	VO	216	76.2 months	39.8 months	NA	NA	HR: 0.4	0.31–0.52	<0.0001		(16)
Median observation time	CO	216	36.4 months								

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
76.4 months (IQR: 52.5–80.5)											
48-Month PFS Median observation time of 52.4 months (IQR: 49.5–56.2	VO	216	74%	NA	NA	NA	NA	NA	NA		(14)
	CO	216	35.4%								

Table 41 GLOW: efficacy results

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS Median follow-up of 64 months	IV	106	NR				HR: 0.46	(0.27–0.79)	0.004	Median survival based on the KM method. HR based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	(21)
	CO	105	NR								
Median OS Median follow-up of 46 months	IV	106	NR				HR: 0.487	(0.26–0.91)	0.021	Median survival based on the KM method. HR based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	(19)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	CO	105	NR								
42-Month OS	IV	106	87.5% (79.4–92.5)								(19)
Median follow-up of 46 months	CO	105	77.6% (68.·2–84.5)								
Median PFS	IV	106	NR				HR: 0.27	(0.18–0.39)	<0.0001	Survival rates based on the KM method. HR based on a Cox proportional hazards	(21)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median follow-up of 64 months.	CO	105	NR							model with adjustment for stratification, and study arm.	
Median PFS Median follow-up of 46 months	IV	106	NR				HR: 0.21	(0.14–0.33)	<0.0001	Survival rates based on the KM method. HR based on a Cox proportional hazards model with adjustment for stratification, and study arm.	(19)
	CO	105	NR								

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
42-Month PFS	IV	106	74.6% (65.0–82.0)								(19)
Median follow-up of 46 months	CO	105	24.8% (16.5–34.1)								

Appendix C. Comparative analysis of efficacy

The methodology and results are fully reported in Section 5.2.6.

Table 42 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Appendix D. Literature searches for the clinical assessment

D.1 Efficacy and safety of the intervention and comparator(s)

NA

Table 1 Bibliographic databases included in the literature search

Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 2 Other sources included in the literature search

e.g. NICE	www.nice.org.uk	dd.mm.yyyy
e.g. EMA website		dd.mm.yyyy

Abbreviations:

Table 3 Conference material included in the literature search

Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement	Skimming through		dd.mm.yyyy

[insert reference]	abstract collection

Abbreviations:

D.1.2 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Table 4 of search strategy table for [name of database]

#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

D.1.3 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion.]

Table 5 Inclusion and exclusion criteria used for assessment of studies

Population
Intervention
Comparators
Outcomes
Study design/publication type
Language restrictions

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document.]

Table 6 Overview of study design for studies included in the technology assessment

Study 1
Study 2

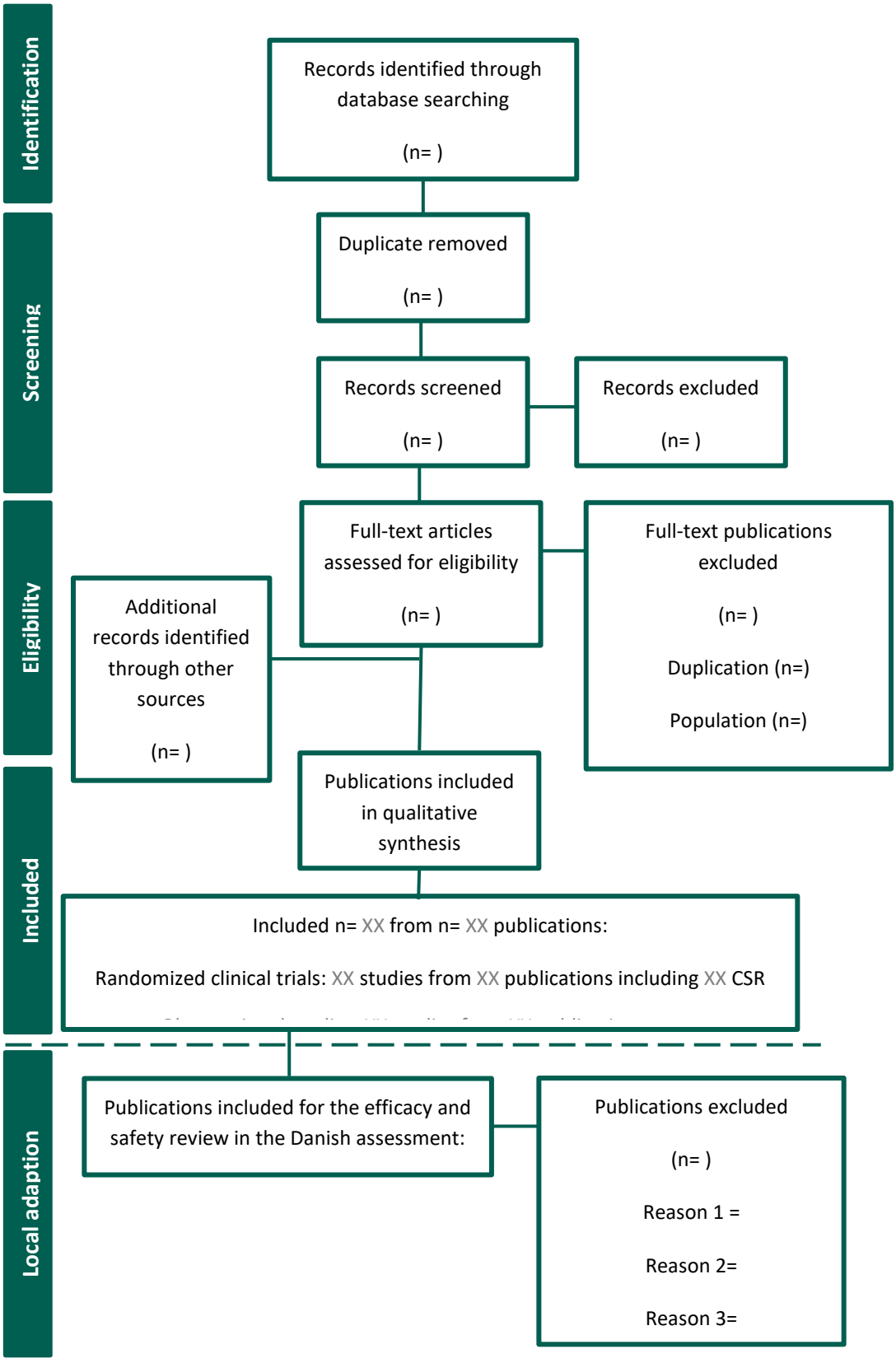
D.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

D.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.

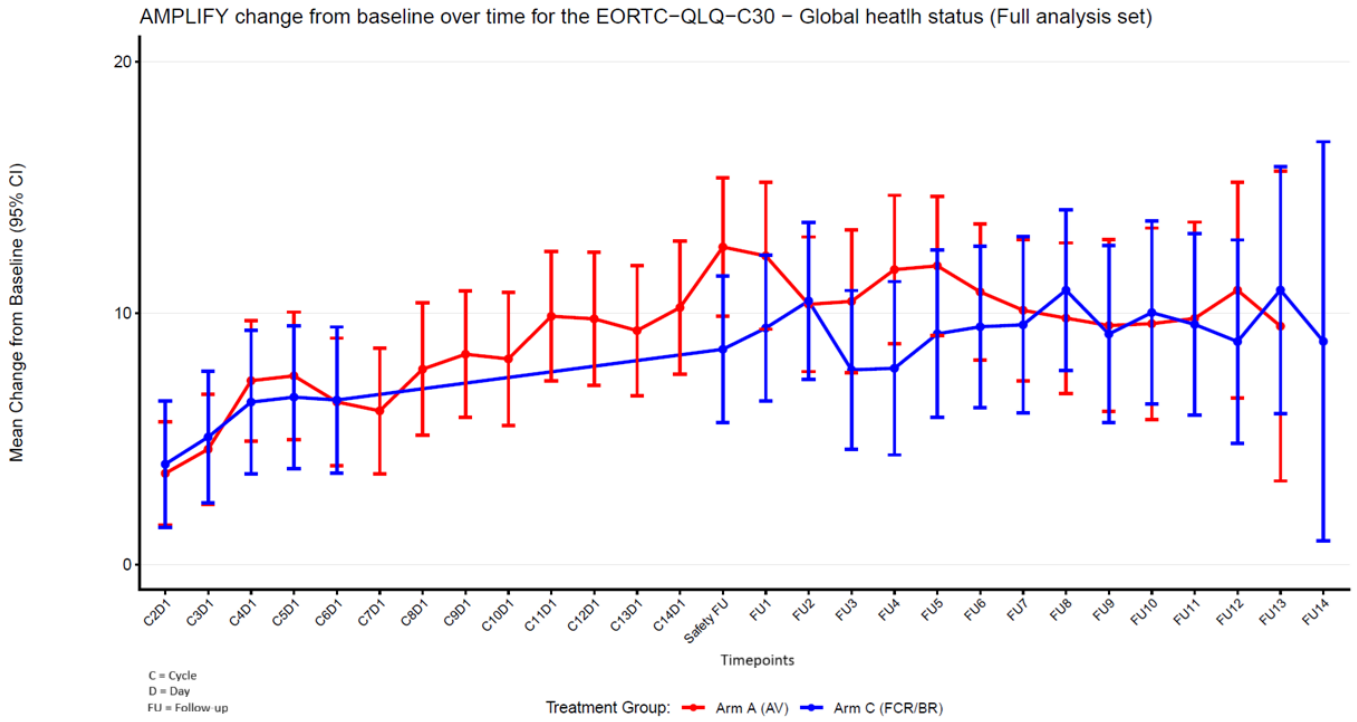


Appendix E. Response to questions

Data collection

All patients who discontinue study drug(s) had a SFU visit 30 (+7) days after the last dose. All patients who discontinue treatment for any reason other than death, loss to follow-up, or withdrawal of consent were to be followed on study. Post-treatment follow-up visits were to occur approximately every 12 weeks for approximately 3 years (144 weeks) and then every 24 weeks until disease progression. Patients who had disease progression were followed on study

Figure 20 EORTC-QLQ-C30 change form baseline



Arm A (AV)	246	247	237	232	237	229	222	227	224	221	225	222	229	219	226	211	203	201	202	199	187	182	149	127	86	55	29	0
Arm C (FCR/BR)	211	207	196	194	186	0	0	0	0	0	0	0	0	180	186	170	169	159	158	148	145	139	139	128	123	109	58	31

Table 43 Arm A (AV), N=291 — Global health status/QoL (EORTC-QLQ-C30) — Full analysis set

Timepoint	n (Result)	Mean (Result)	SD (Result)	n (Change from baseline)	Mean (Change from baseline)	SD (Change from baseline)
Baseline	260	68,97	20,5	—	—	—
Cycle 2 Day 1	268	72,98	17,54	246	3,62	16,41
Cycle 3 Day 1	270	73,86	16,7	247	4,59	17,55
Cycle 4 Day 1	257	76,91	14,29	237	7,31	18,81
Cycle 5 Day 1	254	76,6	16,82	232	7,5	19,68
Cycle 6 Day 1	257	75,19	16,3	237	6,47	19,95

Cycle 7 Day 1	252	75,56	16,94	229	6,11	19,28
Cycle 8 Day 1	245	76,77	16,44	222	7,77	20,04
Cycle 9 Day 1	249	77,77	14,86	227	8,36	19,37
Cycle 10 Day 1	246	78,07	15,44	224	8,18	20,29
Cycle 11 Day 1	242	79,33	14,6	221	9,87	19,52
Cycle 12 Day 1	247	79,45	15,43	225	9,77	20,31
Cycle 13 Day 1	246	78,89	15,34	222	9,3	19,68
Cycle 14 Day 1	253	79,77	15,53	229	10,22	20,47
Safety Follow-Up	243	82,09	14,48	219	12,63	20,81
PTFU1	248	81,92	15,48	226	12,28	22,39

PTFU2	234	81,48	14,67	211	10,35	19,86
PTFU3	225	81,55	15,92	203	10,47	20,63
PTFU4	222	82,46	15,02	201	11,73	21,36
PTFU5	225	81,88	14,41	202	11,88	20,09
PTFU6	220	81,02	15,46	199	10,84	19,48
PTFU7	206	81,34	15,05	187	10,11	19,58
PTFU8	201	80,76	14,75	182	9,8	20,58
PTFU9	166	80,42	16,25	149	9,51	21,27
PTFU10	137	78,95	16,91	127	9,58	21,87
PTFU11	94	81,2	14,96	86	9,79	18,13
PTFU12	58	82,47	13,93	55	10,91	16,26
PTFU13	29	82,76	15,58	29	9,48	16,92

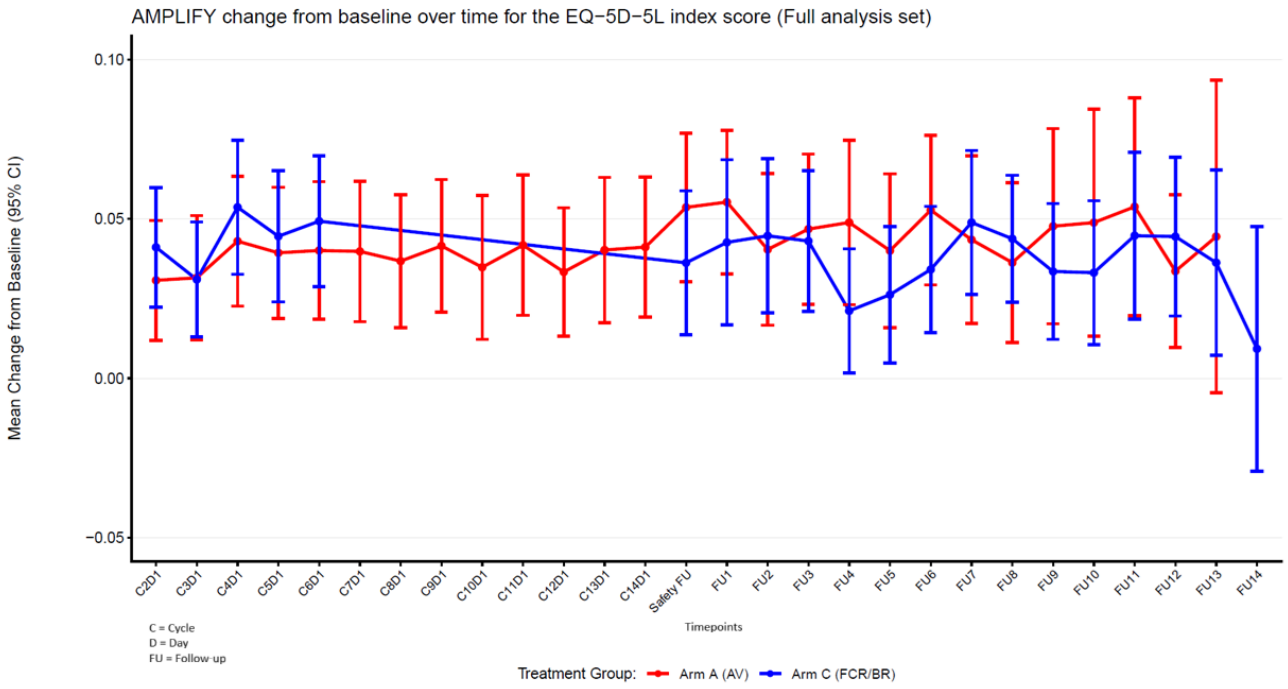
Table 44 Arm C (FCR/BR), N=290 — Global health status/QoL (EORTC-QLQ-C30) — Full analysis set

Timepoint	n (Result)	Mean (Result)	SD (Result)	n (Change from baseline)	Mean (Change from baseline)	SD (Change from baseline)

Baseline	233	67,95	21,42	—	—	—
Cycle 2 Day 1	234	71,97	18,43	211	3,99	18,58
Cycle 3 Day 1	227	72,61	18,83	207	5,07	19,24
Cycle 4 Day 1	216	73,61	17,33	196	6,46	20,34
Cycle 5 Day 1	210	74,68	17,36	194	6,66	20,17
Cycle 6 Day 1	206	74,31	17,59	186	6,54	20,24
Safety Follow-Up	196	77,59	15,87	180	8,56	19,98
PTFU1	205	77,27	16,59	186	9,4	20,12

PTFU2	188	78,23	16,76	170	10,48	20,82
PTFU3	188	76,99	15,98	169	7,74	20,94
PTFU4	176	76,56	17,51	159	7,81	22,2
PTFU5	173	77,79	16,64	158	9,18	21,33
PTFU6	165	78,99	16,65	148	9,46	19,94
PTFU7	159	78,97	16,39	145	9,53	21,56
PTFU8	153	80,12	14,96	139	10,91	19,24
PTFU9	155	78,49	15,19	139	9,17	21,17
PTFU10	142	80,16	15,46	128	10,02	21,03
PTFU11	137	80,04	14,96	123	9,55	20,4
PTFU12	119	78,36	16,21	109	8,87	21,52
PTFU13	61	79,51	13,39	58	10,92	19,07
PTFU14	34	76,96	15,36	31	8,87	22,56
PTFU15	11	81,82	21,67	11	9,09	30,15

Figure 21 EQ-5D-5L change form baseline



Arm A (AV)	241	242	230	228	229	226	219	224	220	218	220	218	226	216	220	207	201	199	200	195	186	180	146	123	83	54	29	0
Arm C (FCR/BR)	207	205	194	193	184	0	0	0	0	0	0	0	0	178	182	168	165	156	156	147	145	136	135	126	120	108	57	29

Table 45 Arm A (AV), N=291 — EQ-5D-5L Index score — Full analysis set

Timepoint	n (Result)	Mean (Result)	SD (Result)	n (Change from baseline)	Mean (Change from baseline)	SD (Change from baseline)
Baseline	256	0,86	0,17	—	—	—
Cycle 2 Day 1	267	0,89	0,12	241	0,03	0,15
Cycle 3 Day 1	268	0,89	0,12	242	0,03	0,16
Cycle 4 Day 1	253	0,9	0,13	230	0,04	0,16
Cycle 5 Day 1	252	0,9	0,11	228	0,04	0,16
Cycle 6 Day 1	252	0,91	0,12	229	0,04	0,17
Cycle 7 Day 1	251	0,9	0,12	226	0,04	0,17
Cycle 8 Day 1	245	0,91	0,11	219	0,04	0,16
Cycle 9 Day 1	248	0,91	0,11	224	0,04	0,16
Cycle 10 Day 1	245	0,91	0,12	220	0,03	0,17
Cycle 11 Day 1	242	0,91	0,1	218	0,04	0,17
Cycle 12 Day 1	245	0,91	0,11	220	0,03	0,15

Cycle 13 Day 1	244	0,91	0,12	218	0,04	0,17
Cycle 14 Day 1	253	0,91	0,12	226	0,04	0,17
Safety Follow-Up	242	0,92	0,12	216	0,05	0,17
PTFU1	245	0,93	0,1	220	0,06	0,17
PTFU2	232	0,92	0,12	207	0,04	0,17
PTFU3	225	0,93	0,11	201	0,05	0,17
PTFU4	222	0,92	0,13	199	0,05	0,19
PTFU5	225	0,92	0,13	200	0,04	0,17
PTFU6	217	0,93	0,11	195	0,05	0,17
PTFU7	206	0,92	0,14	186	0,04	0,18
PTFU8	200	0,91	0,13	180	0,04	0,17
PTFU9	164	0,91	0,12	146	0,05	0,19
PTFU10	135	0,91	0,13	123	0,05	0,2
PTFU11	93	0,93	0,11	83	0,05	0,16
PTFU12	57	0,93	0,1	54	0,03	0,09
PTFU13	29	0,91	0,1	29	0,04	0,13

Table 46 Arm C (FCR/BR), N=290 — EQ-5D-5L Index score — Full analysis set

Timepoint	n (Result)	Mean (Result)	SD (Result)	n (Change from baseline)	Mean (Change from baseline)	SD (Change from baseline)
Baseline	231	0,86	0,17	—	—	—
Cycle 2 Day 1	231	0,9	0,13	207	0,04	0,14
Cycle 3 Day 1	226	0,89	0,14	205	0,03	0,13
Cycle 4 Day 1	214	0,91	0,12	194	0,05	0,15
Cycle 5 Day 1	210	0,91	0,12	193	0,04	0,15
Cycle 6 Day 1	205	0,91	0,12	184	0,05	0,14
Safety Follow-Up	195	0,91	0,14	178	0,04	0,15
PTFU1	202	0,92	0,13	182	0,04	0,18
PTFU2	188	0,91	0,13	168	0,04	0,16
PTFU3	186	0,92	0,12	165	0,04	0,14
PTFU4	174	0,91	0,13	156	0,02	0,12
PTFU5	172	0,91	0,13	156	0,03	0,14

PTFU6	164	0,93	0,11	147	0,03	0,12
PTFU7	159	0,92	0,13	145	0,05	0,14
PTFU8	151	0,92	0,12	136	0,04	0,12
PTFU9	152	0,91	0,14	135	0,03	0,13
PTFU10	140	0,92	0,12	126	0,03	0,13
PTFU11	135	0,93	0,12	120	0,04	0,15
PTFU12	119	0,92	0,12	108	0,04	0,13
PTFU13	61	0,93	0,09	57	0,04	0,11
PTFU14	33	0,91	0,13	29	0,01	0,11
PTFU15	11	0,94	0,1	11	0,06	0,08

Table 47 Arm A (AV), N=291 — EQ-5D-5L VAS score — Full analysis set

Timepoint	n (Result)	Mean (Result)	SD (Result)	n (Change from baseline)	Mean (Change from baseline)	SD (Change from baseline)
Baseline	256	71,43	18,35	—	—	—

Cycle 2 Day 1	267	76,18	15,5	241	4,39	13,91
Cycle 3 Day 1	268	76,12	15,7	242	4,4	15,99
Cycle 4 Day 1	253	78,54	14,17	230	6,46	16,9
Cycle 5 Day 1	252	79,62	13,97	228	8,02	16,87
Cycle 6 Day 1	252	80,86	13,35	229	9,4	17,23
Cycle 7 Day 1	251	80,41	13,67	226	8,54	16,59
Cycle 8 Day 1	245	80,54	12,94	219	8,46	16,58
Cycle 9 Day 1	248	81,39	13,1	224	9,23	17,27
Cycle 10 Day 1	245	81,11	13,19	220	8,78	17,89
Cycle 11 Day 1	242	82,45	12,51	218	10,23	17,71
Cycle 12 Day 1	245	82,26	12,84	220	9,9	17,93
Cycle 13 Day 1	244	81,71	13,2	218	9,81	18,21
Cycle 14 Day 1	253	82,89	13,41	226	10,54	18,58
Safety Follow-Up	242	83,63	14,32	216	11,94	20,95
PTFU1	245	84,2	12,39	220	12,01	18,07

PTFU2	232	83,97	14,29	207	10,94	20,86
PTFU3	225	84,32	12,15	201	11,31	17,92
PTFU4	222	84,66	12,55	199	11,98	18,58
PTFU5	225	83,83	12,53	200	11,2	19,3
PTFU6	217	82,78	16,38	195	9,88	21,79
PTFU7	206	84,14	12,53	186	10,59	17,83
PTFU8	200	83,82	13,27	180	10,67	18,16
PTFU9	164	83,37	13,46	146	11,14	18,48
PTFU10	135	82,51	15,25	123	11,97	19,46
PTFU11	93	84,61	12,95	83	12,82	17,51
PTFU12	57	85,72	10,73	54	11,15	16,29
PTFU13	29	82	19,84	29	8,31	20,4

Table 48 Arm C (FCR/BR), N=290 — EQ-5D-5L VAS score — Full analysis set

Timepoint	n (Result)	Mean (Result)	SD (Result)	n (Change from baseline)	Mean (Change from baseline)	SD (Change from baseline)
Baseline	231	72,58	16,44	—	—	—

Cycle 2 Day 1	231	75,67	15,33	207	2,27	13,97
Cycle 3 Day 1	226	75,91	15,88	205	2,69	14,79
Cycle 4 Day 1	214	77,94	14,44	194	4,69	15,24
Cycle 5 Day 1	210	77,77	15,26	193	4,37	15,3
Cycle 6 Day 1	205	79,07	14,84	184	6,15	13,55
Safety Follow-Up	195	81,18	13,17	178	7,24	15,44
PTFU1	202	81,14	14,2	182	7,36	15,88
PTFU2	188	81,27	13,72	168	8,1	17,1
PTFU3	186	81,33	13,47	165	7,03	16,89
PTFU4	174	80,33	16,43	156	5,9	17,08
PTFU5	172	79,08	17,19	156	5,5	20,24

PTFU6	164	82,18	14	147	8,49	16,08
PTFU7	159	83,02	12,36	145	9,51	16,93
PTFU8	151	83,15	12,18	136	9,48	15,23
PTFU9	152	82,27	13,19	135	8,24	16,57
PTFU10	140	83,09	12,95	126	8,81	16,34
PTFU11	135	82,83	13,53	120	9,34	18,11
PTFU12	119	81,5	13,63	108	7,5	18,05
PTFU13	61	81,18	13,18	57	6,05	15,37
PTFU14	33	81,52	12,29	29	7,24	14,82
PTFU15	11	85,73	8,28	11	12,73	8,44

Table 49 Compliance with EORTC QLQ-C30 by visit (FAS)

Visit	Eligible AV	Completed PRO AV	Compliance rate AV	Eligible FCR/BR	Completed PRO FCR/BR	Compliance rate FCR/BR
Baseline	291	260	89.30%	290	233	80.30%
Cycle 2 Day 1	291	268	92.10%	290	234	80.70%
Cycle 3 Day 1	288	270	93.80%	290	227	78.30%
Cycle 4 Day 1	284	257	90.50%	290	216	74.50%
Cycle 5 Day 1	284	254	89.40%	290	210	72.40%
Cycle 6 Day 1	284	257	90.50%	290	206	71.00%
Cycle 7 Day 1	283	252	89.00%			
Cycle 8 Day 1	283	245	86.60%			
Cycle 9 Day 1	278	249	89.60%			
Cycle 10 Day 1	278	246	88.50%			
Cycle 11 Day 1	278	242	87.10%			
Cycle 12 Day 1	277	247	89.20%			
Cycle 13 Day 1	276	246	89.10%			
Cycle 14 Day 1	275	253	92.00%			
Safety Follow-Up	282	243	86.20%	256	196	76.60%

Table 50 Compliance with EQ-5D-5L by visit (FAS)

Visit	Eligible AV	Completed PRO AV	Compliance rate AV	Eligible FCR/BR	Completed PRO FCR/BR	Compliance rate FCR/BR
Baseline	291	256	88.0%	290	231	79.7%
Cycle 2 Day 1	291	267	91.8%	290	231	79.7%
Cycle 3 Day 1	288	268	93.1%	290	226	77.9%
Cycle 4 Day 1	284	253	89.1%	290	214	73.8%
Cycle 5 Day 1	284	252	88.7%	290	210	72.4%
Cycle 6 Day 1	284	252	88.7%	290	205	70.7%
Cycle 7 Day 1	283	251	88.7%			
Cycle 8 Day 1	283	245	86.6%			
Cycle 9 Day 1	278	248	89.2%			
Cycle 10 Day 1	278	245	88.1%			
Cycle 11 Day 1	278	242	87.1%			
Cycle 12 Day 1	277	245	88.4%			
Cycle 13 Day 1	276	244	88.4%			
Cycle 14 Day 1	275	253	92.0%			
Safety Follow-Up	282	242	85.8%	256	195	76.2%

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