Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

Part 1 for public – redacted

Technology appraisal committee C [12 September 2023]

Chair: Richard Nicholas

External assessment group: Newcastle NIHR TAR

Technical team: Zain Hussain, Sally Doss, Ross Dent

Company: BeiGene

Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ✓ **Recap**
- ❑ Response to consultation

NICE National Institute for Health and Care Excellence

Committee's key conclusions from ACM1

Zanubrutinib is not recommended, within its marketing authorisation, for treating CLL in adults

Key conclusions	
Untreated CLL	**R/R CLL**
VenO and I-V are relevant comparators	VenR is a relevant comparator
Positioning zanubrutinib only for whom FCR or BR is unsuitable creates an important equality issue for younger, fitter patients for whom FCR or BR is suitable	
SEQUOIA trial is applicable regardless of suitability for FCR or BR	
Use of ALPINE data as proxy for 'high-risk' population is acceptable	
Economic models for untreated CLL and R/R CLL built for a cost-utility analysis are more appropriate for decision making	
Impact of adverse events on costs and QALYs for the full model time horizon is more appropriate	
Alternative utility values should be explored	
The use of long-term survival extrapolations based on the most recent data is more appropriate	
Results from the MAIC analyses are uncertain	

Abbreviations: ACM1: Appraisal committee meeting 1; BR: Bendamustine-rituximab; CLL: Chronic lymphocytic leukaemia; FCR: Fludarabine, cyclophosphamide and rituximab; I-V: Ibrutinib plus venetoclax. MAIC: Matching-adjusted indirect comparisons; QALY: Quality-adjusted life years; R/R: Relapsed/refractory; VenO: Venetoclax plus obinutuzumab; VenR: Venetoclax plus rituximab

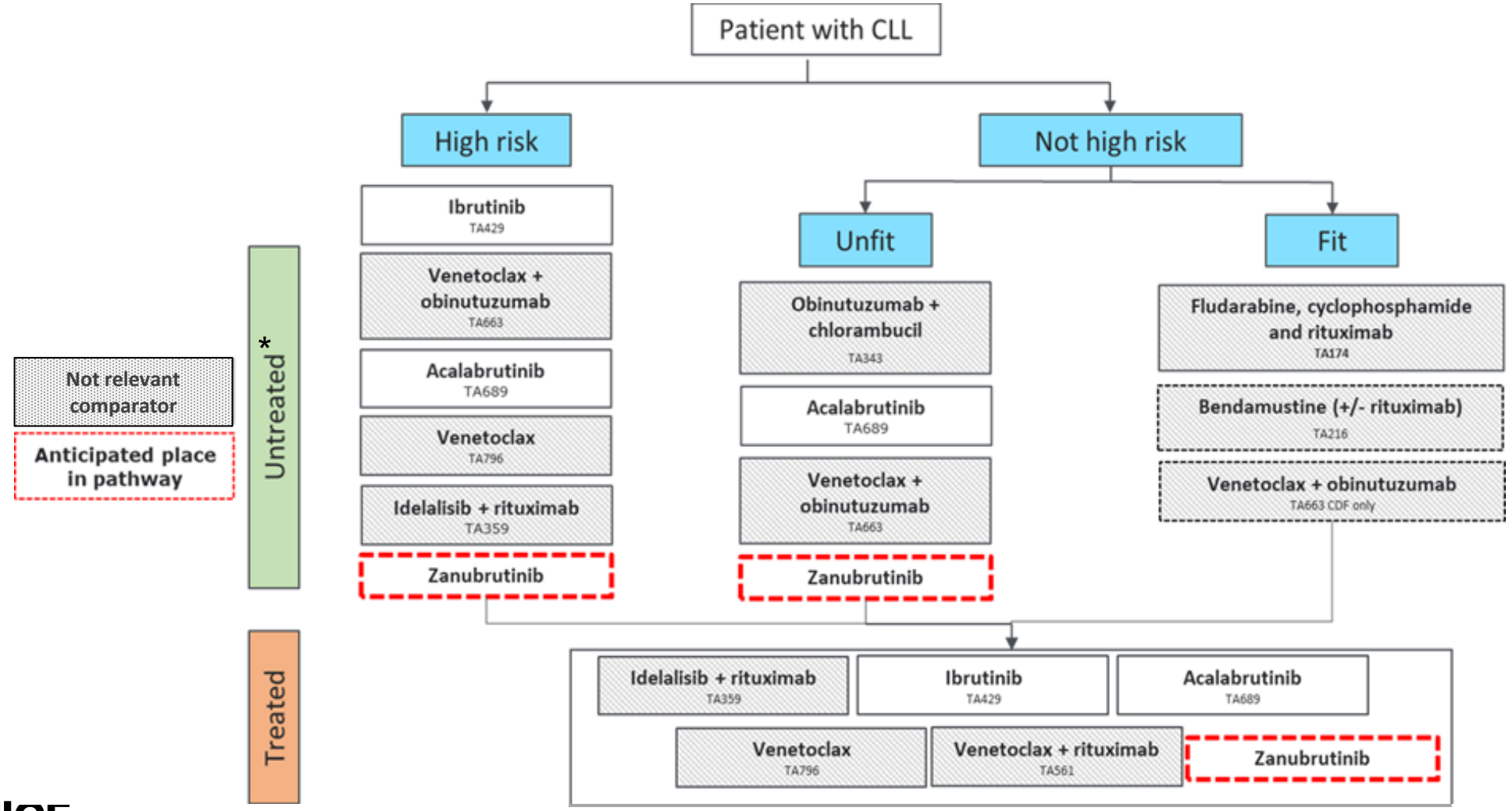
Zanubrutinib (Brukinsa, BeiGene)

Marketing authorisation	• **'Zanubrutinib as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia'**
Mechanism of action	• Highly selective, small molecule, irreversible inhibitor of BTK • Binds with and inhibits BTK which blocks BCR-induced BTK activation. By blocking the signalling pathway, this inhibits the proliferation and survival of malignant B cells
Administration	• Formulation: 80 mg capsules for oral administration • Dosage: 320 mg (4 capsules) orally either once daily or divided into two doses of 160 mg (2 capsules) twice daily
Price	• List price is £4,928.65 for a pack of 120 capsules • Average cost of treatment is £60,005 per patient per year • Zanubrutinib has a confidential simple discount PAS

Abbreviations: BCR: B-cell receptor; BTK: Bruton tyrosine kinase; PAS: Patient access scheme

Company's proposed treatment pathway for zanubrutinib

Alternative BTKi for untreated CLL, alongside acalabrutinib ('unfit' and high-risk' populations) and ibrutinib ('high-risk' population), and R/R CLL



* TA891 (published 31 May 2023) also recommends I-V for use in all untreated CLL populations. I-V was not included in the final scope for this appraisal

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia; I-V: Ibrutinib plus venetoclax; R/R: Relapsed/refractory; TA: Technology appraisal

Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ❑ Recap
- ✓ **Response to consultation**

NICE National Institute for Health and Care Excellence

Consultation responses (1)

Consultation comments received from:

- Janssen Cilag Ltd (comparator – manufacturer of ibrutinib)
- AbbVie UK (comparator – manufacturer of venetoclax)
- Leukaemia Care (patient group)
- UK CLL forum (professional group)
- 2 x web comments

Janssen Cilag Ltd

- Interpretation of ITC problematic since people in SEQUOIA eligible for BR are expected to perform better than those who are not, so outcomes will be biased in favour of zanubrutinib
- RCT presented for the R/R CLL population is an outlier in the body of evidence for the efficacy of ibrutinib in people with R/R CLL, and severely underperforms compared to ibrutinib's registrational study despite including less pre-treated patients
- Use of R/R CLL data in the high-risk population as a proxy to first-line CLL setting is clinically and methodologically concerning and should be interpreted with caution

AbbVie UK

- Venetoclax-based treatment regimens are important treatment options in both untreated CLL and R/R CLL

Abbreviations: BR: Bendamustine-rituximab; CLL: Chronic lymphocytic leukaemia; ITC: Indirect treatment comparison; RCT: Randomised controlled trial; R/R: Relapsed/refractory

Consultation responses (2)

UK CLL Forum

- Chemo-immunotherapy is no longer a standard of care in any setting for CLL ➔ Historical differentiation between “fit” and “unfit” is now redundant
- Inequality of access to continuous BTKi for people with untreated CLL without TP53 mutation who are younger and fitter ➔ Appraisal offers the opportunity to redress this using the SEQUOIA data, where people were deemed to be “fit” to be randomised to BR in the trial
- Zanubrutinib sits as an alternative to other continuous BTKi regimens (acalabrutinib and ibrutinib), unlike time-limited venetoclax-based regimens. Therefore, availability of zanubrutinib is unlikely to impact the clinical decision to treat with a time-limited or a continuous treatment regimen
- Direct comparison with I-V is likely limited by the small sample size in GLOW and CAPTIVATE studies
- Cardiac signal remains in the GLOW study ➔ Awaiting real-world data to complement clinical decision making

Leukaemia Care

- Important that access is available to as many treatment options as possible offering different characteristics, enabling clinicians to provide personalised treatment plan to suit individual patient and their lifestyles

Web comments

- Zanubrutinib is a long duration treatment that competes with other BTKi therapies and not with time-limited treatments ➔ Selection of time-limited or continuous treatment is at patient and consultant’s discretion, steered by cardiac and renal co-morbidities

Abbreviations: BR: Bendamustine-rituximab; BTKi, Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia; I-V: Ibrutinib plus venetoclax; TP53: Tumour protein 53

Committee recommendations for further analysis

Company fulfilled some of the committee's recommendations for further analysis

Committee's recommendations for further analysis	Updated?
Latest data cut for both SEQUOIA and ALPINE may better inform the long-term effectiveness of zanubrutinib for all CLL populations	Yes
Long term survival extrapolations using the most recent data is more appropriate	Partially
SEQUOIA trial is applicable to people regardless of suitability for FCR or BR, so providing analysis for overall untreated CLL population would address the equality issue	No
Clinical and cost-effectiveness evidence of zanubrutinib compared with VenO and I-V for the untreated CLL	Yes
Clinical and cost-effectiveness evidence of zanubrutinib compared with VenR for R/R CLL	Yes
Economic models built for a cost-utility analysis are more appropriate for decision making	Yes
Cost-utility analysis (CUA) including the impact of AEs on both costs and QALYs for the full economic model time horizon would be more appropriate	No
Alternative utility values should be explored using a CUA approach	Yes

Abbreviations: AEs: Adverse events; BR: Bendamustine-rituximab; CLL: Chronic lymphocytic leukaemia; FCR: Fludarabine, cyclophosphamide and rituximab; I-V: Ibrutinib plus venetoclax; QALYs: Quality-adjusted life years; R/R: Relapsed/refractory; VenO: Venetoclax plus obinutuzumab; VenR: Venetoclax plus rituximab

SEQUOIA trial results

Company used updated data cut of SEQUOIA (October 2022) to update the survival and MAIC analyses versus acalabrutinib in the untreated CLL population

Comparison of updated SEQUOIA efficacy data with previous data cut-offs

Outcome	DCO 31 October 2022			DCO 7 May 2021			DCO 7 March 2022 (OS only)		
	Cohort 1		Cohort 2	Cohort 1		Cohort 2	Cohort 1		Cohort 2
	ZANU	BR	ZANU	ZANU (N=241)	BR (N=238)	ZANU (N=110)	ZANU (N=241)	BR (N=238)	ZANU (N=110)
INV assessed PFS									
N events (%)	[redacted]	[redacted]	[redacted]	29 (12.0)	57 (23.9)	[redacted]	-	-	-
HR (95% CI), p-value	0.30 (0.21, 0.43), <0.0001		-	0.42 (0.27, 0.66), <0.0001		-	-	-	-
OS									
N events (%)	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]	[redacted]	-
HR (95% CI), p-value	0.87 (0.50, 1.48), [redacted]			-	-	-	[redacted]		-

As IRC-assessed PFS (primary endpoint) data are not available from SEQUOIA (data cut-off: October 2022), the updates to the survival analyses were performed using INV-assessed PFS from ELEVATE-TN and SEQUOIA to ensure alignment on the definition of PFS

Abbreviations: BR: Bendamustine-rituximab ;CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; DCO: Data cut off; HR: Hazard ratio; INV: Investigator; IRC: Independent central review; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; ZANU: Zanubrutinib

ALPINE trial results – R/R CLL (data cut off: December 2021)

Data from ALPINE trial for R/R CLL used as proxy for untreated "high-risk" CLL informs the comparison of zanubrutinib with ibrutinib in the base case untreated CLL economic model

ORR: Response ratio (95% CI) [p-value]	
INV	IRC
[redacted]	[redacted]

PFS: HR (95% CI) [p-value]	
INV	IRC
[redacted]	[redacted]

DOR: Median (95% CI)			
INV		IRC	
Zanubrutinib	Ibrutinib	Zanubrutinib	Ibrutinib
[redacted]	[redacted]	[redacted]	[redacted]

OS: HR (95% CI)
[redacted]

TTTF: HR (95% CI) [p-value]
[redacted]

*Late-breaking data from ALPINE (data cut-off: 15 May 2023) has been used to validate the survival extrapolations from ALPINE (data cut-off: 1 December 2021) which were previously included in the economic models

Abbreviations: CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; DOR: Duration of response; HR: Hazard ratio; INV: Investigator; IRC: Independent central review; NE: Not estimable; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; TTTF: Time to treatment failure

ITC: zanubrutinib versus BTKis for untreated CLL

Zanubrutinib versus acalabrutinib: updated unanchored MAIC (SEQUOIA [data cut-off: October 2022] and ELEVATE-TN)

- Data for zanubrutinib cohort 1 (arm A) and cohort 2 (arm C) of SEQUOIA trial ([data cut-off: October 2022) were pooled to create a cohort that included people with and without del17p to match the eligibility criteria for ELEVATE-TN
- As IRC-assessed PFS (primary endpoint) data are not available from SEQUOIA (data cut-off: October 2022), the updates to the MAIC were performed using INV-assessed PFS from ELEVATE-TN and SEQUOIA to ensure alignment on the definition of PFS

	PFS (INV)		OS	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Post matching – Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Post matching – Model 2	[redacted]	[redacted]	[redacted]	[redacted]

Zanubrutinib versus ibrutinib: unanchored MAIC (SEQUOIA and ELEVATE-TN)

- Data from ALPINE trial for R/R CLL used as proxy for untreated "high-risk" CLL informs the comparison of zanubrutinib with ibrutinib in the base case untreated CLL economic model

Abbreviations: BTKis: Bruton Tyrosine Kinase inhibitors; CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; INV: Investigator; IRC: Independent central review; ITC: Indirect treatment comparison; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; R/R: Relapsed/refractory

Zanubrutinib positioning and relevance of comparators

Committee considerations at Appraisal committee meeting 1

- Venetoclax plus obinutuzumab and ibrutinib plus venetoclax are relevant comparators for untreated CLL
- Venetoclax plus rituximab is a relevant comparator for R/R CLL
- Positioning zanubrutinib only for whom FCR or BR is unsuitable creates an important equality issue for younger, fitter people for whom FCR or BR is suitable ➔ SEQUOIA trial is applicable regardless of suitability for FCR or BR

Company response to Draft Guidance

- Zanubrutinib will be used as an alternative to BTKis and fixed-duration therapies are not relevant comparators. This is supported by a Delphi panel conducted with 11 UK clinical experts:
  - Zanubrutinib will not alter CLL treatment paradigm or impact continuous or time-limited therapy choice
  - Ibrutinib plus venetoclax does not fully reflect established NHS clinical practice for untreated CLL
  - Change in mechanism of action after progression from first-line to second-line is standard practice for second-line treatment for CLL ➔ Venetoclax plus rituximab not considered an appropriate comparator

EAG comments

- For untreated CLL, MAIC results for zanubrutinib versus ibrutinib plus venetoclax in younger people without comorbidities were incorporated into the economic model

Abbreviations: BR: Bendamustine-rituximab; BTKis: Bruton tyrosine kinase inhibitors; CLL: Chronic lymphocytic leukaemia; FCR: Fludarabine, cyclophosphamide and rituximab; MAIC: Matching-adjusted indirect comparison; R/R: Relapsed/refractory

Comparisons with alternative BTKis

Committee considerations at Appraisal committee meeting 1

- Latest data cut for both SEQUOIA and ALPINE may better inform the long-term effectiveness of zanubrutinib for all CLL populations
- Long term survival extrapolations using the most recent data is more appropriate
- Economic models built for a cost-utility analysis are more appropriate for decision making
- Cost-utility analysis including the impact of adverse events on both costs and QALYs for the full economic model time horizon would be more appropriate
- Alternative utility values should be explored using a cost-utility analysis approach

Company response to Draft Guidance

- Economic models for both untreated CLL and R/R CLL include all appropriate functionality to conduct a cost-utility analysis
  - Maintains that the assumption of constant relative hazards over time is appropriate
  - Applying the cost and disutility associated with adverse events to the first cycle is an appropriate method for decision making given that the duration of the adverse event is taken into account
- Revised base case comparison versus acalabrutinib and ibrutinib for untreated and R/R CLL populations
  - For untreated CLL, latest SEQUOIA data (October 2022) used to update survival and MAIC analyses versus acalabrutinib and ALPINE data (May 2023) used to update hazard ratio versus ibrutinib
  - Additional cardiac adverse events added to both untreated and R/R CLL models and impact of alternative utility values explored within scenario analyses for both untreated and R/R CLL models

Abbreviations: BTKis: Bruton tyrosine kinase inhibitors; CLL: Chronic lymphocytic leukaemia; MAIC: Matching-adjusted indirect comparison; QALYs: Quality-adjusted life years; R/R: Relapsed/refractory

Comparisons with alternative BTKis – EAG critique (1)

Modelling approach

- Untreated CLL
  - The use of PFS hazard ratio estimates to construct TTP and prePS mortality function, imposes strong assumptions on TTP and PrePS despite being a pragmatic approach
  - OS data obtained from the MAIC results could be meaningfully incorporated in the economic model
  - For comparison with ibrutinib, SEQUOIA arm C data should have been used in the base case

Constant relative hazards

- Such assumption could favour zanubrutinib based on the assessment of proportional hazards
- Slight convergence of PFS curves emphasises need for longer-term data
- Consider the potential overestimation of PFS for zanubrutinib and underestimation of PFS for ibrutinib important in the R/R CLL model

Adverse events

- Agree that assigning costs and utilities in the first cycle of the model is a common assumption made in technology appraisals but disagree that this is “standard practice” in economic modelling
- Some concerns about the method adopted by the company and including cardiac adverse events as the base case analysis. However, these assumptions are unlikely to have a meaningful effect on conclusions

Abbreviations: BTKis: Bruton tyrosine kinase inhibitors; CLL: Chronic lymphocytic leukaemia; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival; prePS: Pre-progression survival; OS: Overall survival; R/R: Relapsed/refractory; TTP: Time to progression

Comparisons with alternative BTKis – EAG critique (2)

Utility values

- Unclear why the company presented the results using utility values from both TA663 and GID-TA10756 when they used the same utility values for each health state
- Reiterate concerns surrounding the utility values used in the PD health state sourced from Holzner et al. (2004) since this study is originally based on EORTC QLQ-C30 data
- Noted uncertainty in the cost-effectiveness results when alternative PD utility estimates were used
- EAG is unsure what data cut off the utilities were sourced from SEQUOIA and ALPINE trials

Abbreviations: BTKis: Bruton tyrosine kinase inhibitors; CLL: Chronic lymphocytic leukaemia; PD: Progressed disease

Comparisons with VenO and I-V – untreated CLL

Committee considerations at Appraisal committee meeting 1

- Clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus obinutuzumab and ibrutinib plus venetoclax should be included for the untreated CLL

Company response to Draft Guidance

- Maintains that comparisons with fixed-duration therapies, venetoclax plus obinutuzumab and ibrutinib plus venetoclax, are not relevant
- Nevertheless, conducted exploratory cost-effectiveness analyses versus venetoclax plus obinutuzumab and ibrutinib plus venetoclax in people with untreated CLL
    - Conducted MAIC comparing zanubrutinib (SEQUOIA data cut off: October 2022) with venetoclax plus obinutuzumab in CLL14 and with ibrutinib plus venetoclax in GLOW (older or less fit [with comorbidities]) and CAPTIVATE younger and fitter [without comorbidities]) ➔ All new MAICs conducted in response to draft guidance were validated with UK clinical experts in one-to-one interviews
    - Analyses using ASCEND were conducted to inform PPS and PFS second line modelling following progression on fixed-duration therapy
    - Existing economic model for untreated CLL was adapted to include venetoclax plus obinutuzumab and ibrutinib plus venetoclax as comparators
    - 100% receive acalabrutinib following progression on fixed-duration therapy, modelled using ASCEND PPS

Abbreviations: CLL: Chronic lymphocytic leukaemia; I-V: Ibrutinib plus venetoclax; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival; PPS: Post progression survival; VenO: Venetoclax plus obinutuzumab

ITC: VenO and I-V versus zanubrutinib for untreated CLL

VenO versus zanubrutinib: Results of unanchored MAIC using CLL14 and SEQUOIA – untreated CLL

	PFS (INV)		OS	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model	[redacted]	[redacted]	[redacted]	[redacted]

I-V versus zanubrutinib: Results of unanchored MAIC using GLOW and SEQUOIA – untreated CLL (older patients with and without comorbidities)

	PFS (INV)		OS	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Model 2	[redacted]	[redacted]	[redacted]	[redacted]

I-V versus zanubrutinib: Results of unanchored MAIC using CAPTIVATE and SEQUOIA – untreated CLL (younger patients without comorbidities)

	PFS (INV)	
	Hazard ratio (95% CI)	P-value
Pre-matching	[redacted]	[redacted]
Model 1	[redacted]	[redacted]
Model 2	[redacted]	[redacted]

Abbreviations: CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; HR; Hazard ratio; INV: Investigator; ITC: Indirect treatment comparison; I-V: Ibrutinib plus venetoclax; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival; OS: Overall survival; VenO: Venetoclax plus obinutuzumab

Comparisons with VenO and I-V – untreated CLL (1)

EAG comments

- Unanchored MAICs are subject to uncertainty ➔ Results should be interpreted with caution
- The application of PFS estimates from the MAIC onto TTP and prePS imposes strong assumptions on modelled survival
- It is unclear why the company used ASCEND data to model PPS for VenO and I-V and MURANO data to model PPS for the BTKis. EAG considers this to be a favourable assumption for zanubrutinib, with little justification ➔ Unable to explore the effect of this uncertainty on the cost-effectiveness results because this functionality was not available in the economic model
- **For comparison versus ibrutinib plus venetoclax using GLOW:**
  - Unsure why only data from SEQUOIA arm A (with fewer events) was used in the MAIC comparing zanubrutinib with ibrutinib plus venetoclax in older patients with and without comorbidities using the GLOW study
  - The EAG acknowledge that visually there appears to be a drop in PFS after 12 months with venetoclax-based treatments. However, the EAG cannot comment on what effect a combination of venetoclax and a BTKi has on PFS over the longer-term and whether the company's assumption that the current hazard ratios from the MAIC are conservative

Abbreviations: BTKis: Bruton tyrosine kinase inhibitors; CLL: Chronic lymphocytic leukaemia; I-V: Ibrutinib plus venetoclax; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival; PPS: Post progression survival; PrePS: Pre-progression survival; TTP: Time to progression; VenO: Venetoclax plus Obinutuzumab

Comparisons with VenO and I-V – untreated CLL (2)

EAG comments

- **For comparison versus ibrutinib plus venetoclax using GLOW (continued):**
  - MAIC suggests a time trend in the cumulative hazard plot and the Schoenfeld residuals, which could violate the proportional hazards assumption although, as the Schoenfeld test p-values were not statistically significant across both MAIC models
- **For comparison versus ibrutinib plus venetoclax using CAPTIVATE:**
  - Unclear to the EAG why the low number of events in SEQUOIA was considered an issue in the MAIC with CAPTIVATE but not in the other MAICs
  - Evidence against the use of the proportional hazards assumption further highlights the uncertainty around the long-term comparative effectiveness of zanubrutinib
  - Company used the same utility values for the comparison of zanubrutinib with ibrutinib plus venetoclax in younger and “fitter” patients with untreated CLL

Abbreviations: CLL: Chronic lymphocytic leukaemia; I-V: Ibrutinib plus venetoclax; MAIC: Matching-adjusted indirect comparison; VenO: Venetoclax plus Obinutuzumab

Comparisons with VenR – R/R CLL

Committee considerations at Appraisal committee meeting 1

- Clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus rituximab and ibrutinib plus venetoclax should be included for the R/R CLL population

Company response to Draft Guidance

- Maintains that comparisons with fixed-duration therapy, venetoclax plus rituximab, is not relevant
- Nevertheless, conducted exploratory cost-effectiveness analyses versus VenR in people with R/R CLL
  - Published NMA (Chanan-Khan, 2022) informs comparative efficacy of zanubrutinib and venetoclax plus rituximab ➔ NMA results numerically favour zanubrutinib for INV PFS (HR 0.69, 95% CI 0.32, 1.46) but that VenR was numerically favour for OS (HR 1.27, 95% CI 0.47 to 3.33)
  - For PFS and OS modelling, respective hazard ratios from published NMA are applied to extrapolated zanubrutinib curve
  - Updated economic model for R/R CLL was adapted to include VenR as a comparator
  - 100% acalabrutinib use after first-line venetoclax-based treatment

EAG comments

- Results of NMA uncertain ➔ NMA linked through ELEVATE-RR in people with 'high-risk' R/R CLL only
- Wide 95% CI for INV PFS and OS consistent with benefit and harm for zanubrutinib compared with VenR
- Concerns about the assumption of constant proportional hazards, long-term survival extrapolations and the choice of utility values used in the economic model

Abbreviations: CLL: Chronic lymphocytic leukaemia; INV: Investigator; NMA: Network meta-analysis; OS: Overall survival; PFS: Progression-free survival; R/R: Relapsed/refractory; VenR: Venetoclax plus rituximab

Equality considerations

- Company submission did not include analysis for people for whom chemoimmunotherapy is suitable. However, in response to consultation, company provided analysis for zanubrutinib versus ibrutinib plus venetoclax in younger and fitter people without comorbidities
- Stakeholders are concerned there is a potential equality issue if zanubrutinib is only recommended for people for whom chemoimmunotherapy is unsuitable as this may exclude some people based on age
    - Submissions from all of the patient and professional organisations support broader access that would include these groups
- NICE does not normally recommend a treatment for populations when the cost-effectiveness is unknown, especially if the population is large and there would be significant resource implications for the NHS
- The committee has previously recommended treatments in this population where there is evidence of cost-effectiveness (ibrutinib plus venetoclax, TA891) or plausible cost-effectiveness and more data is being collected (venetoclax plus obinutuzumab recommended for use in CDF in TA663)

Abbreviations: CDF: Cancer Drugs Fund

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Summary of cost-effectiveness results to be presented in part 2

Following cost-effectiveness results will be presented for zanubrutinib in the untreated CLL population:

- Company deterministic and probabilistic base case cost-utility analysis results (zanubrutinib versus acalabrutinib, ibrutinib, venetoclax plus obinutuzumab and ibrutinib plus venetoclax)

Following cost-effectiveness results will be presented for zanubrutinib in R/R CLL population:

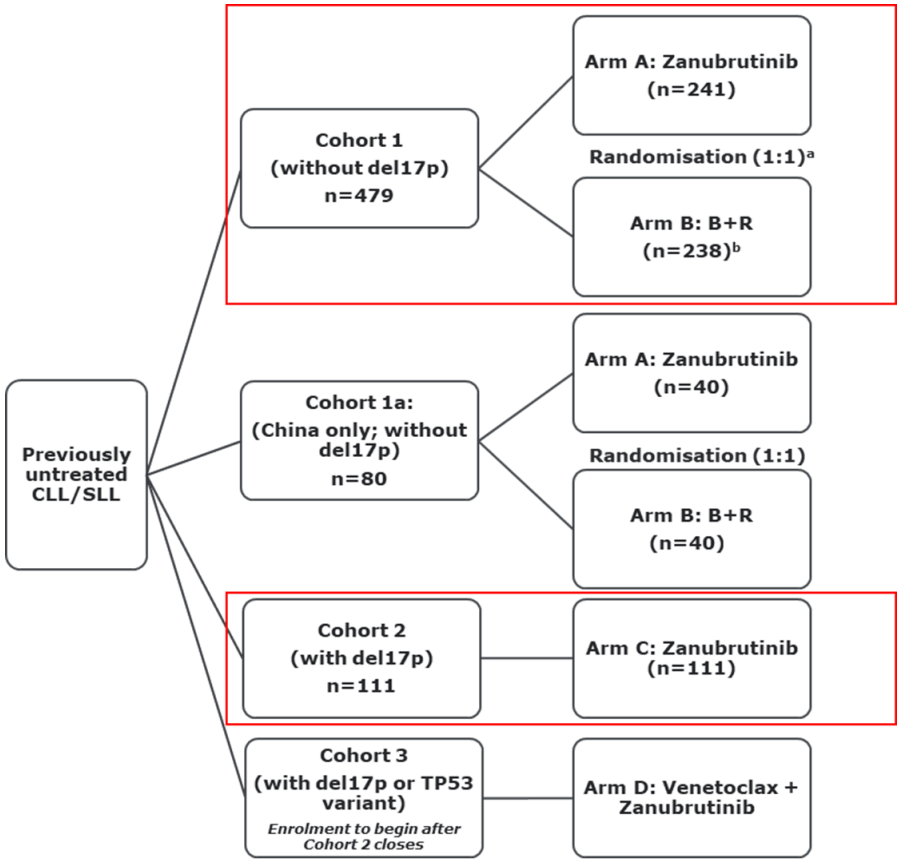
- Company deterministic and probabilistic base case cost-utility analysis results (zanubrutinib versus acalabrutinib, ibrutinib and venetoclax plus rituximab)

Abbreviations: CLL: Chronic lymphocytic leukaemia

Back up slides

Key clinical trial: SEQUOIA (untreated CLL)*

Only cohort 1 and cohort 2 are relevant to this appraisal

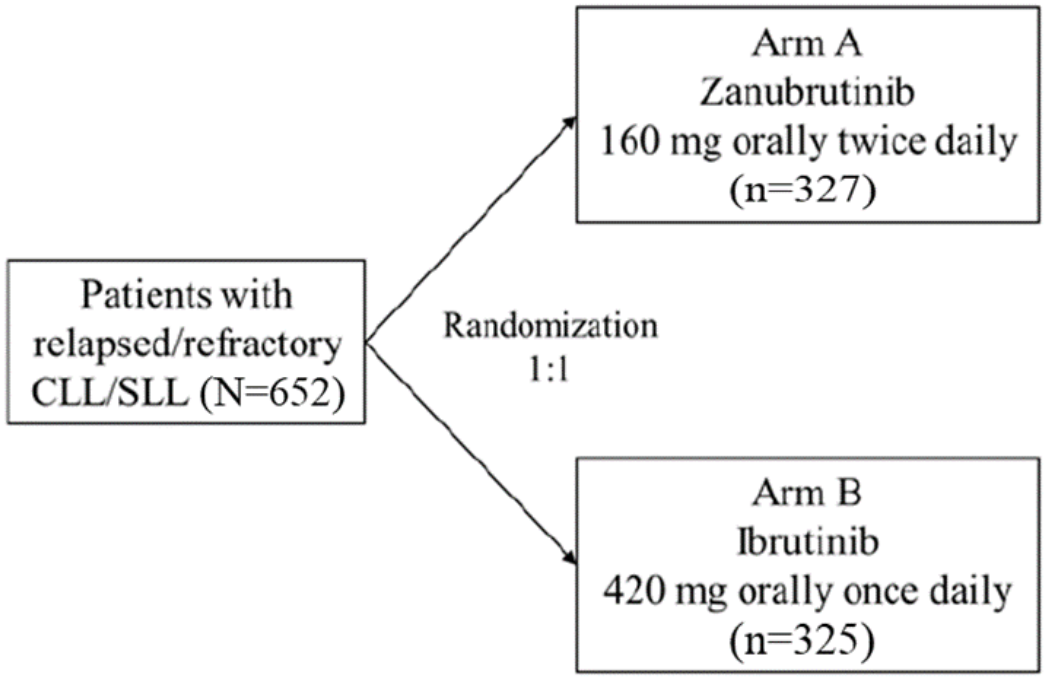


Design	Phase 3, open label, randomised, multicentre
Population	Diagnosis of CD20-positive CLL or SLL that met the iwCLL criteria, no prior treatment
Intervention	Cohort 1 and cohort 2*: Zanubrutinib
Comparator	Cohort 1: Bendamustine-rituximab
Duration	Not reported
Primary outcome	Cohort 1: PFS (IRC)
Secondary outcomes	Cohort 1: ORR, OS, DOR, PFS (INV), HRQoL, AEs and pharmacokinetics Cohort 2: ORR, PFS, DOR, AEs and pharmacokinetics
Used in model?	Yes
*Cohort 2 is a single arm zanubrutinib efficacy and safety assessment	

*Analyses for previously untreated CLL are presented using the latest data cut from SEQUOIA (data cut-off: 31 October 2022)

Abbreviations: AEs: Adverse events; CLL: Chronic lymphocytic leukaemia; DOR: Duration of response; HRQoL: Health-related quality of life; INV: Investigator; IRC; Independent central review; iwCLL: International workshop on chronic lymphocytic leukaemia; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; SLL: Small lymphocytic leukaemia

Key clinical trial: ALPINE (R/R CLL)

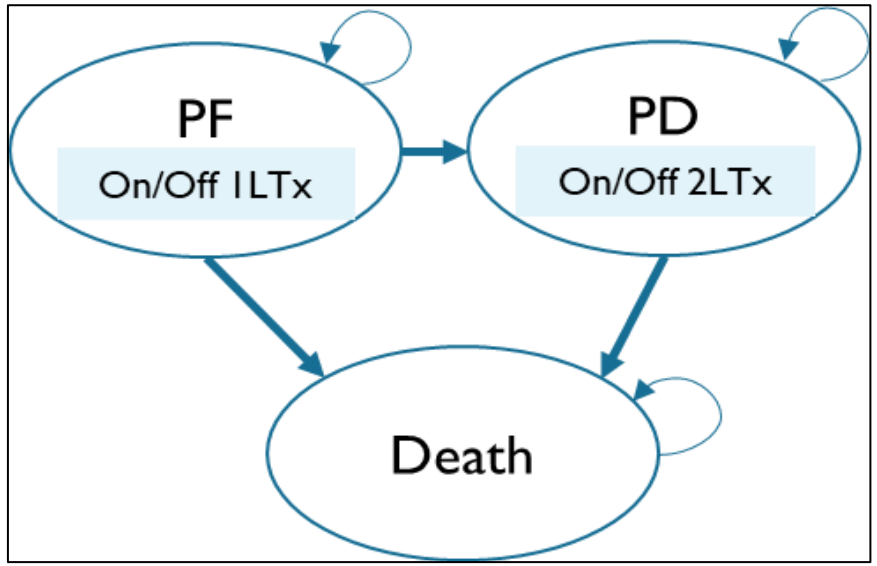


Design	Phase 3, open label, randomised, multicentre
Population	Patients ≥18 years with a diagnosis of CLL/SLL that met the iwCLL criteria, R/R to at least one prior systemic therapy
Intervention	Zanubrutinib
Comparator	Ibrutinib
Duration	Not reported
Primary outcome	ORR
Secondary outcomes	PFS, OS, DOR, TTTF, AEs, HRQoL
Used in model?	Yes

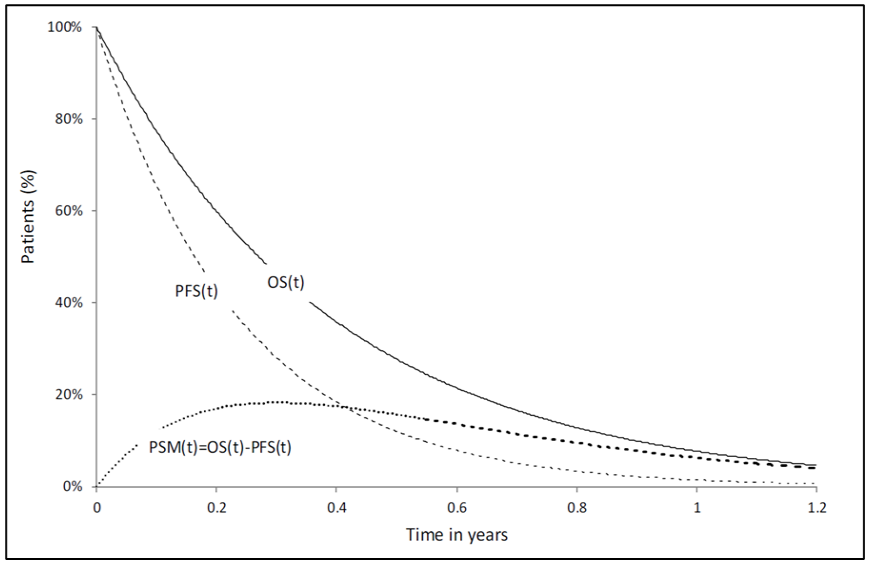
Abbreviations: AEs: Adverse events; CLL: Chronic lymphocytic leukaemia; DOR: Duration of response; HRQoL: Health-related quality of life; iwCLL: International workshop on chronic lymphocytic leukaemia; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; R/R: Relapsed/refractory; SLL: Small lymphocytic leukaemia; TTTF: Time to treatment failure

Company's model overview

Untreated CLL (semi-Markov model with a lifetime time horizon [30 years]):



R/R CLL (partitioned survival model with a lifetime time horizon [30 years]):



- Cost-effectiveness demonstrated using a cost minimisation approach
- Costs affected by lower zanubrutinib costs than comparators
- QALYs affected by assuming equivalent effectiveness of survival and quality of life across treatment arms

Abbreviations: 1LTx: First-line treatment; 2LTx: Second-line treatment; CLL: Chronic lymphocytic leukaemia; PD: Progressed disease; PF: Progression-free; QALYs: Quality-adjusted life years; R/R: Relapsed/refractory

ITC: zanubrutinib versus acalabrutinib for R/R CLL

Anchored MAIC using ALPINE and ELEVATE-RR trial data

- Anchored MAIC following DSU guidelines ➔ ELEVATE-RR and ALPINE had common comparator (ibrutinib)

	PFS (IRC)		PFS (INV)		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post matching – Model 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post matching – Model 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Unanchored MAIC using ALPINE and ASCEND trial data

- ASCEND and ALPINE did not have a common comparator arm, so company did an unanchored MAIC that followed the NICE DSU guidelines

	PFS (IRC)		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Post matching - Model 1	[redacted]	[redacted]	[redacted]	[redacted]
Post matching - Model 2	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; DSU: Decision support unit; HR; Hazard ratio; INV: Investigator; IRC: Independent central review; ITC: Indirect treatment comparison; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival; OS: Overall survival; R/R: Relapsed/refractory

Thank you

NICE