Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

Part 1 for public – redacted

Technology appraisal committee C [11 July 2023]

Chair: Richard Nicholas

Lead team: Stella O'Brien, Rob Forsyth, Pedro Saramago Goncalves

External assessment group: Newcastle NIHR TAR

Technical team: Zain Hussain, Sally Doss, Ross Dent

Company: BeiGene

Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ✓ **Background**
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions
- ❑ Other considerations: Innovation and potential for managed access
- ❑ Summary

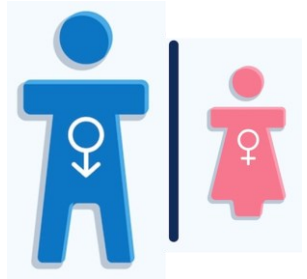
NICE National Institute for Health and Care Excellence

Background on chronic lymphocytic leukaemia (CLL)

CLL is a malignant disorder of the white blood cells (lymphocytes)

Causes

- Bone marrow produces too many immature lymphocytes ➔ Don't work properly

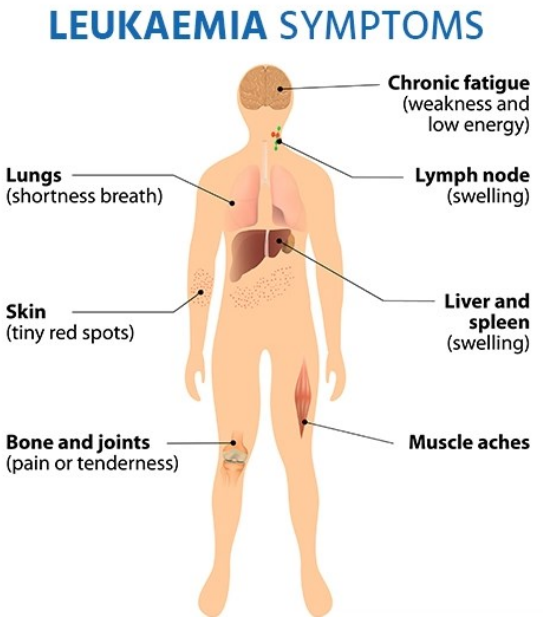


Epidemiology

- CLL is the most common type of leukaemia with an average of 3,331 new cases diagnosed in England between 2016 and 2018
- Risk of developing CLL increases with age and is more common in men

Diagnosis and classification

- Physical examination and complete blood counts determine the clinical staging
- People identified with 'high-risk' disease if they have:
    - Deletion of chromosome 17p (del(17p))
    - Mutation of the tumour protein p53 (TP53)



Symptoms and prognosis

- CLL usually progresses slowly, and symptoms develop over time
- Considerable burden of symptoms and recurrent infections impact quality of life
- High-risk predicts aggressive disease course & poor prognosis

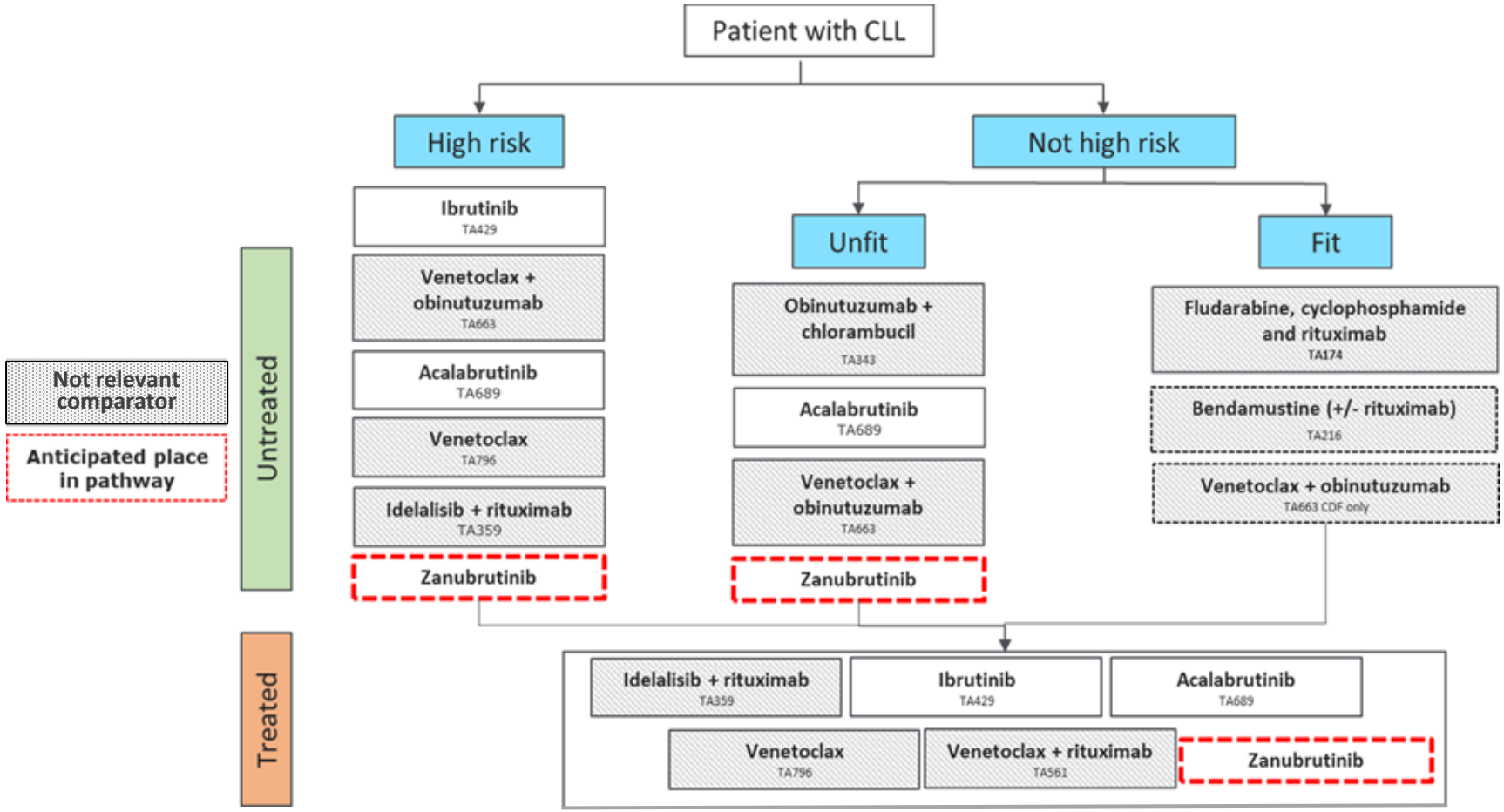
Zanubrutinib (Brukinsa, BeiGene)

Marketing authorisation (MA)	• **'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 patient access scheme (PAS)

Abbreviations: BCR: B-cell receptor; BTK: Bruton tyrosine kinase

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 relapsed/refractory (R/R) CLL



EAG critique:

- Venetoclax-rituximab (VenR) excluded as comparator for R/R CLL
- Concerns about the categorisation of cohort 1 in SEQUOIA trial as "unfit" rather than "fit"
- Data from "fit participants is used as a proxy for the "unfit" population in the model
- Data for acalabrutinib only available for a population combining both "high-risk" and non "high-risk" groups

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia

Patient perspectives

CLL has physical, mental, social and financial impact and affects the quality of life of patients as well as carers and families

Submissions from Lymphoma Action, Leukaemia Care and CLL Support

- Diagnosis of CLL can be emotionally and psychologically challenging for patients and their families
  - Muti-faceted impact of “watch and wait” with potentially a long time living with significant expectations of disease relapse
  - Affects their quality of life and that of their families, friends and carers
- Symptoms, particularly fatigue, affect ability to work at various levels and shared household responsibilities
  - Carers may need to give up jobs or work reduced hours
  - Substantial financial impact on patients, families and carers
- Compromised immune system, recurrent infections and treatment side-effects
  - Isolation and reduced social contact with family and friends for patients and carers due to risk of infections
  - Covid-19 has had further negative impact on social participation and involvement

“It was a huge shock at diagnosis! Incredibly scary. There were no support groups. I eventually learned to put it back in its box between appointments”

"I had to retire because of fatigue and the financial impact has been huge”

“Sometimes I catch my wife staring at me and I know she’s desperately worried I’m going to die”

NICE

Abbreviations: CLL: Chronic lymphocytic leukaemia

Patient perspectives

Access to multiple lines of treatment options is important for all CLL patients

Submissions from Lymphoma Action, Leukaemia Care and CLL Support

- Treatment options are individualised based on CLL subtype, previous treatment, health status, co-morbidities, treatment goals and patient preferences
- Unmet need for additional better treatments options for untreated CLL and R/R CLL providing 'a cure', longer remission and improved quality of life
    - Patients worry about treatment options running out
- Zanubrutinib could address the unmet need for people for a treatment with a better toxicity profile
    - Appears to be effective and produce durable remissions with fewer side effects than the currently available BTKis
    - Survey and community reports: "40% of patients reported no side effects at all, 40% reported bruising or petechia…20% were of an unspecified nature"
- There is a need for a BTKi for the 'fit' population with limited current treatment options available

"It's good to have more non chemo options now for relapsed but it does feel like each treatment is just kicking the can down the road then hope there will be something else available when the time comes"

"My elderly mom has been on Zanubrutinib for 15 months and it's literally been a life saver for her…[She] has had no side effects apart from a rash"

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia; R/R: Relapsed/refractory

Clinical perspectives

Potential to address substantial unmet need, particularly in the first line setting

Submissions from UK CLL Forum and the British Society of Haematology (BSH)

- Currently no cure for CLL
  - Aim of treatment is to induce remission and improve both progression free and overall survival
  - Available treatments limited in efficacy and poorly tolerated due to side effects
  - Unmet need for R/R CLL subgroup of patients for whom treatment options are exhausted and who die of progressive CLL
- Trial results for zanubrutinib are generally promising
  - Better toxicity profile means it is likely better tolerated than current treatments
  - Especially beneficial for patients with pre-existing cardiac issues
  - Long-term impact may be difficult to model
- Additional unmet need for NICE approved targeted agents for patients who:
  - Are treatment naïve for CLL
  - Have non-disrupted TP53 mutation
  - Would otherwise be considered fit for chemoimmunotherapy (CIT)

"A BTKi such as Zanubrutinib with a lower risk of development of AF and a reduced risk of sudden cardiac death is likely to bring significant quality of life benefits"

"it seems likely that Zanubrutinib will…be a superior BTKi…in the front-line setting and afford significant benefit to our young patients in the UK, who cannot currently access single-agent BTKi."

NICE

Abbreviations: AF: Atrial fibrillation; BTKi: Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia; R/R: Relapsed/refractory; TP53: Tumour protein p53

Equality considerations

- Company submission does not include analysis for people for whom chemoimmunotherapy is suitable
- 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: IGHV: Immunoglobulin heavy chain gene

Key issues

Key issues	Resolved?	ICER impact
Decision problem		
Exclusion of venetoclax-rituximab as a comparator in R/R CLL population	No – for discussion	Unknown
Clinical effectiveness		
Applicability of the SEQUOIA trial population to the untreated CLL comparison	No – for discussion	Unknown
Uncertainty in untreated “high-risk” CLL subgroup	No – for discussion	Unknown
Cost-effectiveness		
Interpretation of MAIC results for survival outcomes	No – for discussion	Unknown
Use of a cost-minimisation analysis as the company’s base-case	No – for discussion	Large
Uncertainty in the utility estimates used in the company’s economic model	No – for discussion	Small
Immaturity of trial data and parametric survival functions	No – for discussion	Unknown
Other		
Sensitivity of SLR to capture all relevant studies reporting on clinical evidence and utility values	No – for discussion	Unknown

Abbreviations: CLL: Chronic lymphocytic leukaemia; MAIC: Matching-adjusted indirect comparisons; R/R: Relapsed/refractory; SLR: Systematic literature review

Decision problem (1)

	Final scope	Company	EAG comments
Population	People with CLL	People with CLL[2]	In line with the NICE scope
Intervention	Zanubrutinib	Zanubrutinib	In line with the NICE scope
Outcomes	• overall survival (OS) • progression-free survival (PFS) • response rate • time-to-treatment failure (TTTF) • adverse effects (AEs) • health-related quality of life (HRQoL)	As per NICE scope	Mainly in line with the NICE scope. However, TTTF was not included as an outcome in the SEQUOIA trial
Comparators	**For R/R CLL, including (but not limited to):** • acalabrutinib • ibrutinib • venetoclax[1] • venetoclax with rituximab (VenR) • idelalisib with rituximab	**Adults with R/R CLL who have had at least one previous therapy:** • acalabrutinib • ibrutinib	VenR omitted despite inclusion in the 2022 BSH guidelines

[1] Disease has progressed after a BCR pathway inhibitor

[2] Except for fit for CIT

Abbreviations: BCR: B cell receptor; BSH: British Society of Haematology; CIT: Chemoimmunotherapy; CLL: Chronic lymphocytic leukaemia; R/R: Relapsed/refractory

Decision problem (2)

	Final scope	Company	EAG comments
Comparators	**For untreated CLL, including (but not limited to):** • acalabrutinib[1,2] • ibrutinib[1] • ibrutinib with venetoclax[3] • idelalisib with rituximab[1] • chlorambucil with or without rituximab • obinutuzumab with chlorambucil • bendamustine with or without rituximab • fludarabine, cyclophosphamide and rituximab (FCR) • venetoclax with obinutuzumab (VenO) • venetoclax[1,4]	**Previously untreated adults with CLL who are unsuitable for FCR and bendamustine-rituximab (BR) therapy:** • acalabrutinib **Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom CIT is unsuitable:** • acalabrutinib • ibrutinib	• VenO omitted despite inclusion in the 2022 BSH guidelines • BR is a comparison in the key trial of untreated CLL

[1] 17p deletion or TP53 mutation
[2] Fludarabine or bendamustine based regimens are not suitable
[3] Subject to ongoing NICE appraisal
[4] B-cell receptor pathway inhibitor is unsuitable

Abbreviations: BCR: B cell receptor; BR: Bendamustine-rituximab; BSH: British Society of Haematology; CIT: Chemoimmunotherapy; CLL: Chronic lymphocytic leukaemia; FCR: Fludarabine, cyclophosphamide and rituximab; TP53: Tumour protein p53

Key issue: Exclusion of VenR as a comparator in R/R CLL population (1)

Background

- VenR included as a comparator for R/R CLL in the NICE scope
- Company excluded VenR as a comparator for the R/R CLL population in its submission

EAG comments

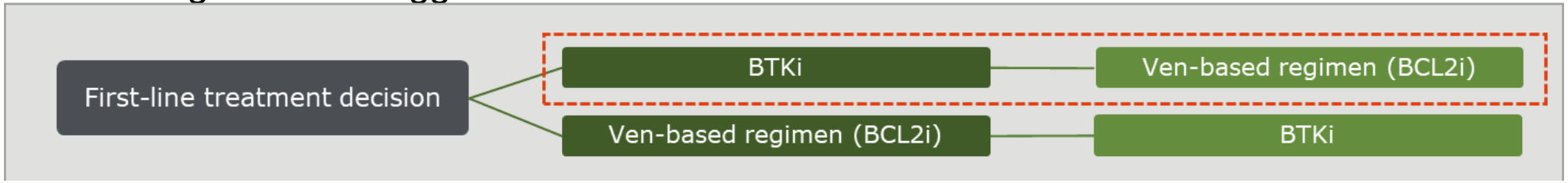
- Concerns that VenR has been excluded as a relevant comparator
  - BSH guidelines recommend VenR as a treatment for R/R CLL
  - Clinical advice to EAG suggests some patients who would previously have received CIT, for whom a BTKi would be a second-line option
- Examined an NMA that could potentially estimate the comparative effectiveness of zanubrutinib versus VenR
  - Point estimates form NMA suggest VenR is more effective than zanubrutinib ➔ But wide 95% CI mean conclusions on the effectiveness and cost-effectiveness versus VenR cannot be drawn
  - Limitations of the analysis include:
    i. Search strategy used to identify evidence for VenR may not be sufficient and beyond the time limits of appraisal to conduct a new literature search
    ii. The node “Control” is broader than the EAG would prefer, including BR (MURANO) and investigators’ choice of BR or idelalisib plus rituximab (MURANO, ASCEND, ALPINE)
    iii. ELEVATE-RR includes only “high-risk” patients with 17p deletion or 11q deletion, whereas MURANO, ASCEND, ALPINE included a combination of “high-risk” and “low-risk” patients

Abbreviations: BCL2i: B-cell lymphoma 2 inhibitor; BSH: British society of haematologists; BR: Bendamustine-rituximab; BTKi: Bruton tyrosine kinase inhibitor; CIT: Chemoimmunotherapy; CLL: Chronic lymphocytic leukaemia; NMA: Network meta-analysis; R/R: Relapsed/refractory; SLR: Systematic literature review; VenR: Venetoclax-rituximab

Key issue: Exclusion of VenR as a comparator in R/R CLL population (2)

Company response

- BSH 2022 guidelines suggest choice of 1st line treatment class drives choice of 2nd line treatment class



- Although VenR is recommended by NICE for R/R CLL irrespective of prior therapy received, there is lack of data for use of venetoclax-based regimen after relapse. VenR is primarily used in patients previously offered a BTKi
- UK prescribing data indicates that the treatment sequencing algorithm in patients not treated with a BTKi in the first-line is to receive a BTKi in second-line and a BCL2i in third-line
- Patients eligible for zanubrutinib are those who have not previously had treatment with a BTKi (aligned with ALPINE inclusion/exclusion criteria) ➔ Confirmed by advisory board with UK experts
- NMA versus VenR is subject to substantial uncertainty ➔ Analysis unsuitable to inform decision making

Abbreviations: BCL2i: B-cell lymphoma 2 inhibitor; BSH: British society of haematologists; BTKi: Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia; NMA: Network meta-analysis; R/R: Relapsed/refractory; VenR: Venetoclax-rituximab

Key issue: Exclusion of VenR as a comparator in R/R CLL population (3)

EAG critique

- Based on company's quantitative survey, EAG considers that a majority of patients receive VenR as a second-line therapy, a second preferred choice after ibrutinib
- NMA versus VenR was to illustrate the plausibility of a network between zanubrutinib and VenR and not to draw any conclusions based on these results due to the uncertainty in the derived estimates

Professional organisation and clinical expert comments

- For UK haematologists, venetoclax-based therapy for R/R CLL remains a valid treatment option for:
  - People whose disease relapses after CIT who prefer a time-limited treatment option
  - People whose disease relapses after CIT with significant cardiac issues where clinician preference might be to avoid a BTKi
  - People whose disease relapses after newly approved ibrutinib plus venetoclax therapy
- Covid-19 may have skewed the market survey data. Venetoclax therapy requires multiple hospital visits over the first 4-5 weeks and clinicians tried to avoid covid-19 exposure to patients

Is VenR a relevant comparator to zanubrutinib for R/R CLL population?

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor; CIT: Chemoimmunotherapy; CLL: Chronic lymphocytic leukaemia; NMA: Network meta-analysis; R/R: Relapsed/refractory; VenR: Venetoclax-rituximab

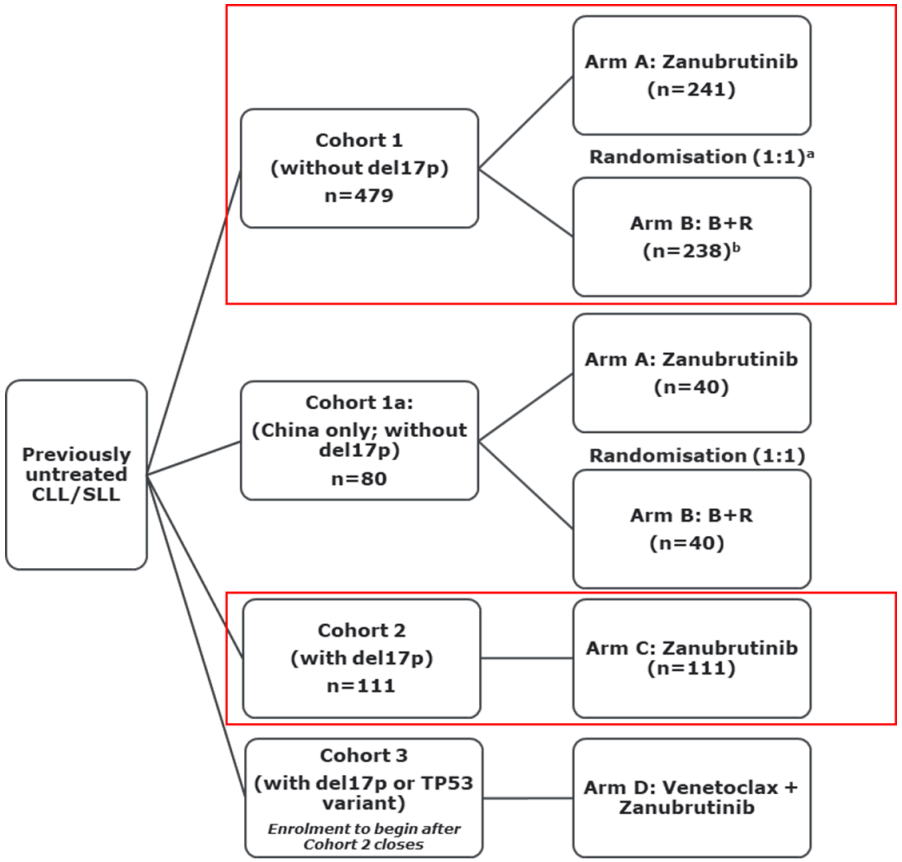
Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ❑ Background
- ✓ **Clinical evidence and key clinical issues to consider**
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions
- ❑ Other considerations: Innovation and potential for managed access
- ❑ Summary

NICE National Institute for Health and Care Excellence

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 (Independent central review [IRC])
Secondary outcomes	Cohort 1: ORR, OS, DOR, PFS (Investigator [INV]), HRQoL, AEs and pharmacokinetics Cohort 2: ORR, PFS, DOR, AEs and pharmacokinetics
Used in model?	Yes

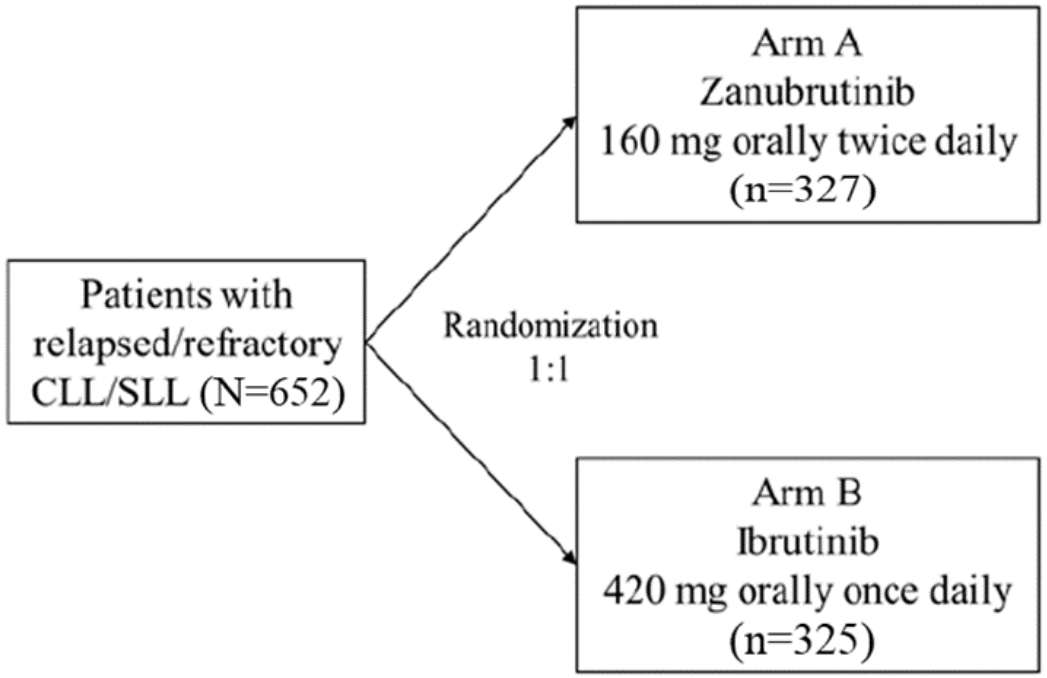
*Cohort 2 is a single arm zanubrutinib efficacy and safety assessment

EAG comments:

- Cohort 1a exclusion considered appropriate by EAG's clinical advisor
- Agree with the company that cohort 3 was not relevant

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; 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

SEQUOIA trial results – untreated CLL

May 2021 data cut – unless otherwise stated

Cohort 1 – zanubrutinib versus BR (n=479)				Cohort 2 – zanubrutinib only (n=110)	
PFS HR (95% CI) [p-value]					
IRC		INV		IRC	INV
0.42 (0.28, 0.63) [p<0.0001]		0.42 (0.27, 0.66) [p<0.0001]		-	-
ORR OR (95% CI) [p-value]					
IRC		INV		IRC	INV
[redacted]		[redacted]		-	-
DOR Median, months (95% CI)					
IRC		INV		IRC	INV
Zanubrutinib	BR	Zanubrutinib	BR	Zanubrutinib	Zanubrutinib
NE (NE, NE)	30.6 (25.5, NE)	NE (NE, NE)	30.6 (26.2, NE)	[redacted]	[redacted]
OS (March 2022): HR (95% CI) [p value]					
[redacted]				-	

*OS data (March 2022) from the SEQUOIA trial was not used in the untreated CLL economic model as there were too few events to provide robust long-term extrapolations

Abbreviations: BR: Bendamustine-rituximab; CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; DOR: Duration of response; HR: Hazard ratio; INV: Investigator; IRC: Independent central review; NE: Not estimable; OR: Odds ratio; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival

ALPINE trial results – R/R CLL

December 2021 data cut – zanubrutinib versus ibrutinib

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]

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

Indirect treatment comparison (ITC)

In the absence of direct evidence, company conducted matching adjusted indirect comparisons (MAICs) to compare the efficacy and safety of zanubrutinib versus comparators

Comparisons included in ITC

Trial name	Comparison
Untreated CLL population	
SEQUOIA ELEVATE-TN	versus acalabrutinib (unanchored MAIC)
ALPINE*	versus ibrutinib (direct)
SEQUOIA MATO	versus ibrutinib (naïve comparison)
R/R CLL population	
ALPINE ELEVATE-RR	versus acalabrutinib in R/R CLL (anchored MAIC)
ALPINE ASCEND	versus acalabrutinib (unanchored MAIC)

EAG comments:

- Appropriate to conduct MAICs given underlying assumption of network meta-analyses would not be valid
- Disagree with exclusion of comparison versus VenR in R/R CLL
- Consider VenO a potential comparator in untreated CLL and del17p or TP53 mutation, or where FCR or BR are unsuitable

*Company assumes R/R CLL data from ALPINE as a proxy for untreated “high-risk” CLL for the comparison of zanubrutinib with ibrutinib in the base case untreated CLL economic model

Abbreviations: BCL2i: B-cell lymphoma 2 inhibitor; BR: Bendamustine-rituximab; CLL: Chronic lymphocytic leukaemia; FCR: Fludarabine, cyclophosphamide and rituximab; R/R: Relapsed/refractory; TP53: Tumour protein 53; VenO: Venetoclax-Obinutuzumab; VenR: Venetoclax-rituximab

ITC: zanubrutinib versus acalabrutinib for untreated CLL

Unanchored MAIC (SEQUOIA and ELEVATE-TN)

- Data for zanubrutinib cohort 1 (arm A) and cohort 2 (arm C) of SEQUOIA trial were pooled to create a cohort that included patients with and without del17p to match the eligibility criteria for ELEVATE-TN
  - Pooled population adjusted to match the average baseline characteristics reported in ELEVATE-TN for participants receiving acalabrutinib ➔ Two matching models were considered in the analyses
- Analyses were conducted in the MAIC using IRC-assessed PFS and OS
  - Adjusted KM curves were estimated and plotted alongside unadjusted KM curves
  - Relative treatment effect for zanubrutinib versus acalabrutinib estimated by combining IPD from the SEQUOIA with the restructured IPD of ELEVATE-TN
  - Weighted Cox proportional hazard regression models were fitted to derive estimates of comparative effect after population adjustment

EAG comments:

- No major concerns with the methodological conduct or outcomes reported
- SEQUOIA and ELEVATE-TN reported reasonably similar important baseline characteristics
- Accepts uncertainty with unanchored MAICs is unavoidable as ELEVATE-TN and SEQUOIA did not contain a common comparator arm ➔ Unanchored MAIC followed NICE DSU guidelines

Abbreviations: CLL: Chronic lymphocytic leukaemia; DSU: Decision support unit; IPD: Individual patient-level data; IRC: Independent central review; ITC: Indirect treatment comparison; KM: Kaplan Meier; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival

ITC: zanubrutinib versus acalabrutinib for untreated CLL

Summary of unanchored MAIC results – SEQUOIA and ELEVATE-TN

	PFS (IRC)		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]

- **Company:** MAIC demonstrates that zanubrutinib is at least non-inferior to acalabrutinib in untreated people unsuitable for FCR and BR therapy ("unfit"), in participants both with and without del17p or TP53 mutation ("high-risk") ➔ [redacted]

EAG comments

- Results insufficient to conclude that zanubrutinib is non-inferior to acalabrutinib for IRC-assessed PFS
  - 95% CI indicates the lower limit is consistent with zanubrutinib being associated with reduced PFS compared with acalabrutinib
  - Clinical advice to the EAG suggested these differences were clinically meaningful

Abbreviations: BR: Bendamustine-rituximab; CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; FCR: Fludarabine, cyclophosphamide and rituximab; IRC: Independent central review; ITC: Indirect treatment comparison; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; TP53: Tumour protein 53

ITC: zanubrutinib versus ibrutinib for untreated CLL

Naïve comparison (SEQUOIA and Mato et al., 2018)

- Clinical efficacy for people with 17p deletion treated with ibrutinib was extracted from Mato et al., (2018) and compared with cohort 2 (arm C) of SEQUOIA
- A formal MAIC was not conducted given that baseline characteristics for people with a 17p deletion were not published in Mato et al.
- Instead, an unstratified Cox regression model was used to estimate HRs for PFS and OS
- Two matching models were considered for inclusion of prognostics factors in the MAIC
- Based on this naïve comparison, there was no statistically significant difference in PFS between zanubrutinib and ibrutinib ([redacted]). However, there was a statistically significant difference in OS between zanubrutinib and ibrutinib ([redacted])
- However, 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

EAG comments:

- Acknowledge that the naïve comparison using data from Mato et al., complements the MAICs and supports data for the previously untreated “high-risk” population
- Mato et al., was a retrospective study at risk of potential confounding bias as factors such as age and IGHV mutation were not controlled for in the comparison

Abbreviations: CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; HR: Hazard ratio; IGHV: Immunoglobulin heavy chain gene; ITC: Indirect treatment comparison; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival;

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)
- Methodology similar to unanchored MAIC versus acalabrutinib in untreated CLL (see slide 21)
- Matching model including all mutually available covariates led to an insufficiently low ESS (zanubrutinib arm = 31, Ibrutinib arm = 25) ➔ To increase ESS company used a matching model that only included covariates considered effect modifiers and prognostic factors with effect modifying potential were excluded

Summary of anchored MAIC results – ALPINE and ELEVATE-RR

	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]

EAG comments

- Trade-off between maximising the ESS and ensuring that important prognostic factors are included
- Disagrees that ESS is likely to be sufficient at detecting differences in outcomes present
- Trial with the shorter follow-up (ALPINE = 24.3 months versus ELEVATE-RR = 40.9 months) may not have the power to detect any differences between interventions
- Results insufficient to conclude non-inferiority of zanubrutinib versus acalabrutinib

Abbreviations: CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; DSU: Decision support unit; ESS: Effective sample size; 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

ITC: zanubrutinib versus acalabrutinib for R/R CLL

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
- Methodology was similar to unanchored MAIC versus acalabrutinib in untreated CLL

Summary of unanchored MAIC results – ALPINE and ASCEND

	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]

EAG comments

- No major concerns with methodology ➔ Accepts uncertainty with unanchored MAICs is unavoidable
- Trial with the shorter follow-up (ASCEND = 16.1 months versus ALPINE = 24.3 months) may not have the power to detect any differences between interventions
- Results insufficient to conclude non-inferiority of zanubrutinib versus acalabrutinib

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

Key issue: Applicability of the SEQUOIA trial population to the untreated CLL comparison (1)

Background

- Company uses evidence from SEQUOIA cohort 1 'fit' patients for 'unfit' CLL population

EAG comments:

- Concerns surrounding the categorisation of participants in the SEQUOIA trial as "unfit"
- Participants in SEQUOIA cohort 1 would have been considered "fit"
  - Company defines "unfit" patients with CLL as those unsuitable for FCR or BR. However, in SEQUOIA, participants were randomised to either zanubrutinib or BR

Company response

- Agree that fitness is non-binary, driven by patient characteristics rather than treatment eligibility
  ➔ Supported by clinical advice to company
- SEQUOIA trial more akin to eligibility criteria and patient characteristics of ELEVATE-TN trial which was deemed representative of untreated "unfit" patients with CLL by NICE.
- BR was used as a comparator in SEQUOIA trial because at the time of study design, the standard front-line treatment in patients without 17p deletion or TP53 mutation was CIT ➔ Clinical advice to company confirms BR would not be appropriate for SEQUOIA trial population based on current guidelines
- EMA confirms applicability of the SEQUOIA patient population to the previously untreated "unfit" population

Abbreviations: BR: Bendamustine-rituximab; CIT: Chemoimmunotherapy; CLL: Chronic lymphocytic leukaemia; EMA: European Medicines Agency; FCR: Fludarabine, cyclophosphamide and rituximab; TP53: Tumour protein p53

Key issue: Applicability of the SEQUOIA trial population to the untreated CLL comparison (2)

EAG critique

- Acknowledge the ambiguity in defining "fitness"
- Main issue is uncertainty caused by the definition of "fitness" in the submission, which potentially creates uncertainty in the generalisability of the SEQUOIA trial, as these patients were considered “fit” for BR

Professional organisation and clinical expert comments

- Historically, “unfit” defined patients in whom toxicity with CIT limited its use due to unacceptable side effects and poorer outcomes ➔ Separation of “fit” and “unfit” patients is now largely redundant
- Not clear why SEQUOIA data not used as evidence for use of zanubrutinib upfront in a “fitter” population
  ➔ They have the unmet need in the UK of not being able to access continuous, single-agent BTKi

Patient organisation comments

- Important to recognise the unmet need across all CLL subgroups, including in the fit population

Comparator company comments

- Toxicity with BR might have impacted randomisation to BR arm ensuring patient fit enough to tolerate it

Is evidence for zanubrutinib from SEQUOIA trial cohort 1 relevant to untreated ‘unfit’ CLL population?

Abbreviations: BR: Bendamustine-rituximab; BTKi: Bruton tyrosine kinase inhibitor; CIT: Chemoimmunotherapy; CLL: Chronic lymphocytic leukaemia; CS: Company submission

Key issue: Uncertainty in untreated "high-risk" CLL subgroup

Background

- NICE scope suggested presenting subgroup analyses for those with del17p or TP53 mutation ("high-risk") in the untreated CLL population

EAG comments

- Data for acalabrutinib only available for a population combining both "high-risk" and non "high-risk" groups
- Data for untreated "high-risk" CLL patients comparing zanubrutinib with ibrutinib was based on the ALPINE trial, which was undertaken in an R/R CLL population with only 23% of participants considered "high-risk"

Company

- Lack of data in "high-risk" CLL evident across several previous appraisals. In NICE TA689 and TA429, data from the R/R CLL was accepted as proxy for untreated "high-risk" population
- Mato et al (2018), was the only ibrutinib study identified for the "high-risk" population in the clinical SLR

Professional organisation and clinical expert comments

- For patients with TP53 disruption in the R/R setting do not have the same genetic profile as patients with TP53 disruption in the untreated setting
- Real world data and long-term follow-up will inform some comparisons but this will take years

Is the evidence for the "high-risk" untreated CLL subgroup sufficient to make recommendations?

Abbreviations: CLL: Chronic lymphocytic leukaemia; R/R: Relapsed/refractory; SLR: Systematic literature review; TP53: Tumour protein 53

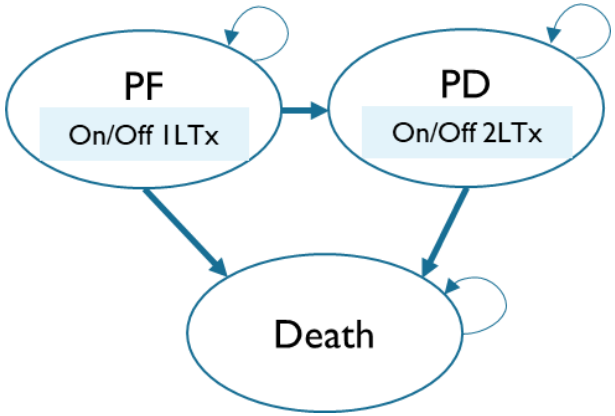
Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ✓ **Modelling and key cost effectiveness issues to consider**
- ❑ Base case assumptions
- ❑ Other considerations: Innovation and potential for managed access
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company's model overview – untreated CLL

- Semi-Markov model with a lifetime time horizon (30 years)
- No stopping rule ➔ Treatment until disease progression or death in all arms
- Cost-effectiveness demonstrated using a cost minimisation approach ➔ Justification based on MAIC analyses comparing data from SEQUOIA and ELEVATE-TN for comparison versus acalabrutinib and ALPINE trial results as proxy for untreated 'high-risk' CLL for comparison versus ibrutinib
- TTP and PrePS data from SEQUOIA, extrapolated to model patients leaving the PF health state. TTP modelled using pooled patient data across arm A and arm C from SEQUOIA



- PrePS curve was a simple average between parametric survival curve for pooled arm A and arm C data, and a parametric curve for arm B from SEQUOIA
- Mortality in PrePS curves was constrained so that it could not fall below UK general population mortality
- In PD health state, patients receive treatment with VenR therapy
  - One-time monitoring cost for VenR associated with laboratory TLS prophylaxis
- Model accounted for ≥ grade 3 AEs that occurred in ≥ 1% of the patient population
- 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; AE: Adverse events; CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; MAIC: Matching-adjusted indirect comparison; PAS: Patient access scheme; PD: Progressed disease; PF: Progression-free; PrePS: Pre-progression survival; QALYs: Quality-adjusted life years; TTP: Time-to-progression; TLS: Tumour lysis syndrome; VenR: Venetoclax-rituximab;

Zanubrutinib TTP extrapolation – untreated CLL model

IRC-assessed time to progression with extrapolated parametric survival curves and goodness-of-fit statistics (pooled arm A and arm C from SEQUOIA)

[redacted]

Distribution	Zanubrutinib (stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

EAG comments

- Statistical assessment of the progression hazards between the “unfit” (arm A) and “high-risk” (arm C) should have been provided using KM TTP data from both arms of SEQUOIA
- In absence of statistical analysis between arm A and arm C, significant differences in disease progression across untreated CLL patients with del17p versus patients without del17p is uncertain

NICE

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CLL: Chronic lymphocytic leukaemia; IRC: Independent central review; KM: Kaplan-Meier; TTP: Time-to-progression

Zanubrutinib PrePS extrapolation – untreated CLL model

IRC-assessed PreProgression survival with extrapolated parametric survival curves constrained by general population mortality and goodness-of-fit statistics (pooled SEQUOIA arm A and arm C for zanubrutinib compared to arm B for BR)

Distribution	Zanubrutinib (pooled arm A and arm C)		BR (arm B)	
	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Does not consider company's methods as a simple average between the two parametric extrapolations of arms A and C, and arm B separately, to be the most appropriate approach
- Unclear why the company did not pool the IPD across all arms before deriving the parametric PrePS curve

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BR: Bendamustine-rituximab; CLL: Chronic lymphocytic leukaemia; IPD: Individual patient data; IRC: Independent central review; KM: Kaplan-Meier; PrePS: Pre-progression survival

PPS extrapolation – untreated CLL model

Kaplan-Meier and extrapolated survival curves for OS to model PPS (MURANO VenR arm)

Distribution	MURANO VenR OS	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

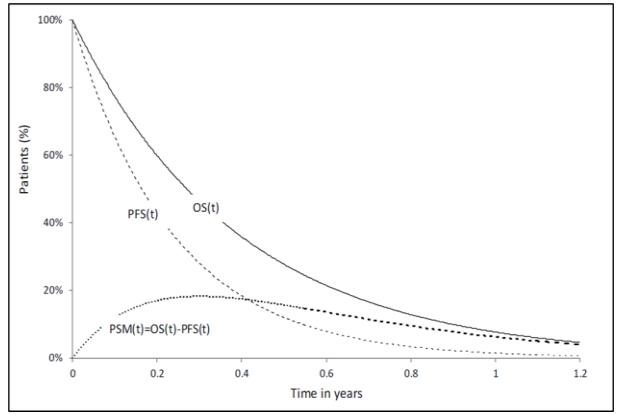
EAG comments

- Comparing ibrutinib versus acalabrutinib, OS data from the MURANO study suffers from censoring and is highly uncertain over the long time-horizon considered in this model (TA689)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CLL: Chronic lymphocytic leukaemia; OS: Overall survival; PPS: Post-progression survival; VenR: Venetoclax-rituximab

Company's model overview – R/R CLL

- Partitioned survival model with a lifetime time horizon (30 years)
- Cost-effectiveness demonstrated using a cost minimisation approach ➔ Justification based on MAIC analyses comparing data from ALPINE with either ELEVATE-RR or ASCEND for comparison versus acalabrutinib and ALPINE trial results for comparison versus ibrutinib
- PFS and OS for zanubrutinib extrapolated by applying parametric models to ALPINE trial data
- In PD health state, patients receive treatment with VenR or idelalisib-rituximab
  - One-time monitoring cost for VenR associated with laboratory TSL prophylaxis
- Model accounted for ≥ grade 3 AEs that occurred in ≥ 2% of the patient population
- Costs affected by lower zanubrutinib costs than comparators
- QALYs affected by assuming equivalent effectiveness of survival and quality of life across treatment arms



Abbreviations: AE: Adverse events; CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; MAIC: Matching-adjusted indirect comparison; PAS: Patient access scheme; OS: Overall survival; PD: Progressed disease; PFS: Progression-free survival; QALYs: Quality-adjusted life years; TLS: Tumour lysis syndrome; VenR: Venetoclax-rituximab;

Zanubrutinib PFS extrapolation – R/R CLL model

INV-assessed PFS with extrapolated parametric survival curves and goodness-of-fit statistics (ALPINE)

Distribution	Zanubrutinib (stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

EAG comments

- Uncertainty in long term estimates due to comparisons with literature presented having a follow-up of less than five years

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CLL: Chronic lymphocytic leukaemia; INV: Investigator; PFS: Progression-free survival; R/R: Relapsed/refractory

Zanubrutinib OS extrapolation – R/R CLL model

INV-assessed OS with extrapolated parametric survival curves and goodness-of-fit statistics (ALPINE)

[redacted]

Distribution	Zanubrutinib (stratified)	
	AIC	BIC
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

- Assessment of the visual and statistical fit was not sufficient, so the OS curve selection was validated by clinical experts from an advisory board conducted by the Company ➔ Suggested that ~50% of patients would be expected to be alive at 10 years

EAG comments

- Unclear why the BIC coefficient was not mentioned during the assessment of statistical fit

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CLL: Chronic lymphocytic leukaemia; INV: Investigator; OS: Overall survival; R/R: Relapsed/refractory

Key issue: Interpretation of MAIC results for survival outcomes

Background

- Based on MAICs, company claims non-inferiority of zanubrutinib versus comparators in the submission

EAG comments:

- Company's conclusion confuses a lack of statistical significance with non-inferiority or equivalence

Company response

- Whilst the MAICs did not demonstrate a statistically significant difference in PFS, all MAICs demonstrated a numerical improvement in PFS for zanubrutinib compared to acalabrutinib
- Zanubrutinib is a next-generation BTKi and results of the ALPINE trial, MAICs and clinical expert opinion support the plausible equivalence of zanubrutinib compared to alternative BTKis

EAG critique

- Maintains that main MAIC results show an absence of evidence of no difference, rather than demonstrating no difference in effectiveness between zanubrutinib and acalabrutinib

Do MAIC results demonstrate similarity of zanubrutinib versus comparators in untreated CLL and R/R CLL?

Abbreviations: BTKi: Bruton tyrosine kinas inhibitor; CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival; R/R: Relapsed/refractory

Key issue: Use of a cost-minimisation analysis as the company's base-case (1)

Background

- Company present a CMA as the base-case approach based on multiple MAIC analyses (versus acalabrutinib and ibrutinib) and ALPINE trial results (versus ibrutinib). CUA presented only as scenario analysis

EAG comments

- CMA approach was not considered to be the most appropriate method to represent the decision problem
  - MAICs do not provide sufficient evidence of non-inferiority
  - R/R CLL data from ALPINE trial as a proxy for untreated "high-risk" CLL only included 23% of participants with del17p and/or TP53 mutation ➔ Clinical advice to EAG also suggests R/R CLL not a good proxy
  - Mato et al., (2018) is an observational retrospective study, where a naïve comparison does not control for potential confounders such as age or IGHV mutation
- EAG modified company's model, for CUA scenarios, albeit strong assumptions and structural uncertainties, to present an alternative application of the CUA and improve the accuracy of results

Abbreviations: CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; IGHV: Immunoglobulin heavy chain gene; R/R: Relapsed/refractory; TP53: Tumour protein 53

Key issue: Use of a cost-minimisation analysis as the company's base-case (2)

Company response

- To alleviate uncertainty in the MAIC estimates and align with previous appraisals in CLL, a conservative approach is taken by assuming equal efficacy and safety within a CMA approach
- In NICE TA689 and TA429, it was agreed that data from the R/R CLL is an appropriate proxy to inform the clinical effectiveness of two BTKis (acalabrutinib and ibrutinib) in untreated "high-risk" population
- Equal efficacy in patients with untreated "high-risk" CLL was validated with UK clinical experts
- Clinical expert advice supported Mato et al., evidence is sufficient to demonstrate at least equal efficacy of zanubrutinib versus other BTKis in untreated "high-risk" CLL population
- In TA689, MAIC analysis were used to justify the use of a CMA approach ➔ Accepted by the Committee
- In all company and EAG's CUA scenarios, zanubrutinib is below NICE's willingness-to-pay threshold

EAG critique

- Maintains that CUA more appropriate across both untreated and R/R CLL populations, except for the comparison with ibrutinib in R/R CLL
- MAIC for "high-risk" patients utilises data from R/R CLL patients from ALPINE and ELEVATE-RR
- Despite favourable results for zanubrutinib in EAG analysis, strong assumptions were made in CUA

Is a CUA approach more appropriate than CMA approach for decision making?

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; MAIC: Matching-adjusted indirect comparison; PFS: Progression-free survival; R/R: Relapsed/refractory

Key issue: Uncertainty in the utility estimates used in the company economic model

Background

- Company used UK general population age-sex matched utility values for PF health state and literature values (Holzner et al., 2004) for PD health state

EAG comments:

- Cost-effectiveness results were sensitive to changes in utility values when a CUA approach was chosen

Company response

- Choice of utility values will not affect the cost-minimisation estimates
- Explored alternative utility values, accepted by NICE in past CLL appraisals, in scenario analysis in response to technical engagement

EAG critique

- Although, Holzner et al., (2004) was previously accepted by NICE, there are concerns within the study methodology ➔ Still consider utility values uncertain, especially as PD utilities are a primary driver of effectiveness across both untreated CLL and R/R CLL populations
- Cannot comment on the quality of searches as these have not been reported
- Alternative utility scenarios provided by the company were tested across the company and EAG base-case models and the cost-effectiveness results did not change

Which utility values are most appropriate for decision making under a CUA approach?

Abbreviations: CLL: Chronic lymphocytic leukaemia; CUA: Cost-utility analysis; PD: Progressed disease; PF: Progression-free; R/R: Relapsed/refractory

Key issue: Immaturity of trial data and parametric survival functions

Background

- Company uses follow-up data from SEQUOIA trial and ALPINE trial to model long term survival over 30 years for untreated CLL and R/R CLL respectively

EAG comments

- Follow-up data from the SEQUOIA trial and ALPINE trial used in the economic model is relatively short coupled with data immaturity from low event numbers for key survival outcomes
- In absence of real-world evidence, selection of survival models is heavily reliant on clinical expert opinion

Company response

- Acknowledge immature trial data but economic models made best use of the data available
- Level of data immaturity reported in the zanubrutinib clinical trials is aligned with that in previous appraisals

EAG critique

- Acknowledges that data immaturity is not exclusive to this CLL appraisal alone
- Parametric models and probabilistic and sensitivity analyses presented by company and EAG are informative to assess parameter uncertainty, but may not incorporate structural or other uncertainties

Is the evidence from SEQUOIA and ALPINE trials appropriate to make long terms survival extrapolations to inform the untreated CLL and R/R CLL economic models respectively?

Abbreviations: CLL: Chronic lymphocytic leukaemia; R/R: Relapsed/refractory

Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ✓ **Base case assumptions**
- ❑ Other considerations: Innovation and potential for managed access
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company and EAG base case assumptions – untreated CLL

Company uses cost-minimisation analysis, EAG prefers a cost-utility analysis

Parameter		Company: Assumption (source)	EAG: Assumption (source) if different
Survival models	TTP	Generalised Gamma (SEQUOIA trial)	-
	PrePS	Generalised Gamma (SEQUOIA trial)	-
	PPS	Exponential (MURANO trial)	-
	PrePS - 2L	Gompertz (MURANO trial)	-
Hazard ratios	TTP	1 (CMA assumption)	CUA (HR estimates from different MAIC models)
	PrePS	1 (CMA assumption)	CUA (HR estimates from different MAIC models)
Adverse events	Zanubrutinib	(SEQUOIA trial)	-
	Acalabrutinib	(RESONATE-2 trial)	-
	Ibrutinib	(ELEVATE-TN trial)	-
Utility values	PF	0.783 (NICE TA689)	-
	PD	0.6 (Holzner et al. 2004)	-
Costs and resource use	Resource use	Resource use values from literature (NICE TA689)	-
	End of life	Resource use and costs (Round 2015)	-
	TLS management	One-time monitoring for venetoclax (Seymour 2018 and NICE TA561)	-
	Drug acquisition	PAS discount applied to zanubrutinib (BNF, company data)	-
	Treatment duration	Until progression or death (Assumption)	-
	Subsequent treatment	VenR (BSH guidelines)	-

Abbreviations: BNF: British national formulary; BSH: British society for haematology CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; HR: Hazard ratios; MAIC: Matching-adjusted indirect comparison; PAS: Patient access scheme; PD: Progressed disease; PF: Progression-free; PrePS: Pre-progression survival; PPS: Post-progression survival; TLS: Tumour lysis syndrome; TTP: Time-to-progression; VenR: Venetoclax-rituximab

EAG's CUA approach – untreated CLL economic model

- Applied the HR of OS and PFS to modelled PrePS and TTP curves as follows:
  1. The HR for OS from the MAIC between SEQUOIA and ELEVATE-TN model 1, was applied to zanubrutinib PrePS to derive the PrePS curve of acalabrutinib. The HR for OS from the ALPINE trial was used on the zanubrutinib PrePS curve to model ibrutinib PrePS
  2. The TTP from zanubrutinib and the PrePS for acalabrutinib and ibrutinib were combined to generate PFS for each comparator respectively
  3. The HR for PFS from the MAIC between SEQUOIA and ELEVATE-TN, model 1, was applied to the acalabrutinib PFS curve, to then derive TTP for acalabrutinib. Similarly, the HR for PFS from the ALPINE trial was used on the PFS curve of ibrutinib to derive TTP respectively
- **Key caveats:**
  1. Assumes that relative hazard estimates of OS can be applied to the current SEQUOIA PrePS data
  2. Assumes that a partitioned-survival approach was appropriate to derive TTP from PFS
  3. Assumes of constant relative hazards over time, and that treatment effects have a lifetime duration,

Abbreviations: CLL: Chronic lymphocytic leukaemia; CUA: Cost-utility analysis; HR: Hazard ratios; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; PrePS: Pre-progression survival; TTP: Time-to-progression

Company and EAG base case assumptions – R/R CLL

Company uses cost-minimisation analysis, EAG prefers a cost-utility analysis

Parameter		Company: Assumption (source)	EAG: Assumption (source) if different
Survival models	PFS	Weibull (ALPINE trial)	-
	OS	Weibull (ALPINE trial)	-
Hazard ratios	PFS	1 (CMA assumption)	CUA (HR estimates from different MAIC models)
	OS	1 (CMA assumption)	CUA (HR estimates from different MAIC models)
Adverse events	Zanubrutinib	(ALPINE trial)	-
	Acalabrutinib	(ASCEND trial)	-
	Ibrutinib	(ALPINE trial)	-
Utility values	PF	0.748 (NICE TA561)	-
	PD	0.6 (Holzner et al. 2004)	-
Costs and resource use	Resource use	Resource use values from literature (NICE TA689)	-
	End of life costs	Resource use and costs (Round 2015)	-
	TLS management	One-time monitoring for venetoclax (Seymour 2018 and NICE TA561)	-
	Treatment acquisition	PAS discount applied to zanubrutinib (BNF, company data)	-
	Treatment duration	Until progression or death (Assumption)	-
	Subsequent treatment	80% VenR, 20% idelalisib-rituximab (BSH guidelines, assumption)	-

Abbreviations: BNF: British national formulary; BSH: British society for haematology CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; HR: Hazard ratios; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PAS: Patient access scheme; PD: Progressed disease; PF: Progression-free; PFS: Progression-free survival; R/R: Relapsed/Refractory; TLS: Tumour lysis syndrome; VenR: Venetoclax-rituximab

EAG's CUA approach – R/R CLL economic model

- Applied the relative effectiveness estimates from the MAIC results of model 2 comparing ALPINE and ASCEND on the OS and the PFS curves of zanubrutinib from ALPINE to derive the OS and PFS for acalabrutinib
- OS and PFS curves for ibrutinib were derived from the ALPINE trial directly
- **Key caveats:**
  1. Method to derive the survival curves for acalabrutinib assumed a constant relative hazard over-time
  2. The effect of the treatments was assumed to last for as long as patients stay in the PF state

Abbreviations: CLL: Chronic lymphocytic leukaemia; CUA: Cost-utility analysis; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PF: Progression free; PFS: Progression-free survival; R/R: Relapsed/refractory

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 – Untreated CLL

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

1. Company deterministic and probabilistic base case CMA results (zanubrutinib versus acalabrutinib and ibrutinib)
2. EAG deterministic and probabilistic base case CUA results (zanubrutinib versus acalabrutinib and ibrutinib)
3. EAG scenario analysis with largest impact on EAG CUA base case ICERs (zanubrutinib versus acalabrutinib and ibrutinib)
    i. **PFS HR vs acalabrutinib: [redacted] OS HR vs acalabrutinib: [redacted]**
    ii. **SEQUOIA-derived utilities: [redacted]**
    iii. **SEQUOIA-derived PD disutility applied to base-case PF: PD = [redacted]**
    iv. **Weibull distribution for TTP and PrePS**
    v. **MURANO OS Generalised Gamma**

Abbreviations: CI: Confidence interval; CLL: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; HR: Hazard ratios; ICERs: Incremental cost-effectiveness ratios; OS: Overall survival; PD: Progressed disease; PF: Progression-free; PFS: Progression-free survival; PrePS: Pre-progression survival; TTP: Time-to-progression

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

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

1. Company deterministic and probabilistic base case CMA results (zanubrutinib versus acalabrutinib and ibrutinib)
2. EAG deterministic and probabilistic base case CUA results (zanubrutinib versus acalabrutinib and ibrutinib)
3. EAG scenario analysis with largest impact on EAG CUA base case ICERs (zanubrutinib versus acalabrutinib and ibrutinib)
    - **i. ALPINE derived utilities** [redacted]
    - **ii. ALPINE derived PD utility =** [redacted]
    - **iii. Log-normal distribution for PFS**
    - **iv. Gompertz distribution for PFS**
    - **v. Log-normal distribution for OS**
    - **vi. Exponential distribution for OS**

Abbreviations: Chronic lymphocytic leukaemia; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; ICERs: Incremental cost-effectiveness ratios; OS: Overall survival; PD: Progressed disease; PF: Progression-free; PFS: Progression-free survival; R/R: Relapsed/refractory

Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions
- ✓ **Other considerations: Innovation and potential for managed access**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Other considerations

Innovation

- Introduction of zanubrutinib into the treatment pathway for CLL is desirable as it can delay progression and provide an alternative treatment option for patients with CLL
- Zanubrutinib is associated with improved tolerance and safety when compared to 1st generation and 2nd generation BTKis ➔ Potential to reduce treatment discontinuation due to intolerance

Potential for managed access

- Company submission highlighted ‘a managed access proposal is not considered relevant for zanubrutinib for treating patients with previously untreated CLL or R/R CLL’

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor; CLL: Chronic lymphocytic leukaemia; R/R: Relapsed/refractory

Zanubrutinib for treating chronic lymphocytic leukaemia (ID5078)

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions
- ❑ Other considerations: Innovation and potential for managed access
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issues	Resolved?	ICER impact
Decision problem		
Exclusion of venetoclax-rituximab as a comparator in R/R CLL population	No – for discussion	Unknown
Clinical effectiveness		
Applicability of the SEQUOIA trial population to the untreated CLL comparison	No – for discussion	Unknown
Uncertainty in untreated “high-risk” CLL subgroup	No – for discussion	Unknown
Cost-effectiveness		
Interpretation of MAIC results for survival outcomes	No – for discussion	Unknown
Use of a cost-minimisation analysis as the company’s base-case	No – for discussion	Large
Uncertainty in the utility estimates used in the company’s economic model	No – for discussion	Small
Immaturity of trial data and parametric survival functions	No – for discussion	Unknown
Other		
Sensitivity of SLR to capture all relevant studies reporting on clinical evidence and utility values	No – for discussion	Unknown

NICE

Abbreviations: CLL: Chronic lymphocytic leukaemia; MAIC: Matching-adjusted indirect comparisons; R/R: Relapsed/refractory; SLR: Systematic literature review

Back up slides

Key issue: Sensitivity of SLR to capture all relevant studies reporting on clinical evidence and utility values

Background

- Company undertook one integrated SLR to identify existing clinical, cost-effectiveness, HRQoL and cost and resource use in CLL

EAG comments

- Concerned whether SLR was sensitive enough to capture all relevant studies
  - Company did not consider a comprehensive and up-to-date range of grey literature sources

Company response

- SLR methods were in line with the NICE literature searching and evidence submission guidelines
- Grey literature and hand searches did not identify any additional publications

EAG critique

- Unable to support company's assertion of following NICE methods guide
- Unable to support company's assertion of no key publications were missed ➔ Did not provide search strategy for grey literature and hand searches requested during clarification for methodological critique

Professional organisation and clinical expert comments

- Familiar issue with new and maturing data for drugs emerging between SLR cut-off and time of appraisal

Does the company's SLR capture all relevant clinically relevant evidence for the treatment of CLL?

Abbreviations: CLL: Chronic lymphocytic leukaemia; HRQoL: Health related quality of life; SLR: Systematic literature review

Thank you

NICE