Pirtobrutinib for treating chronic lymphocytic leukaemia after 1 or more BTK inhibitors

For public – confidential information redacted

Technology appraisal committee C [ACM2, 3 March 2026]

Chair: Richard Nicholas

Lead team: Gochi Nwulu, Elizabeth Thugar

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Technical team: Sammy Shaw, Sam Slayen, Adam Brooke

Company: Eli Lilly & Company

Pirtobrutinib for treating chronic lymphocytic leukaemia after 1 or more BTK inhibitors

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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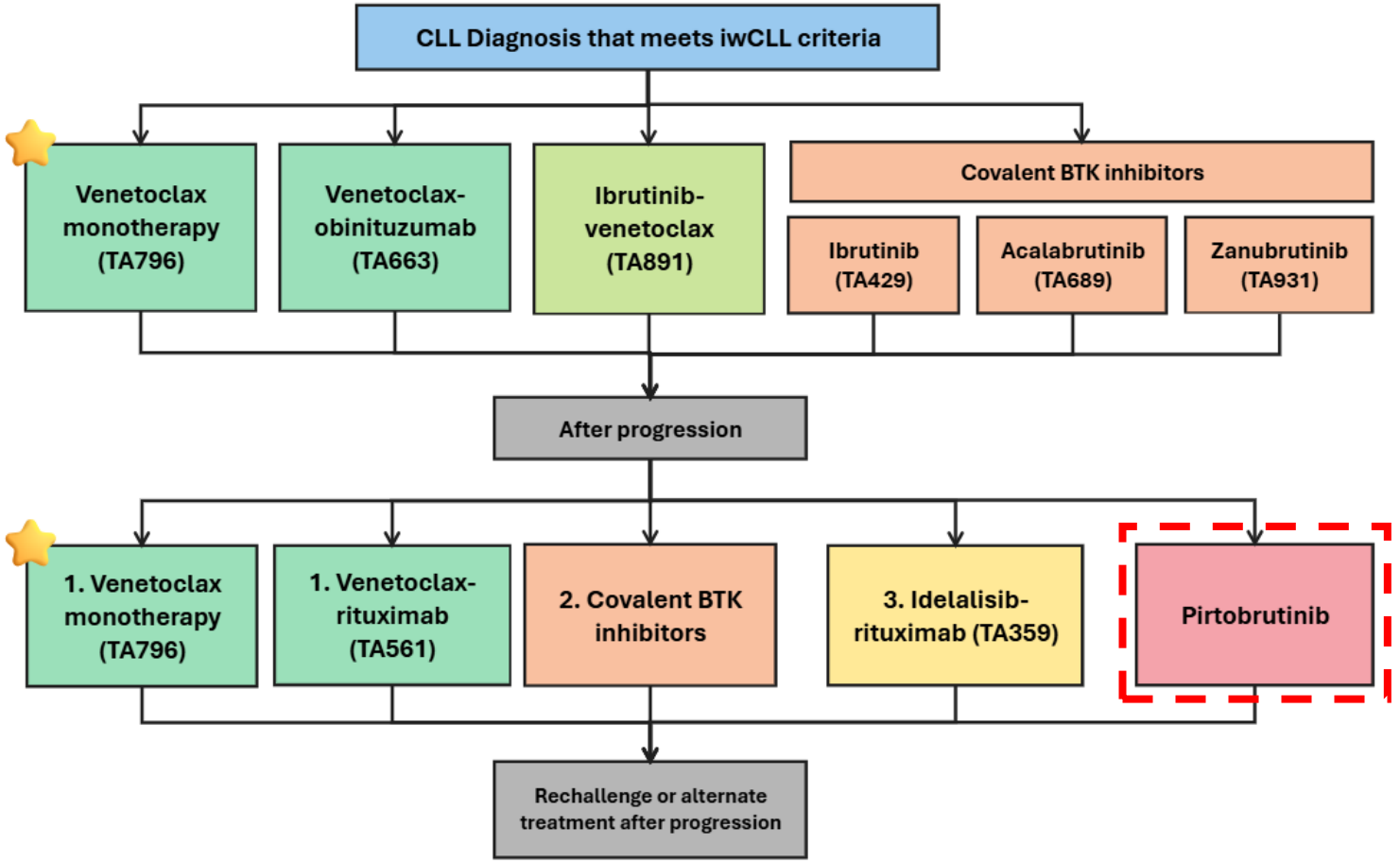
Treatment options

Note: Some NICE-recommended treatments omitted due to limited usage.

ACM1 clinical expert advice:

- Ven-mono is used in 2L when rituximab unsuitable
  - added as a relevant comparator
- BCL2i rechallenge if disease progresses 2/3 years after finishing BCL2i treatment
- cBTKi rechallenge if not refractory to previous cBTKi
- IdelaR or BSC used if rechallenge not possible



Which population(s) would be most likely to receive pirtobrutinib?

Key

- pirtobrutinib
- added after ACM1

Mechanisms of action: BCL2i/CD20i | BCL2i/cBTKi | cBTKi | PI3Ki | Non-covalent BTKi

Abbreviations: ACM1, appraisal committee meeting 1; BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CD20i, CD20 inhibitor; CDF, cancer drugs fund; CLL, Chronic lymphocytic leukaemia; IdelaR, idelalisib plus rituximab; IwCLL, International Workshop on Chronic Lymphocytic Leukaemia; PI3Ki, phosphoinositide 3-kinase inhibitor; VenR, venetoclax plus rituximab.

Key treatments in the pathway

Treatment	Abbreviation	Posology
Venetoclax* (oral) + obinutuzumab (IV)	VenO	**12 cycles total** 12 cycles of venetoclax: 6 with obinutuzumab, followed by 6 cycles alone.
Ibrutinib (oral) + venetoclax* (oral)	VenI	**15 cycles total** Ibrutinib alone for 3 cycles, followed by 12 cycles of ibrutinib plus venetoclax.
Venetoclax monotherapy (oral)	Ven-mono	20mg once daily for 7 days. Dose gradually increased over 5 weeks up to daily dose of 400mg. Venetoclax is given over 12 cycles of 28 days.
Ibrutinib, acalabrutinib or zanubrutinib (oral)	cBTKis	Offered until progression or until it is no longer tolerated.
Venetoclax* (oral) + rituximab (IV)	VenR	Venetoclax is taken for up to 24 months from cycle 1 day 1 of rituximab. Rituximab administered for 6 cycles.
Idelalisib (oral) + rituximab (IV)	IdelaR	Idelalisib taken until disease progression or unacceptable toxicity. 8 doses of rituximab administered.
Pirtobrutinib (oral)	-	200mg, once daily, until disease progression or unacceptable toxicity.

Note: 1 cycle = 28 days

* Venetoclax component follows posology described for venetoclax monotherapy

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Abbreviations: cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; IdelaR, idelalisib plus rituximab; IV, intravenous; Ven-mono, venetoclax monotherapy; VenI, ibrutinib plus venetoclax; VenO, venetoclax plus obinutuzumab; VenR, venetoclax plus rituximab.

Population summary

Several populations may be relevant to decision making

Population	Description	Comparators	Notes
1	Post-cBTKi or dual-exposed, BCL2i suitable.	VenR, Ven-mono	- Relapsed after BCL2i treatment finished (relapsed defined as progression after 6+ months of response) ⭐ **Committee at ACM1:** Ven-mono relevant
2	Post-cBTKi or dual-exposed, suitable for cBTKi.	cBTKi (ibrutinib, zanubrutinib, acalabrutinib)	- Not refractory to cBTKi - May have discontinued cBTKi due to intolerance - May have relapsed after finishing fixed duration cBTKi (dual exposed)
3	Post-cBTKi or dual-exposed, BCL2i or cBTKi not suitable.	IdelaR	- May be refractory to BCL2i and/or cBTKi - May not be able to tolerate BCL2i - May not be able to tolerate active treatment ⭐ **Committee at ACM1:** BSC not relevant

Abbreviations: ACM1, appraisal committee meeting 1; BCL2i, B-cell lymphoma-2 inhibitor; BSC, best supportive care; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor, IdelaR, idelalisib plus rituximab; Ven-mono, venetoclax monotherapy; VenR, venetoclax plus rituximab.

Pirtobrutinib (Jaypirca, Eli Lilly & Company)

Marketing authorisation	• The treatment of adults with relapsed or refractory chronic lymphocytic leukaemia who have been previously treated with a BTKi. • Granted conditional marketing authorisation on 13/08/2025.
Mechanism of action	• Non-covalent BTKi, reversible binding of the ATP pocket of BTK. • Inhibits downstream proliferative BTK signalling.
Administration	• Oral tablet (200mg) taken once daily.
Price	• 28 tablets of 50mg pirtobrutinib: £2,081.50. • 56 tablets of 100mg pirtobrutinib: £8,326.00. • A simple PAS applies to pirtobrutinib ⭐ This simple PAS was updated in December 2025

Abbreviations: ATP, Adenosine triphosphate; BTKi, Bruton's tyrosine kinase inhibitor; PAS, patient access scheme.

Key issues

Issue	Resolved?	ICER impact	ACM1 committee conclusion
Cost comparison with VenR	No – for discussion	Unknown – Potentially large	• Equivalence between VenR and pirtobrutinib uncertain • Requested exploration of RWE to understand Ven-mono and VenR equivalence, and network to link pirtobrutinib to VenR for CUA
Cost comparison with Ven-mono	No – for discussion	Unknown – Potentially large	• Clinical experts confirmed Ven-mono used in NHS where rituximab is unsuitable, so committee requested comparison against it
No cost effectiveness results for comparisons of pirtobrutinib with cBTKi or BSC	Partially – for discussion	Unknown – Potentially large	• cBTKis may be relevant for those rechallenged after fixed-duration VenI • BSC not relevant
Comparison of pirtobrutinib vs IdelaR	Partially – for discussion	Small to large – depends on population	• Relevant comparator for small population

See appendix for issues resolved at ACM1

Abbreviations: ACM1, appraisal committee meeting 1; BSC, best supportive care; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CUA, cost utility analysis; ICER, incremental cost effectiveness ratio; IdelaR, idelalisib plus rituximab; RWE, real-world evidence; Ven-mono, venetoclax monotherapy; VenI, venetoclax plus ibrutinib; VenR, venetoclax plus rituximab.

Committee requests from ACM1

Committee sought evidence to underpin pirtobrutinib/comparators equivalent efficacy assumptions used in cost comparisons

Committee requested:

- Further characterisation of the comparison with VenR where possible, including potential updates from ongoing trials
- A comparison with venetoclax-monotherapy (all potentially useful available relative effect data, including RWE referenced by the clinical expert in the meeting comparing it with VenR)
- Further clarity around the issue of rechallenge with cBTKi therapies for people who had fixed-duration VenI or discontinued because of intolerance, but recognised this was a smaller population/issue for decision-making

Abbreviations: ACM1, appraisal committee meeting 1; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; RWE, real-world evidence; VenI, venetoclax plus ibrutinib; VenR, venetoclax plus rituximab.

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Summary of clinical evidence

BRUIN CLL-321: pirtobrutinib improved PFS and (adjusted) OS vs IdelaR or BR

- Key trial demonstrated 46% improvement in PFS and 22% in treatment switching-adjusted OS when taking pirtobrutinib compared with IdelaR/BR
- Data limited VenR/cBTKi comparisons to be modelled – pirtobrutinib equivalence was assumed and modelled as cost comparisons

BRUIN CLL-321 outcomes

Outcome	Pirtobrutinib	IdelaR/BR	HR
Median PFS, months (95% CI)	14.0 (11.2 to 16.6)	8.7 (8.1 to 10.4)	0.54 (0.39 to 0.75)
ITT 18-month OS rate, % (95% CI)	73.4 (63.9 to 80.7)	70.8 (60.9 to 78.7)	1.09 (0.68 to 1.75)
Two-stage AFT-adjusted OS, (95% CI)			0.78 (0.48 to 1.26)

After ACM1

VenR comparison (population 1)

- Company conducted "**post-ACM1 NMA**" of cBTKi-naïve trials including latest BRUIN CLL-314 data for pirtobrutinib and five others to support equivalence assumption in post-cBTKi population
  - Pirtobrutinib vs VenR PFS HR = [redacted] (95% CI = [redacted] to [redacted])
- At committee's request, company and EAG reviewed Mato (2019) RWE comparing Ven-mono to VENcombo (VenO or VenR)

Mato (2019) outcomes

Outcome	Ven-mono vs VENcombo
PFS HR (95% CI)	1.0 (0.6 to 1.8)
OS HR (95% CI)	1.2 (0.6 to 2.3)

Abbreviations: ACM1, appraisal committee meeting 1; AFT, accelerated failure time; BR, bendamustine plus rituximab; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CI, confidence interval; EAG, external assessment group; HR, hazard ratio; IdelaR, idelalisib plus rituximab; ITT, intention-to-treat; NMA, network meta-analysis; PFS, progression-free survival; RWE, real-world evidence; OS, overall survival; Ven-mono, venetoclax monotherapy; VenO, venetoclax plus obinutuzumab; VenR, venetoclax plus rituximab.

Summary of clinical evidence (2/2)

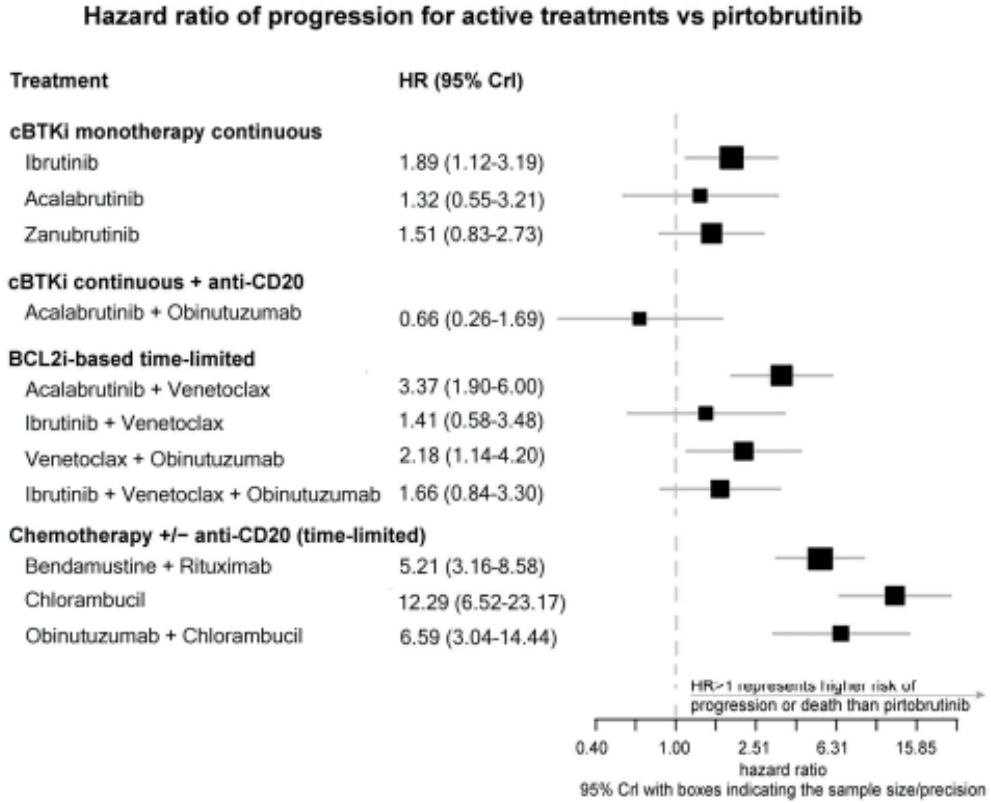
Tech team identified studies to consider pirtobrutinib vs cBTKis

After ACM1

cBTKi comparison (population 2)

- Company presented no additional evidence
- Tech team present two cBTKi-naïve studies for context
- Woyach (2025) BRUIN CLL-314 trial compares pirtobrutinib with ibrutinib in treatment-naïve (1L) & R/R CLL/SLL – results were presented for ITT (n=662) and for R/R (n=437) or treatment naïve (n=225)
    - In cBTKi-naïve R/R population, pirtobrutinib vs ibrutinib PFS HR = 0.73 (95% CI: 0.47 to 1.13)
- Eyre (2026) Bayesian 2-network-connected NMA of RCTs for treatments in treatment-naïve (1L) CLL (10 studies)
    - Pirtobrutinib offers numerically (or statistically for ibrutinib) better PFS than cBTKi monotherapies in 1L

Eyre (2026) PFS NMA HRs vs pirtobrutinib

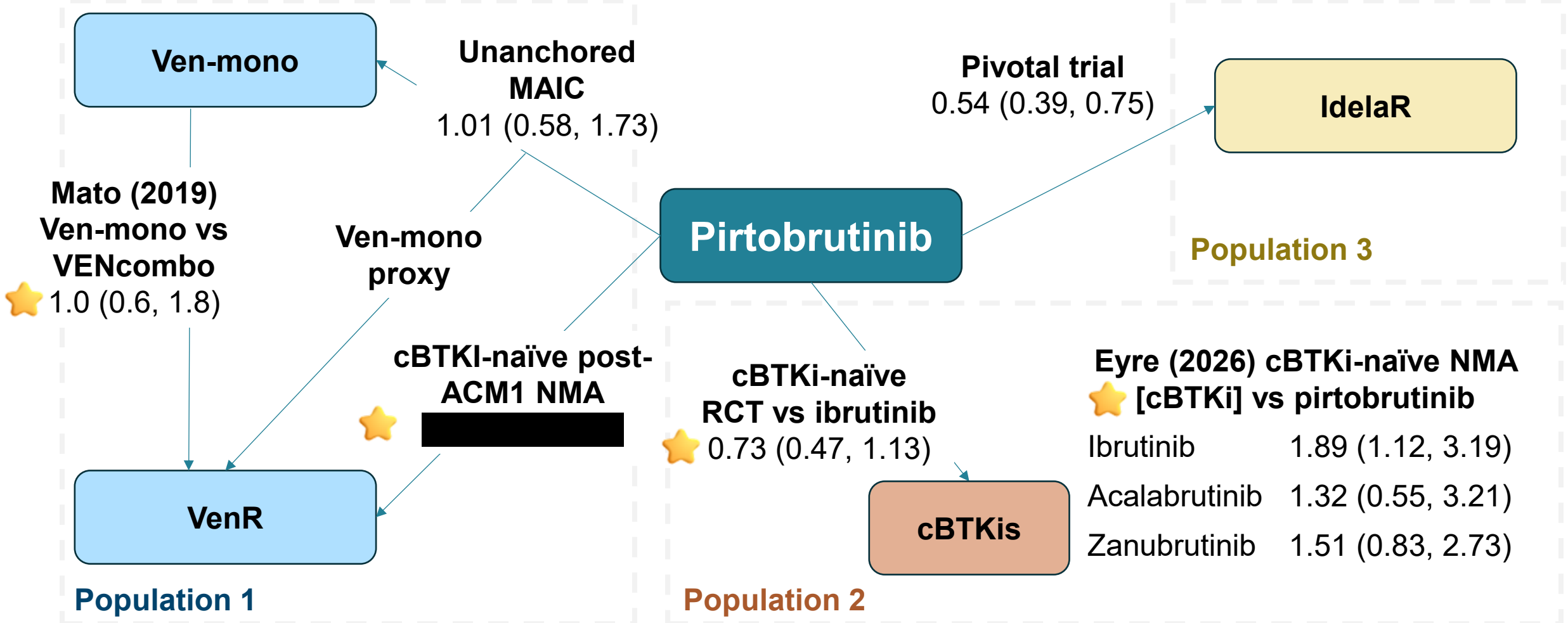


Post-hoc analysis from Eyre (2026) which relies upon an assumption that FCR is equivalent to FCR or BR to join two networks.

Abbreviations: 1L, first line; ACM1, appraisal committee meeting 1; BR, bendamustine plus rituximab; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukaemia; FCR, fludarabine plus cyclophosphamide and rituximab; HR, hazard ratio; ITT, intention-to-treat; NMA, network meta-analysis; PFS, progression-free survival; R/R, relapsed or refractory; RCT, randomised controlled trial; SLL, small lymphocytic leukaemia.

Evidence available for pirtobrutinib comparisons

Clinical effectiveness presented as PFS HRs (95% CI/CrI)



Abbreviations: cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CI, confidence interval; CrI, credible interval; HR, hazard ratio; IdelaR, idelalisib plus rituximab; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; RCT, randomised controlled trial; Ven-mono, venetoclax monotherapy; VENcombo, venetoclax combination (venetoclax plus obinutuzumab or venetoclax plus rituximab); VenR, venetoclax plus rituximab.

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Cost effectiveness analyses summary

Various cost effectiveness analysis presented for different sub-populations

Analyses updated using new PAS price

Population	Comparator	Model approach	Supporting clinical evidence
1. Post-cBTKi or dual-exposed, BCL2i suitable	VenR	CC	• Al-Sawaf (2024) unanchored MAIC pirtobrutinib vs Ven-mono; Ven-mono assumed proxy for VenR • Post-ACM1 NMA to support equivalence assumption • Mato (2019) RWE Ven-mono vs VENcombo (VenO or VenR)
	⭐ Ven-mono	CC	• Al-Sawaf (2024) unanchored MAIC
2. Post-cBTKi or dual-exposed, cBTKi suitable	cBTKis	CC	Based only on EAG's clinical expert opinion.
3. Post-cBTKi or dual-exposed, BCL2i or cBTKi not suitable	IdelaR	CUA	Cost utility analysis informed by BRUIN CLL-321 trial versus IC (IdelaR or BR). Trial PFS and switching-adjusted trial OS

Abbreviations: ACM1, appraisal committee meeting 1; BCL2i, B-cell lymphoma 2 inhibitor; BR, bendamustine plus rituximab; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CC, cost comparison; CUA, cost utility analysis; IC, investigator's choice; IdelaR, idelalisib plus rituximab; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RWE, real-world evidence; Ven-mono, venetoclax monotherapy; VenO, venetoclax plus obinutuzumab; VenR, venetoclax plus rituximab.

Key issue: Cost comparison with VenR (population 1)

Company

- Post-ACM1, performed ITC for cBTKi-naïve population based on new data availability for BRUIN CLL-314
- NMA PFS HR = [redacted] (95% CrI: [redacted], [redacted]), BRUIN CLL-314 OS data too immature for comparison
- Comparable efficacy in cBTKi-naïve population supports equivalence assumption in post-cBTKi population
- At committee's request, explored Ven-mono/VenR equivalence using Mato (2019) RWE which compared Ven-mono to VENcombo (VenO, n=13, VenR, n=38) in R/R CLL – consistent with wider evidence but insufficient:
  - PFS HR = 1.0 (95% CI: 0.6, 1.8), OS HR = 1.2 (95% CI: 0.6, 2.3)
- Pirtobrutinib vs VenR cost comparison in post-cBTKI population done using new PAS

EAG comments

- Agrees BRUIN CLL-314 (100% BTKi-naïve) more aligned to MURANO (≥97% BTKi-naïve) and other trials in company's original FA, but post-ACM1 NMA results not generalisable to post-cBTKi population
- Generalisability of NMA results limited because prior treatment with a cBTKi is a treatment effect modifier
- IdelaR and BR equivalence (implied in NMA) introduces uncertainty
- Wide intervals around NMA HRs span clinically important harm/benefit for pirtobrutinib relative to VenR
- Agrees Mato 2019 is of limited use as results were reported for VENcombo, small number had VenR, wide HRs

Is it reasonable to assume equal efficacy between VenR and pirtobrutinib?
Is the presented cost comparison with VenR suitable for decision making?

Abbreviations: ACM1, appraisal committee meeting 1; AE, adverse event; BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; EAG, external assessment group; IdelaR, idelalisib plus rituximab; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; Ven-mono, venetoclax monotherapy; VenR, venetoclax plus rituximab.

Key issue: Cost comparison with Ven-mono (population 1)

Company

- Post-ACM1, produced Ven-mono comparison in post-cBTKi, assuming pirtobrutinib/Ven-mono equivalence
- Al-Sawaf (2024) unanchored MAIC demonstrates equivalence: PFS HR = 1.01 (95% CI: 0.58, 1.73), OS HR = 0.64 (95% CI: 0.25, 1.67) suggest similar of better efficacy of pirtobrutinib relative to Ven-mono
- Results of post-ACM1 NMA (in cBTKi-naïve) and Al-Sawaf (2024) support equivalence assumption

EAG comments

- Al-Sawaf (2024) unanchored MAIC does not conclusively demonstrate comparable efficacy - wide 95% Cis for PFS and OS HRs
- Company did not provide additional clinical effectiveness evidence for Ven-mono comparison

Is it reasonable to assume equal efficacy between Ven-mono and pirtobrutinib?
Is the presented cost comparison with Ven-mono suitable for decision making?

Abbreviations: ACM1, appraisal committee meeting 1; BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CI, confidence interval; EAG, external assessment group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; r/r CLL, relapsed or refractory chronic lymphocytic leukaemia; RWE, real-world evidence; SoC, standard of care; Ven-mono, venetoclax monotherapy; VenO, venetoclax plus obinutuzumab; VenR, venetoclax plus rituximab.

Key issue: No cost effectiveness results for comparisons of pirtobrutinib with cBTKi (population 2)

Company

- No analyses versus cBTKi as they are not relevant. UK clinical experts: unlikely to rechallenge with cBTKi in patients showing disease progression → this is likely due to resistance mutations.
  - BSH and ESMO guidelines recommend venetoclax-based therapies as the next line of treatment post-cBTKi.
- ⭐ Post-ACM1, lack of evidence and limited used in practice, so no analyses conducted vs cBTKi

EAG comments

- cBTKi is relevant. People having fixed VenI at 1L would be eligible for cBTKi after relapse
- Strong concern about the lack of supporting evidence for pirtobrutinib vs cBTKi .
  - Assuming equal efficacy is last-resort approach, cost comparison only exploratory without evidence.
- Provided cost comparisons: pirtobrutinib vs ibrutinib, zanubrutinib, or acalabrutinib (post-cBTKi population).
  - Use company cost comparison model (pirto vs VenR) as base with equal AEs but costs adjusted per cBTKi.
  - Reasonable to assume similar efficacy vs cBTKis in R/R CLL like with VenR → approach justified by evidence suggesting cBTKis are at least as effective as BCL2i's in first-line CLL.
- ⭐ Post-ACM1, reran its exploratory scenarios using new PAS price for pirtobrutinib

Are cBTKi therapies a relevant comparator to pirtobrutinib in the target population?
Is it reasonable to assume equal efficacy for pirtobrutinib and cBTKis?
Is the presented cost comparison with cBTKis suitable for decision making?

Abbreviations: ACM1, appraisal committee meeting 1; AE, adverse event; BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; BSH, British Society for Haematology; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CLL, chronic lymphocytic leukaemia; ESMO, European Society for Medical Oncology; IdelaR, idelalisib plus rituximab; PAS, patient access scheme; VenR, venetoclax plus rituximab; R/R, relapsed or refractory.

Population 3: post-cBTKi or dual-exposed, BCL2i or cBTKi not suitable

Small to large ICER impact

Key issue: Comparison of pirtobrutinib vs IdelaR (population 3)

Recap

- Company CUA compared pirtobrutinib vs IdelaR based on head-to-head BRUIN CLL-321 trial data
- EAG considered IdelaR unsuitable comparator as limited NHS use due to toxicity and intolerance
- Clinical experts did not consider IdelaR as SoC after relapse but stated that it was used as last resort option
  - SACT data shows <100 per year had it
- Committee thought IdelaR important for a small population of r/r CLL where other options have been exhausted
- QALY weighting for severity applied to dual-exposed part of population 3

Company

- Post-ACM1, presented results of updated CUA in dual-exposed population using new PAS price

EAG comments

- Applied new PAS price to pirtobrutinib comparisons vs IdelaR in post-cBTKi and dual-exposed populations

Is the presented analysis with IdelaR suitable for decision making?

Abbreviations: ACM1, appraisal committee meeting 1; BCL2i, B-cell lymphoma 2 inhibitor; BR, bendastamine rituximab; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; CLL, chronic lymphocytic leukaemia; CUA, cost utility analysis; EAG, external assessment group; IC, investigator's choice; ICER, incremental cost effectiveness ratio; IdelaR, idelalisib plus rituximab; R/R, relapsed or refractory; PAS, patient access scheme; SACT, systemic anti-cancer therapy; SoC, standard of care.

Summary of company and EAG base case assumptions

Assumptions in post-ACM1 company and EAG base case

Population	Company base case	EAG base case
1. Pirtobrutinib vs VenR	Modelled as cost comparison of whole population 1	Modelled as cost comparison of whole population 1
1. Pirtobrutinib vs Ven-mono	Modelled as cost comparison of whole population 1	Modelled as cost comparison of whole population 1
2. Pirtobrutinib vs cBTKis	No cost effectiveness results provided	Modelled as cost comparison of whole population 2 vs cBTKis
3. Pirtobrutinib vs IdelaR	Modelled as cost-utility analysis of subgroup: • dual-exposed	Modelled as cost-utility analysis of whole population 3

Note: Cost comparison base cases by Company and EAG are modelled for the whole population. They refer to this differently in their submissions:

- **Company:** refers to "post-cBTKi" which includes the post-cBTKi monotherapy **and** dual-exposed subgroups
- **EAG:** referred to the whole population in each comparison

Abbreviations: ACM1, appraisal committee meeting 1; AE, adverse event; cBTKi, covalent Bruton tyrosine kinase (BTK) inhibitor; EAG, external assessment group; IdelaR, idelalisib plus rituximab; Ven-mono, venetoclax monotherapy; VenR, venetoclax plus rituximab.

Cost effectiveness results

Confidential discounts for comparators – ICERs in Part 2 slides

ICER ranges presented below

Summary:

- Cost utility analyses only in population 3 comparisons of pirtobrutinib versus IdelaR
- Company produced base cases in post-cBTKi and dual-exposed populations separately
  - **Post-cBTKi:** ICER higher than £30,000 per QALY gained
  - **Dual-exposed:** ICER lower than £30,000 per QALY gained

Scenario analyses:

- Pirtobrutinib is cost-saving in some of the cost comparisons but not others

Abbreviations: cBTKi, covalent Bruton's tyrosine kinase inhibitor; ICER, incremental cost effectiveness ratio; IdelaR, idelalisib plus rituximab; QALY, quality adjusted life years.

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Managed access

- Current company proposed positioning in the following sub-populations (distinct from the population classification used on previous slides):
  1. Post-cBKTi, can receive SoC
  2. Post-cBKTi, cannot receive SoC
  3. Dual-exposed
- Company: Lack of data for direct comparison or ITC for relevant comparators of post-cBTKi but suitable for SoC population (pirtobrutinib vs VenR and pirtobrutinib vs cBTKis)
  - Only reliable proxy is for this population is pirtobrutinib vs IdelaR in ITT population
- Company remain open to discussing managed access for post-cBTKi sub-population suitable for current SoC

Abbreviations: cBTKi, covalent Bruton's tyrosine kinase inhibitor; IdelaR, idelalisib plus rituximab; ITT, intention-to-treat; SoC, standard of care; VenR, venetoclax plus rituximab

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Cost comparison with Ven-mono	No – for discussion	Unknown – Potentially large	• Clinical experts confirmed Ven-mono used in NHS where rituximab is unsuitable, so committee requested comparison against it
No cost effectiveness results for comparisons of pirtobrutinib with cBTKi or BSC	Partially – for discussion	Unknown – Potentially large	• cBTKis may be relevant for those rechallenged after fixed-duration VenI • BSC not relevant
Comparison of pirtobrutinib vs IdelaR	Partially – for discussion	Small to large – depends on population	• Relevant comparator for small population

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Supplementary appendix

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Background on chronic lymphocytic leukaemia

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

Causes

- Gene controlling blood development ➔ bone marrow produces too many $CD5^+$ B lymphocytes ➔ do not work properly

Epidemiology

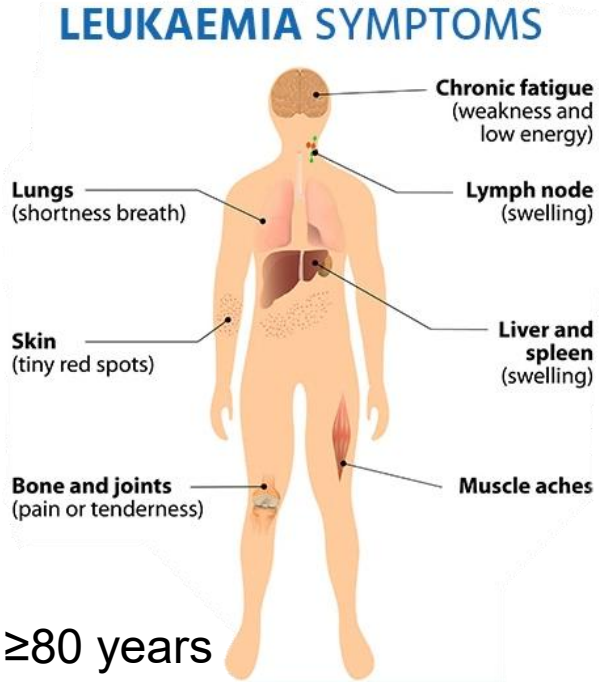
- CLL most common type of leukaemia with approximately 4,000 people diagnosed each year in UK
- Risk of developing CLL increases with age and is more common in men (approximately 63% are men)

Diagnosis and classification

- Physical examination and complete blood counts determine the clinical staging
- 'High-risk' disease is defined by the presence of del(17p) or TP53 mutation.

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
- 5-year survival rate is about 95% for those <60 years, and around 70% for those aged ≥80 years



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Abbreviations: $CD5^+$, cluster of differentiation 5+; CLL, Chronic lymphocytic leukaemia; del, deletion; TP53, tumour protein p53

Patient perspectives

CLL impacts physical, mental, social, and financial well-being

Joint Submission from CLL Support, Blood Cancer UK, Leukaemia Care, Lymphoma Action and Leukaemia UK

The condition

- Diagnosis of CLL can have emotional and psychological impact on patients and families
  - Uncertainty during the 'watch and wait' and monitoring period increases anxiety for patients and carers → worries about progression, treatment failure, mortality
  - Younger patients have increased risk of anxiety and depression, as they have ongoing work and family responsibilities
  - Older patients may self-isolate to reduce infection risk, which can worsen anxiety, loneliness, and depression

What is important to patients and unmet need

- Unmet need in small group of 'double refractory' patients for whom many treatments have failed and for whom cellular therapies are unsuitable due to age or comorbidities
- Patients see pirtobrutinib as an option that offers:
  - Another potential lifeline with quality-of-life improvement and minimal side effects
  - Outpatient management, reducing NHS burden
  - Favourable safety profile (low rates of atrial fibrillation and bleeding), making it suitable for older/co-morbid patients

"Diagnosed with CLL in my early 40s. I seem to respond well to treatments initially, then I have a relapse. My worry is where I go from my current treatment"

"All treatments eventually stop working, so knowing a different type of treatment is available is comforting"

"Living in a state of permanent anxiety pretty much sums up the emotional feelings in the early stages"

Abbreviations: CLL, Chronic lymphocytic leukaemia

Clinical perspectives

Potential to address unmet need for CLL in relapse setting and improve QoL

Submissions from BOPA and The Leeds Teaching Hospitals NHS Trust

- Current treatment landscape
  - Aim of CLL treatment is to control disease, achieve remission, and relieve symptoms.
  - Third-line options are limited after cBTKi and VenR; clinical trials are often relied on, but access is variable.
  - For relapsed CLL previously treated with cBTKi who are unsuitable for VenR or IdelaR and not eligible for clinical trials, BSC is the only option.
- Unmet need
  - Could provide extra option after first or second relapse (including for dual-exposed after VenR), especially for previously treated with cBTKi and who aren't suitable for current treatments.
  - Unmet need for older, frailer patients who progress on front-line cBTKi therapy, where venetoclax based therapy is not suitable and often have no suitable options for second-line treatment.
- Potential benefits of pirtobrutinib
  - Pirtobrutinib offers an oral, at-home alternative with no additional hospital procedures beyond monitoring, likely improving quality and duration of life compared to BSC.
  - Provides an option for patients who currently only have access to idelalisib clinical trials or BSC.

Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; BOPA, British Oncology Pharmacy Association; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, Chronic lymphocytic leukaemia; QoL, quality-of-life; IdelaR, idelalisib plus rituximab; VenR, venetoclax plus rituximab

Key issues resolved at ACM1

Company's and EAG's post-ACM1 analyses incorporate below assumptions

Issue	ICER impact	ACM1 committee conclusion
Post-progression utility values do not align with trial evidence	Small	PD utility from BRUIN CLL-321
Incorrect calculation of cost of stem cell transplant	Small	EAG calculation using finished consultant episodes
QALY weightings for severity	Large	Applied where QALY shortfall is demonstrated for a given comparator

Additional clinical evidence: Eyre (2026)

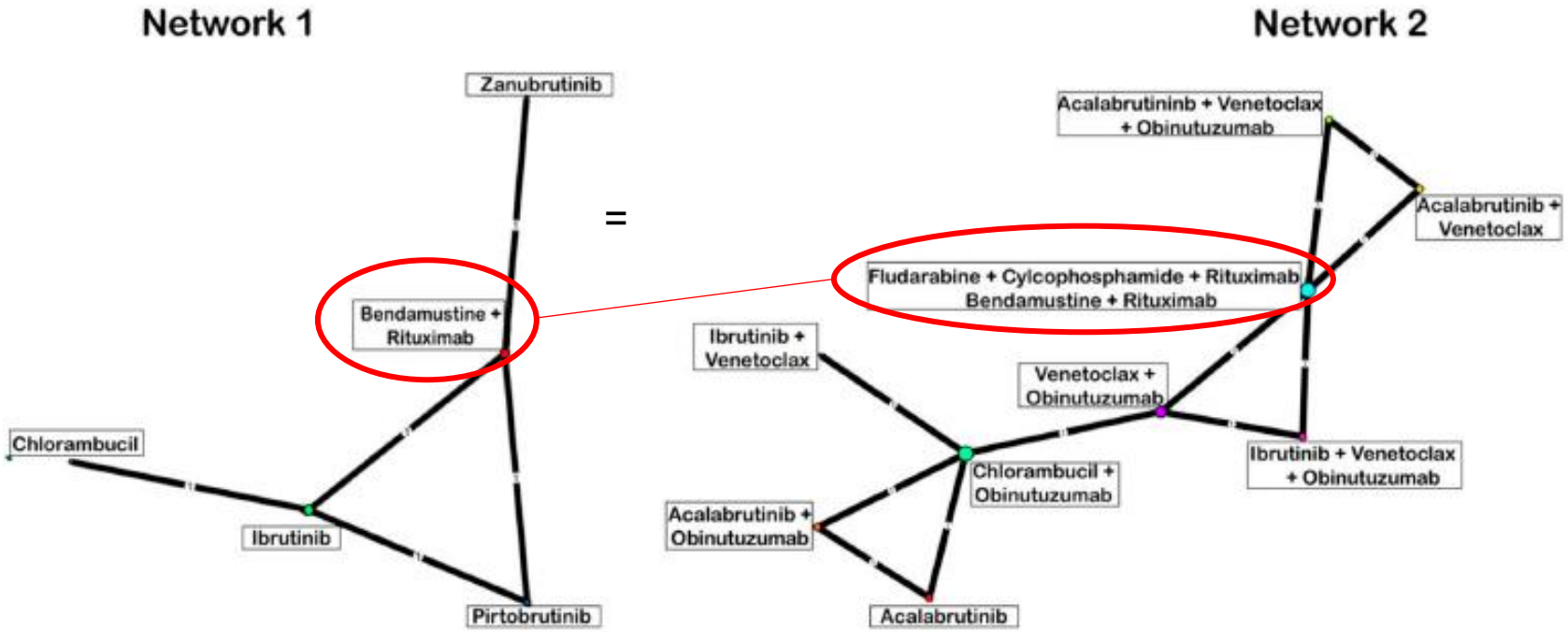


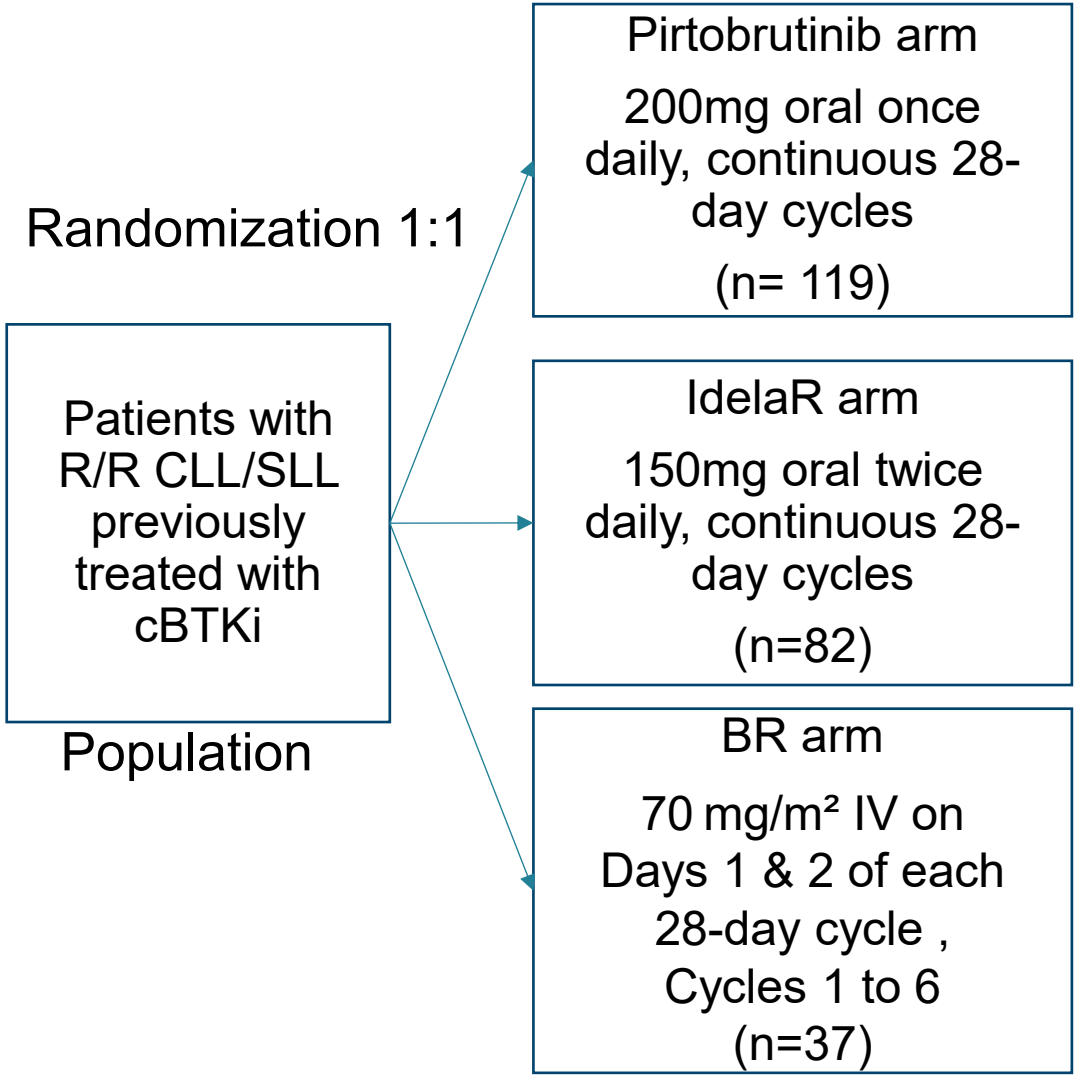
Figure 2. Networks of evidence.

- The results presented from the Eyre study are from a post-hoc analysis to compare pirtobrutinib (in network 1) to treatments in network 2
- This requires an assumption that BR is equivalent to FCR/BR investigators choice

Return to clinical evidence slide

Abbreviations: BR, bendamustine with rituximab; FCR, fludarabine plus cyclophosphamide and rituximab.

Key clinical trial: BRUIN CLL-321



	BRUIN CLL-321
Design	Ongoing phase 3, open label, randomised, multicentre
Population	Adult patients with confirmed diagnosis of CLL/SLL with R/R disease previously treated with a covalent BTKi
Intervention	Pirtobrutinib
Comparators	Investigator's choice (IdelaR or BR)
Primary outcome	IRC-assessed PFS
Key secondary outcomes	OS, investigator-assessed PFS, ORR, BOR, DoR, EFS, TTNT, TTW of CLL/SLL-related symptoms, TTW of physical function and safety
Used in model?	Yes

Abbreviations: BR, bendamustine with rituximab; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; DoR, duration of response; EFS, event-free survival; IdelaR, idelalisib plus rituximab; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; SLL; small lymphocytic leukaemia; TTNT, time to next treatment; TTW, time to worsening

Clinical trial baseline characteristics – BRUIN CLL-321 (1)

Pirtobrutinib was compared to investigator's choice of IdelaR or BR

Baseline characteristic	Pirtobrutinib (n=119)	IdelaR or BR (n=119)
Female, n (%)	36 (30.3)	36 (30.3)
Age (years), median (range)	66 (42 to 90)	68 (42 to 85)
Histology type, n (%)		
CLL	109 (91.6)	108 (90.8)
SLL	10 (8.4)	11 (9.2)
ECOG PS, n (%)		
0	51 (42.9)	50 (42.0)
1	56 (47.1)	64 (53.8)
2	12 (10.1)	5 (4.2)

Clinical advice to the EAG:

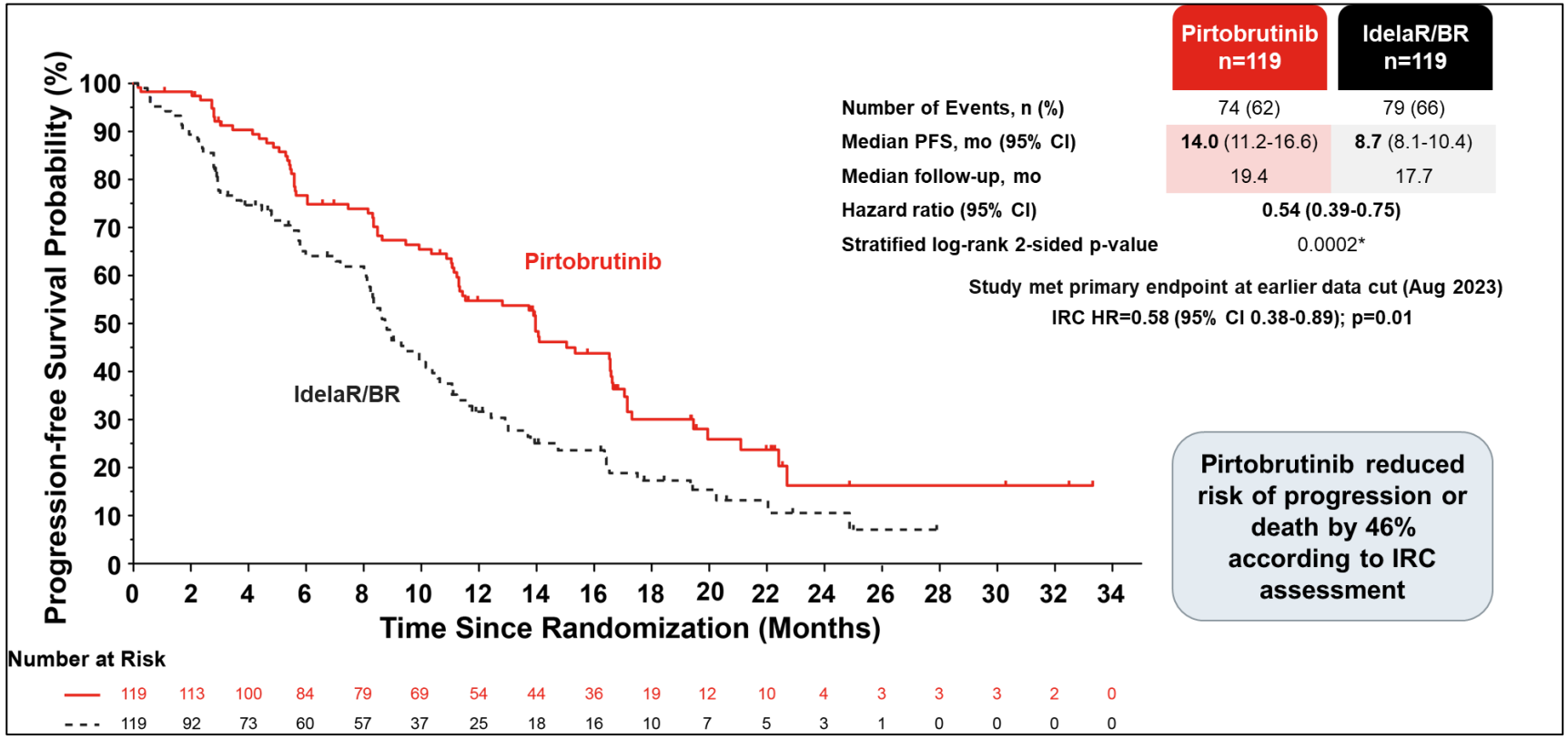
- BRUIN CLL-321 ITT population is broadly representative of NHS patients with R/R CLL previously treated with cBTKis
- Compared to NHS patients, trial participants were:
  - Younger
  - More heavily pretreated, with more dual-exposed patients and more prior chemotherapy.

Abbreviations: BR, bendamustine with rituximab; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, Chronic lymphocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IdelaR, idelalisib plus rituximab; ITT, intention-to-treat; R/R, relapsed or refractory; SLL, small lymphocytic leukaemia

Key clinical trial results – BRUIN CLL-321: PFS (1/2)

Pirtobrutinib (n=119) improves IRC-assessed PFS compared to investigator's choice (n=119)

ITT population



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39-0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38-0.89); p=0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

HR (95% CI; p-value)	0.54 (0.39 to 0.75); p=0.0002[a]

[a] Nominal p-value

Abbreviations: Arm A, Pirtobrutinib; Arm B, IdelaR or BR; CI, confidence interval; CLL, Chronic lymphocytic leukaemia; HR, hazard ratio; IRC, independent review committee; IPCW, inverse probability censoring weighting; PFS, progression free survival

Key clinical trial results – BRUIN CLL-321: PFS (2/2)

Pirtobrutinib (n=119) improves IRC-assessed PFS compared to investigator's choice (n=119)

Dual-exposed population

Arm	HR (95% CI)
Pirto vs IC (prior Ven)	0.536 (0.347-0.829)
Pirto vs IC (no prior Ven)	0.621 (0.385-1.001)

- Pirtobrutinib may have greater efficacy in a population that has not had prior treatment with venetoclax

Key	Arm	Prior Ven treatment	Patients	Events	Median
1	Pirtobrutinib	Yes	60	41	11.43
2	IC			44	8.25
3	Pirtobrutinib	No	59	33	15.34
4	IC			35	10.38

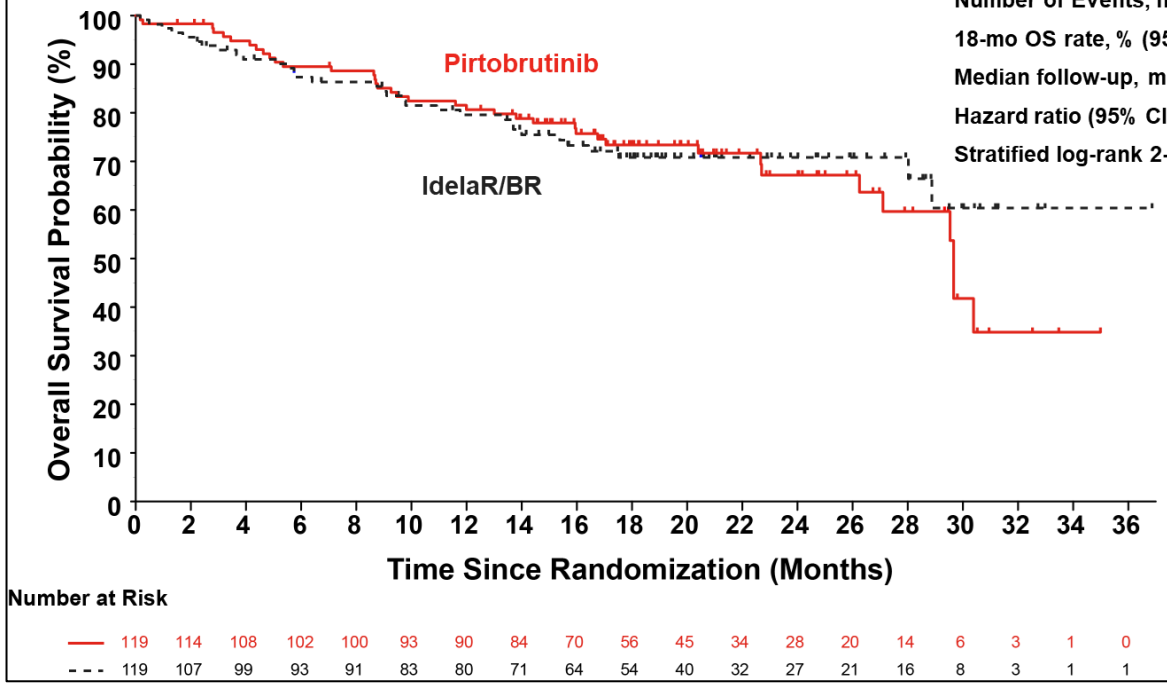
NICE

Abbreviations: Arm A, Pirtobrutinib; Arm B, IdelaR or BR; CI, confidence interval; HR, hazard ratio; IC, investigators choice; IRC, independent review committee; PFS, progression free survival; Ven, venetoclax

Key clinical trial results – BRUIN CLL-321: OS (1/2)

Pirtobrutinib numerically improves OS vs investigator's choice when adjusted for treatment switching

ITT population



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	38 (32)	32 (27)
18-mo OS rate, % (95% CI)	**73.4** (63.9-80.7)	**70.8** (60.9-78.7)
Median follow-up, mo	20.4	19.2
Hazard ratio (95% CI)	**1.09 (0.68-1.75)**	
Stratified log-rank 2-sided p-value	0.7202	

Crossover Rate: 76% (50/66[a])

- IPCW crossover adjusted OS analysis: HR 0.87 (0.51-1.5)
- Two-stage AFT crossover adjusted OS analysis: HR 0.78 (0.48-1.26)

OS analysis	Pirto vs IC, HR (95% CI)
Unadjusted	1.090 (0.679 to 1.749)
Post-hoc sensitivity analyses	
IPCW method	0.872 (0.507 to 1.500)
Two-stage AFT method	0.776 (0.479 to 1.258)

- Uncertainty in ITT OS results with HR of 1.090, a wide 95% CI (0.679–1.749), and overlapping KM curves.
- 75.8% of people in the IC arm crossed over to have pirtobrutinib after progression
- EAG considers two-stage AFT method to be most appropriate approach to account for treatment switching → more robust than IPCW when switch rates are high and does not rely on reweighting non-switchers so less bias

Abbreviations: AFT, accelerated failure time; Arm A, Pirtobrutinib; Arm B, IdelaR or BR; CI, confidence interval; HR, hazard ratio; IC, investigator's choice; IPCW, inverse probability censoring weighting; ITT, intention-to-treat; OS, overall survival

Key clinical trial results – BRUIN CLL-321: OS (2/2)

Pirtobrutinib has unclear effect on OS compared to investigator's choice

Dual exposed population

- [a] Based on the stratified Cox proportional hazards model, with stratification factors from IWRS data: del 17p presence and receipt of prior venetoclax treatment.
- [b] 2-sided p-value is based on the stratified log-rank test for comparing Arm A (pirtobrutinib) vs Arm B (IdelaR or BR).

Key	Arm	Patients	Events	Median	HR (95% CI) [a]	P value[b]
1	Pirtobrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	IC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Abbreviations: CI, confidence interval; HR, hazard ratio; NR: not reached; OS, overall survival; IC, investigator's choice; IWRS, Interactive Web Response System

Adverse event rates for pirtobrutinib and VenR/Ven-mono

Company and EAG assumed equivalent efficacy and AEs across treatment arms for comparisons of pirtobrutinib with VenR and Ven-mono

BRUIN CLL-321 pirtobrutinib AE rates and VENCLEXTA prescribing information VenR AE rates

Adverse event	Pirt	VenR/M	Adverse event	Pirt	VenR/M
ALT increased	0.9%	0%	Leukopenia	NR	46%
Anaemia	11.2%	12%	Lower respiratory tract infection	NR	2%
Cardiac failure	[redacted]	0%	Lymphocyte count increased	[redacted]	0%
COVID-19	0%	0%	Lymphopenia	[redacted]	56%
Diarrhoea	0%	3%	Neutropenia	14.7%	64%
Fatigue	NR	2%	Neutrophil count decreased	5.2%	0%
Febrile neutropenia	[redacted]	0%	Platelet count decreased	1.7%	0%
Hyperkalaemia	[redacted]	3%	Pneumonia	15.5%	7%
Hyperuricemia	NR	36%	Thrombocytopenia	[redacted]	15%
Hypocalcaemia	NR	5%	Upper respiratory tract infection	NR	2%
Hypertension	2.6%	0%	WBC count decreased	[redacted]	0%
Infusion-related reaction	[redacted]	0%			

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; EAG, external assessment group; NR, not reported; Pirt, pirtobrutinib; Ven-mono/VenM, venetoclax monotherapy; VenR, venetoclax plus rituximab; WBC, white blood cell.

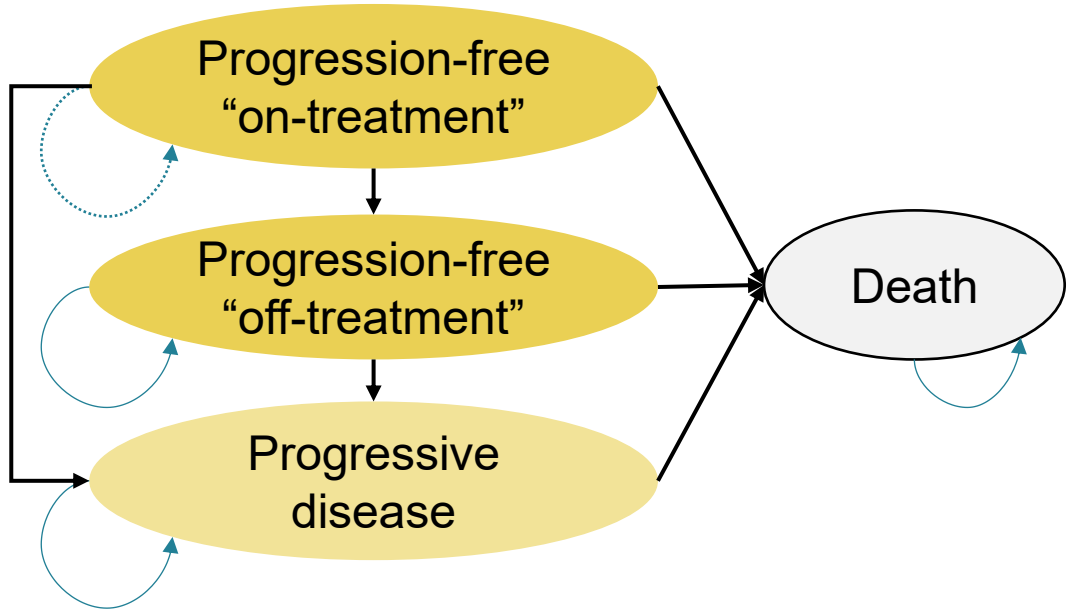
Company's model overview

CUA model used only for comparison with IdelaR and BSC

- Partitioned survival model lifetime horizon (76 years in model but less than [redacted] of patients alive in either model arm by 20 years).
- 28-day cycle, in line with BRUIN CLL-321 dosing schedule.
- On-treatment and off-treatment reflect maximum duration of treatment.

The company's cost-utility model simulates:

1. Post-cBTKi population: R/R CLL patients previously treated with a cBTKi.
2. Dual-exposed population: R/R CLL patients previously treated with both a cBTKi and a BCL2i (either in sequence or together).

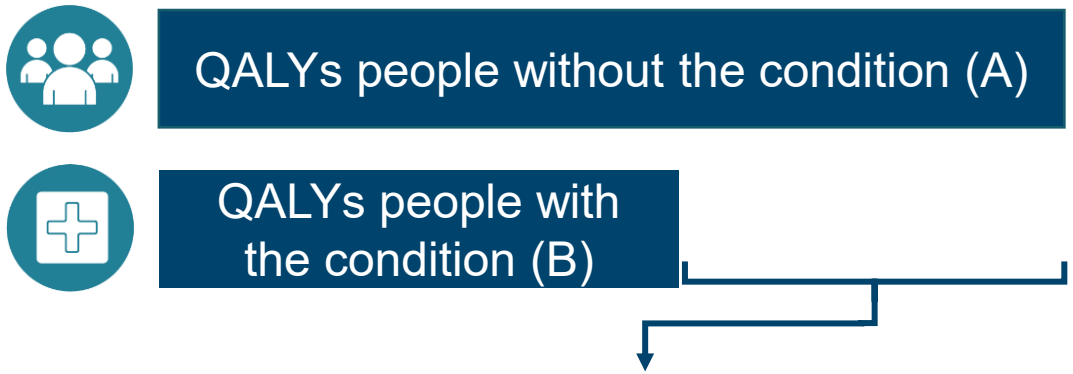


Technology affects:	
Costs	• Having different price than current treatments (after PAS discount). • Being oral tablet, rather than IV at hospital (rituximab).
QALYs	• Increasing OS and time in PF state.
Biggest effect on ICER	• HR used to adjust OS curve for IC. • Post-progression costs for post-cBTKi. • Distribution chosen to model TTD for dual-exposed population.

Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, Chronic lymphocytic leukaemia; IdelaR, idelalisib plus rituximab; IC, investigator's choice; ICER, incremental cost effectiveness ratio; IV, intravenous; OS, overall survival; PAS, patient access scheme; PF, progression-free; R/R, relapsed or refractory; TTD, time to treatment discontinuation

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

QALY weightings for severity (2/2)

Background

- Company: 1.2 disease severity modifier applied to dual-exposed population only (previously treated with cBTKi and BCL2i), no severity modifier applied to post-cBTKi population (previously treated with cBTKi).
- EAG agrees 1.2 QALY shortfall should be applied to:
  - Company's dual-exposed population.
  - EAG's population of R/R CLL for whom treatment with a cBTKi or a BCL2i is unsuitable.
- EAG corrected company's error: applied 1.2 multiplier to incremental QALYs rather than total QALYs.

QALY shortfall for dual-exposed population:

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	Absolute QALY shortfall (has to be >12)	Proportional QALY shortfall (has to be >0.85)	QALY weight
Company	9.89	1.32	8.57	86.7%	1.2
EAG	10.21	1.51	8.70	85.2%	1.2

Does the committee agree it is appropriate to apply a QALY weighting for severity?

Abbreviations: CLL, chronic lymphocytic leukaemia; BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; QALY, quality-adjusted life year R/R, relapsed or refractory

Recent NICE appraisals for CLL

Recent NICE appraisals

Technology appraisal	Drug	Recommendation
GID-TA11501	Pirtobrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma	In progress