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

For public – confidential information redacted

Technology appraisal committee C [ACM1, 11 November 2025]

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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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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

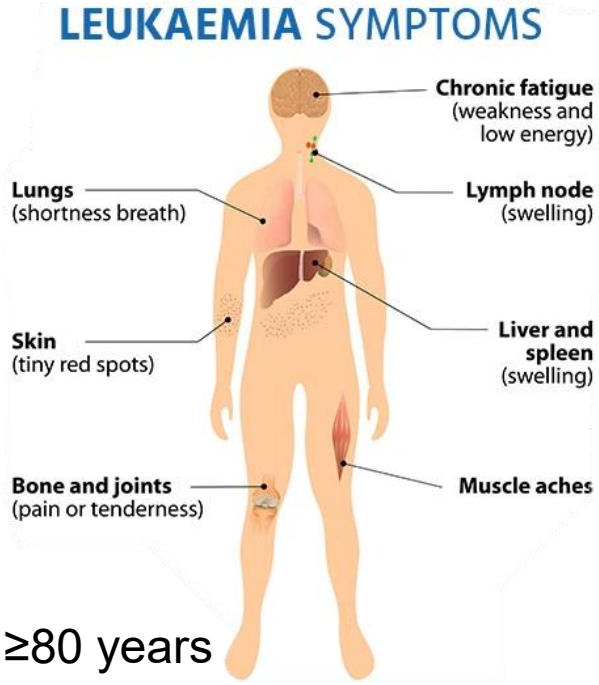
- CLL most common type of leukaemia with approximately 4,000 people diagnosed each year in UK
- Risk of developing CLL increases with age and is more common in men (approximately 63% are men)

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.

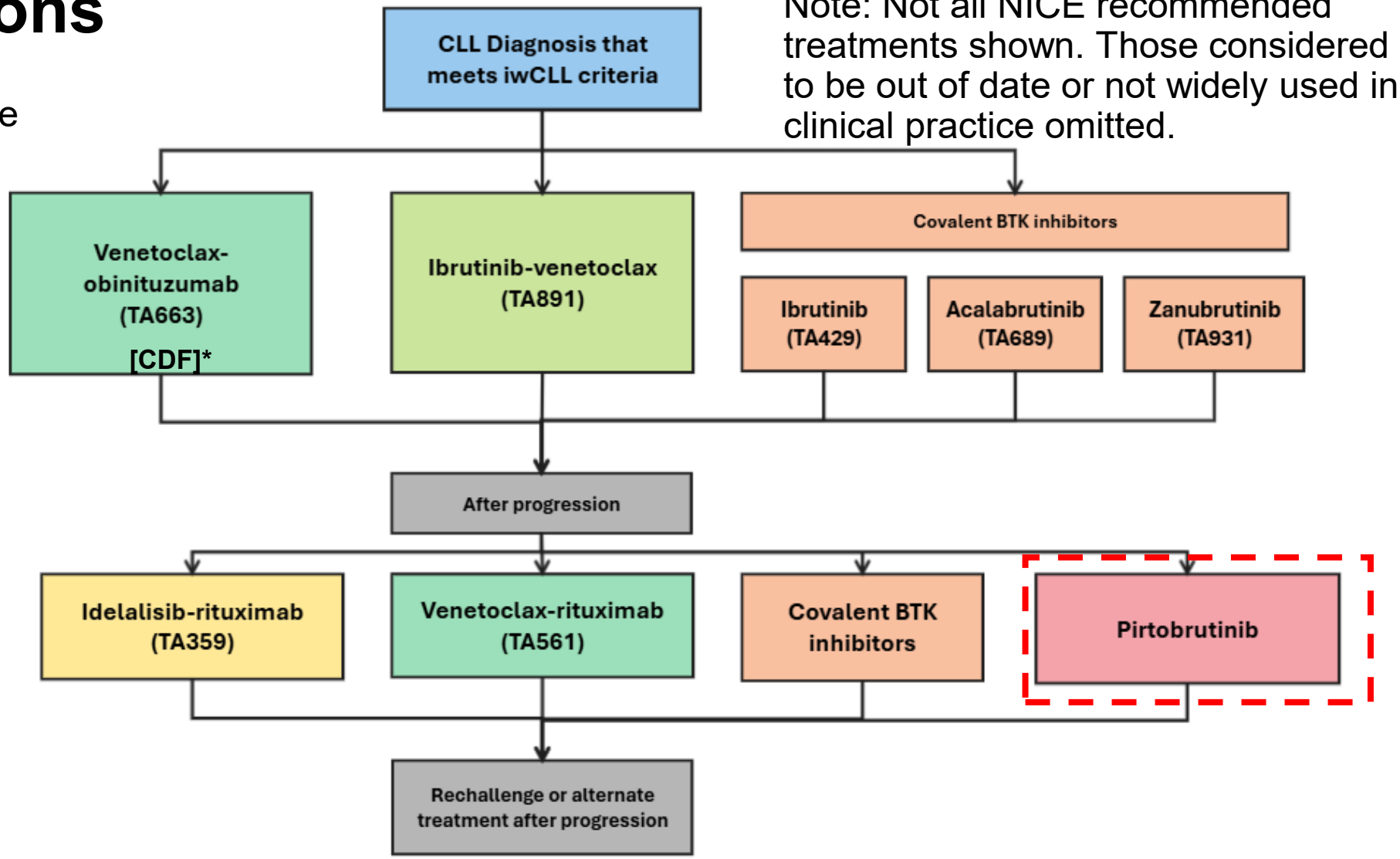
Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; BOPA, British Oncology Pharmacy Association; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, Chronic lymphocytic leukaemia; QoL, quality-of-life; IdelaR, idelalisib plus rituximab; VenR, venetoclax plus rituximab

Treatment options

Note: Not all NICE recommended treatments shown. Those considered to be out of date or not widely used in clinical practice omitted.

<u>Rechallenge</u>

- BCL-2i rechallenge if disease progresses after finishing BCL2i treatment
  - EAG expert: 6 months
  - BSH guideline: 3 years
- cBTKi rechallenge if not refractory to previous cBTKi
- IdelaR or BSC used if rechallenge not possible



Mechanisms of action

- BCL-2i/CD20i
- BCL-2i/cBTKi
- cBTKi
- PI3Ki
- Non-covalent BTKi

Does this diagram reflect the treatment options and pathway used in NHS practice? How long would clinicians wait before offering BCL2i rechallenge?

Abbreviations: 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. *CDF rec for those without 17p or TP53 mutations

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* (IV)	VenI	**15 cycles total** Ibrutinib alone for 3 cycles, followed by 12 cycles of ibrutinib plus venetoclax.
Ibrutinib, Acalabrutinib, Zanubrutinib (oral)	cBTKis	Offered until progression or until it is no longer tolerated.
Venetoclax* (oral)- rituximab (IV)	VenR	Venetoclax is taken for 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.

*Venetoclax starting dose: 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.

- Note: 1 cycle = 28 days

Abbreviations: IV, intreavenous; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin

Population summary

Several populations may be relevant to decision making

Population	Description	Comparators	Notes
1	Post-cBTKi or dual-exposed, BCL2i suitable.	VenR	- Relapsed after BCL2i treatment finished (relapsed defined as progression after 6+ months of response)
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, BSC	- May be refractory to BCL2i and/or cBTKi - May not be able to tolerate BCL2i - May not be able to tolerate active treatment

Is this a fair representation of the populations that exist in NHS clinical practice?

Abbreviations: BCL2i, B-cell lymphoma-2 inhibitor; BSC, best supportive care; cBTKi, covalent BTK inhibitor, IdelaR, idelalisib-rituximab; VenR, venetoclax-rituximab

Technology (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.

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

Key Issues

Issue	Resolved?	ICER impact
No clinical evidence for relevant comparators	No – for discussion	Unknown – Potentially large
Cost comparison with VenR	No – for discussion	Unknown – Potentially large
No cost effectiveness results for comparisons of pirtobrutinib with cBTKi or BSC	No – for discussion	Unknown – Potentially large

Other issues

Issue	Resolved?	ICER impact
Post-progression utility values do not align with trial evidence	No – for discussion	Small
Incorrect calculation of cost of stem cell transplant	No – for discussion	Small

Abbreviations: BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; ICER, incremental cost effectiveness ratio; VenR, venetoclax-rituximab

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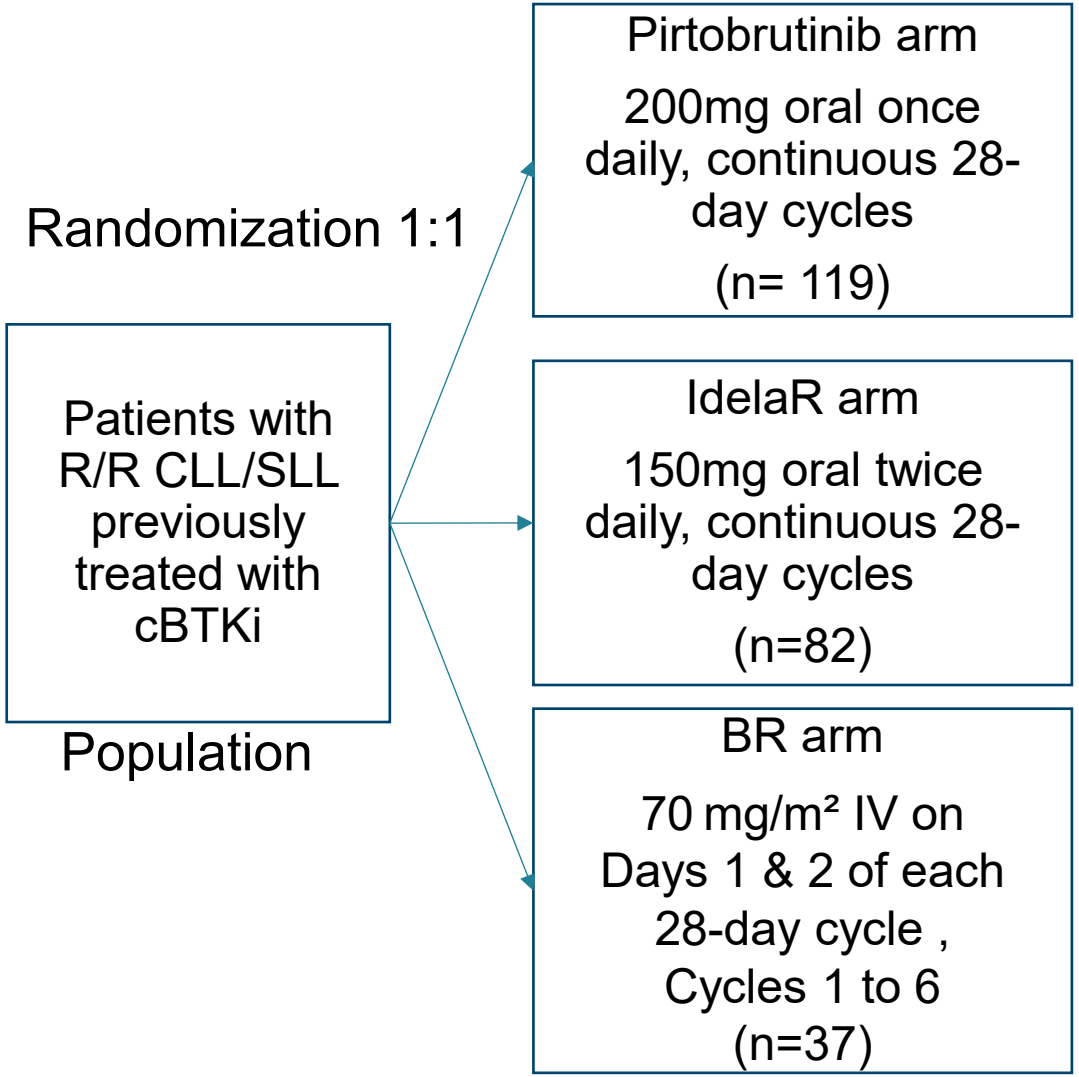
Key clinical trial: BRUIN CLL-321



	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:

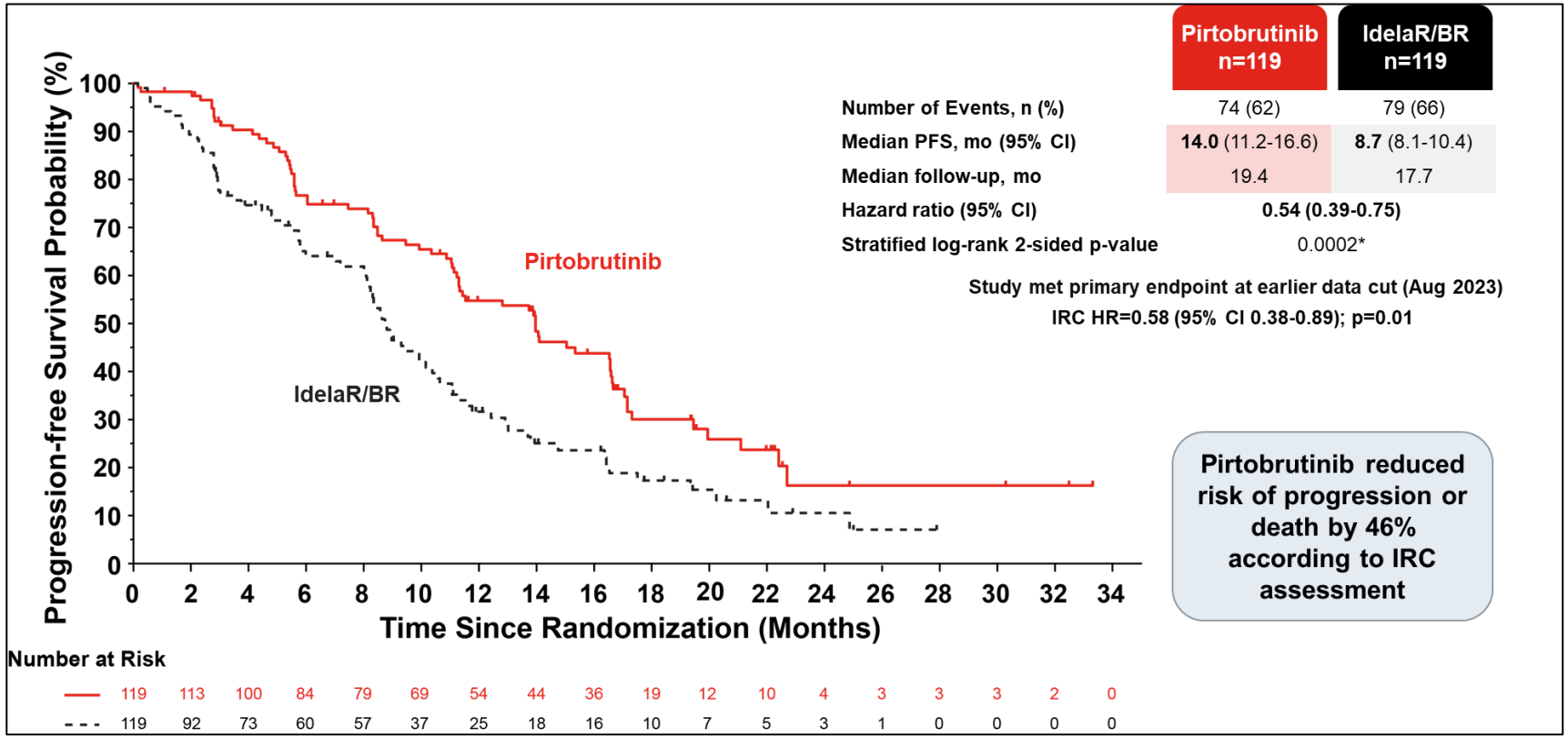
- BRUIN CLL-321 ITT population is broadly representative of NHS patients with R/R CLL previously treated with cBTKis
- Compared to NHS patients, trial participants were:
  - Younger
  - More heavily pretreated, with more dual-exposed patients and more prior chemotherapy.

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

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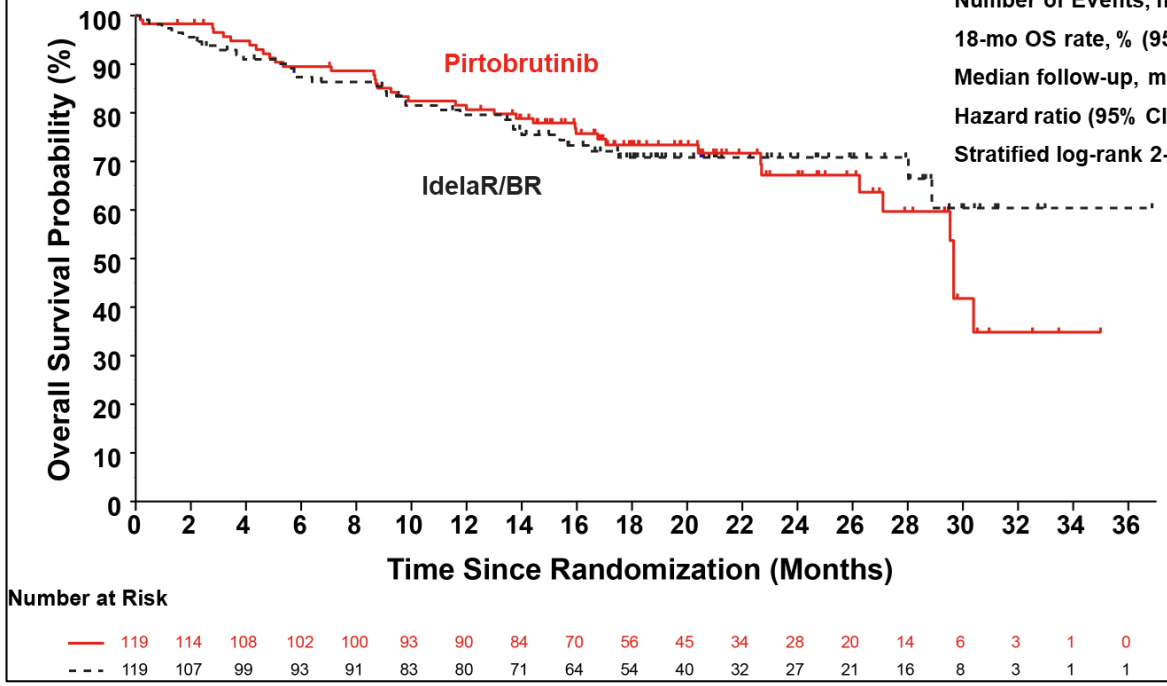
Abbreviations: Arm A, Pirtobrutinib; Arm B, IdelaR or BR; CI, confidence interval; HR, hazard ratio; IC, investigators choice; IRC, independent review committee; PFS, progression free survival; Ven, venetoclax

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	60	26	26.25	[redacted]	0.345
2	IC	62	19	NR	-	-

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

Key Issue: No clinical evidence for relevant comparators (1/2)

Unknown - Potentially large ICER impact

Background

- Clinical effectiveness evidence provided only for pirtobrutinib vs investigator's choice (IdelaR or BR).
- No evidence for relative effectiveness versus cBTKi, VenR or BSC in any population.

Company

- Considered cBTKis and BSC are not relevant comparators for pirtobrutinib → most people discontinue cBTKis due to progression not intolerance → progression is sign of cBTKi resistance.
- BSC should not be offered when IdelaR is available.
- Conducted feasibility assessment and concluded ITCs not appropriate because limited studies identified which assessed treatments of interest in the populations of interest.
- 25 RCTs identified in SLR, 18 excluded (mainly due to including no or only 1 treatment of interest).
- Of the 7 studies that progressed to feasibility assessment there was:
  - limited reporting of many potential effect modifiers (many trials excluded people with prior BTKi usage).
  - major heterogeneity identified in number of prior treatments, prior treatment types, disease stage, co-mutations and ECOG performance status.
- Investigators choice (IdelaR or BR) used in 2 studies, this would require a lumped node (and assumption of transitivity) in an ITC.
- ML-NMR or MAIC could be used but reweighting can lead to over-reliance on certain patient groups → potentially skewing results and reducing generalisability and ESS.

Abbreviations: BR, bendamustine with rituximab; BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, Chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IdelaR, idelalisib plus rituximab; ITC, indirect treatment comparison; MAIC, Matching-Adjusted Indirect Comparison; ML-NMR, Multilevel Network Meta-Regression; RCT, randomised controlled trial; SLR, systematic literature review; VenR, venetoclax plus rituximab

Key Issue: No clinical evidence for relevant comparators (2/2)

Unknown - Potentially large ICER impact

EAG comments

- Most relevant comparators are cBTKi, VenR or BSC. Agree feasibility assessment suggests ITC not appropriate.
- IdelaR rarely used in NHS. Most R/R CLL patients previously treated with cBTKi that are unsuitable for cBTKi or BCL2i and have good performance status enrolled into trials.
- Analysis of pirtobrutinib compared to IdelaR is of limited use to decision makers for two populations modelled
- Clinical advice to EAG for dual-exposed R/R CLL patients who:
  - discontinued cBTKi due to intolerance may be rechallenged with cBTKi.
  - progressed after fixed-duration venetoclax regimen may be rechallenged with VenR or cBTKi rechallenge.
- CAPTIVATE trial supports rechallenge with cBTKi or BCL2i in dual-exposed patients:
  - VenI was given as fixed-duration 15-month regimen.
  - Only 1/40 patients with progression post-VenI had BCL2 resistance mutation (A113G).
  - 19/22 patients retreated with ibrutinib on progression responded (CR or PR).
- Clinical advice on pirtobrutinib's relative effectiveness vs key comparators may be informative.

Other considerations

- TA931: 'IdelaR rarely used in clinical practice due to intensive dosing regimen and increased infection risk'.
- TA891: Clinical advice to the AC: Fixed-duration VenI lowers resistance risk. NHS England advised allowing rechallenge with cBTKi or BCL2i for patients who responded well to first-line VenI in first-line setting.

Can the clinical evidence be used to inform decision making for comparisons other than with idelaR?

Abbreviations: AC, appraisal committee, BCL2, B-cell lymphoma 2; BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, Chronic lymphocytic leukaemia; CR, complete response; IdelaR, idelalisib plus rituximab; ITC, indirect treatment comparison; PR, partial response; R/R, relapsed or refractory; VenI, ibrutinib with venetoclax; VenR, venetoclax plus rituximab

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Cost effectiveness analyses summary

Various cost effectiveness analysis present for different sub-populations

Population	Comparator	Cost-utility analysis	Cost comparison	Notes
1. Post-cBTKi or dual-exposed, BCL2i suitable	VenR	No	Yes	Company clarification analysis. Assumes equivalency with VenR
2. Post-cBTKi or dual-exposed, cBTKi suitable	cBTKis	No	Yes	EAG analyses. Assumes equivalency with cBTKis
3. Post-cBTKi or dual-exposed, BCL2i or cBTKi not suitable	BSC	Yes	No	EAG analysis, may be conservative to pirtobrutinib
3. Post-cBTKi or dual-exposed, BCL2i or cBTKi not suitable	IdelaR	Yes	No	EAG consider this is of limited relevance to NHS practice

Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; IdelaR, idelalisib plus rituximab; VenR, venetoclax plus rituximab

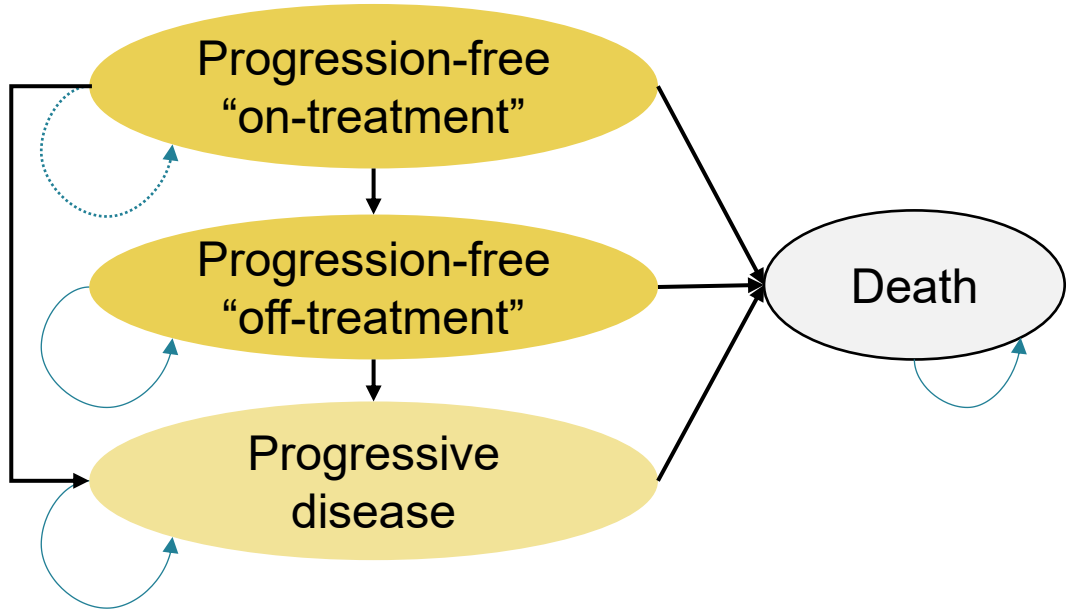
Company's model overview

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

Unknown - Potentially large ICER impact

Key Issue: Cost comparison with VenR (population 1)

Company

- No suitable VenR data available for this population.
- Lack of RCTs for post-cBTKi and dual-exposed populations → NMA/ ITC not feasible.
- Identified unanchored MAIC: pirtobrutinib (BRUIN) vs Ven-mono (Phase 2, post-cBTKi population, Jones 2018).
  - PFS HR: 1.01 (95% CI: 0.58 to 1.73), similar efficacy for pirtobrutinib and Ven-mono.
  - OS HR: 0.64 (0.25 to 1.67), numerically favours pirtobrutinib over Ven-mono.
- Cost comparison: pirtobrutinib vs VenR (post-cBTKi, BCL2i-naïve and dual-exposed populations).
  - PFS, OS and TTD for VenR assumed equal as pirtobrutinib based on assumption of equivalence with Ven-mono from MAIC.
  - Adverse events expected to differ, with VenR rates based on MURANO trial (grade 3 ≥ AEs only).

EAG comments

- Small differences in QALYs for this comparison → only related to disutilities from AEs.

Unanchored MAIC

- Equal effectiveness assumption (Ven-mono = VenR) highly uncertain → clinical advice: VenR more effective than Ven-mono.
- MAIC only included grade ≥3 TEAEs in both trials, as not all AE differences could be included prefer not to model AEs
- EAG base case removed AE differences → minimal impact.

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

Abbreviations: AE, adverse event; BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; IdelaR, idelalisib plus rituximab; QALY, quality-adjusted life year; TTD, Time to treatment discontinuation; VenR, venetoclax plus rituximab

Population 2: post-cBTKi or dual-exposed, suitable for cBTKi

Unknown - Potentially large ICER impact

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

Company

- No analyses for pirtobrutinib vs cBTKi in post-cBTKi, BCL2i-naïve and dual-exposed populations.
- cBTKis 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.
  - BSH sequencing guidance supports BCL2i following R/R disease when BCL2i-naïve.

EAG comments

- Strong concern about the lack of supporting evidence for pirtobrutinib vs cBTKi .
  - Assuming equal efficacy is considered a last-resort approach, cost comparison used only to provide an exploratory analysis in the absence of supporting evidence.
- Provided cost comparisons: pirtobrutinib vs ibrutinib, zanubrutinib, or acalabrutinib (post-cBTKi population).
  - Used company's cost comparison model (pirtobrutinib vs VenR) as base.
  - AEs were set equal across treatments; costs and dosing adjusted for each 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.

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

Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; BSH, British Society for Haematology; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; ESMO, European Society for Medical Oncology; IdelaR, idelalisib plus rituximab; VenR, venetoclax plus rituximab; R/R, relapsed or refractory

Unknown - Potentially large ICER impact

Key Issue: No cost effectiveness results for comparisons of pirtobrutinib with BSC (population 3)

Company

- No analysis for pirtobrutinib vs BSC in dual-exposed population. BSC inappropriate when IdelaR is available.

EAG comments

- Cost-utility: pirtobrutinib vs BSC (population unsuitable for cBTKi or BCL2i)
  - Used company's cost-utility model for dual-exposed patients.
  - Assumed equal OS for BSC and IdelaR, with all patients in the PD state.
  - Assume all patients on BSC have progressed disease (PFS and TTD for IdelaR arm=0).
  - Removed IdelaR costs, PFS benefits, and AEs from model.
  - Excluded subsequent therapies cBTKi costs and reweighted remaining treatments.
  - May underestimate QALY gain for pirtobrutinib vs BSC as IdelaR may offer some survival benefit over BSC, potentially overestimating the ICER.

Is the presented cost-utility analysis with BSC suitable for decision making?

Abbreviations: AEs, adverse events; 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; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality-adjusted life year; TTD, Time to treatment discontinuation; VenR, venetoclax plus rituximab

Key Issue: Comparison of pirtobrutinib vs IdelaR

Company

- Presented analysis for pirtobrutinib vs IdelaR for R/R CLL previously been treated with one or more cBTKis.
- Efficacy data informed by IC of IdelaR or BR from BRUIN CLL-321 trial.
  - Basket comparator used to maintain trial randomisation and sufficient sample size for PFS testing → 70.6% in BRUIN CLL-321 comparator arm received IdelaR.
  - Clinical experts: confirmed basket comparator data generalisable to UK patients treated with IdelaR.

EAG comments

- Consider IdelaR to be unsuitable comparator →IdelaR rarely used in NHS clinical practice due to toxicity and patient intolerability → IdelaR is of limited use in decision-making for the two populations modelled.
- Clinical advice to EAG:
  - IdelaR is an NHS treatment option for relapsed/refractory CLL that is:
    - Unsuitable for BCL2is and refractory to cBTKis, or
    - dual-exposed and refractory to both cBTKis and BCL2 inhibitors.
  - BR rarely used in NHS practice for treating R/R CLL.
- IdelaR slightly more effective than BR for R/R CLL → using data from the IC arm as a proxy for IdelaR may lead to overestimation of relative efficacy for pirtobrutinib.

Clinical expert: "Neither IdelaR or BR are considered to be current standard of care after relapse".
SACT data: suggests less than 100 people per year have accessed IdelaR in recent years.

Is the presented analysis with IdelaR relevant and suitable for decision making?

Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; BR, bendastamine rituximab; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; IC, investigator's choice; IdelaR, idelalisib plus rituximab; R/R, relapsed or refractory; SACT, systemic anti-cancer therapy

Key Issue: Post-progression utility values do not align with trial evidence

Small ICER impact

Background

- Progressed disease utility value used by the company may lack face validity.

Company

- Limited utility data for PD state from trial participants so SLR identified Holzner 2004: PD utility value = 0.600.
  - Applied to both post-cBTKi and dual-exposed groups
  - Dual-exposed population (BRUIN CLL-321 trial) baseline utility: [redacted]
  - Patients in progressed state after ≥2 prior treatments.
  - Clinical expert opinion: patients often heavily pretreated and clinically complex, typically associated with lower QoL.
- Post-cBTKi ITT population (BRUIN CLL-321 trial) baseline utility: [redacted]
  - Values consistent with those seen in advanced hematologic malignancies.

EAG comments

- Noted that there is very little difference in utility at progression by line of treatment (based on baseline utilities from BRUIN CLL-321 trial).
- Used dual-exposed population progressed disease (BRUIN CLL-321 trial) baseline utility: [redacted]
- **EAG for TA931:** Although Holzner 2004 was previously accepted by NICE, concerns remain regarding methodology → utility values still considered uncertain. PD utilities are key driver of effectiveness.

Model health state	Company utility value	EAG utility value
PF	[redacted]	[redacted]
PD	0.600	[redacted]

Which utility value is appropriate to represent post-progression utility?

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Abbreviations: cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; ITT, intention to treat; PD, progressed disease, PF, progression-free; PP, post-progression, QoL, quality of life, SLR, systematic literature review

Small ICER impact

Key Issue: Incorrect calculation of cost of stem cell transplant

Company

Total allogenic SCT cost = £114,141.

Stem Cell Harvesting Cost:

- Used number of submissions as weights from National Cost Collection.
- Base case: weighted cost of £5,992.

Allogenic SCT Cost:

- Reported cost: £61,328.
- Included following items: SA20, SA21, SA27, SA38.
- Did not fully align with methodology used in a previous appraisal (TA975).

EAG comments

Total allogenic SCT cost = £96,469.

Stem Cell Harvesting Cost:

- Corrected the weighting method by using finished consultant episodes instead of submissions.
- Recalculated cost to £1,495, significantly lower than company's estimate.

Allogenic SCT Cost:

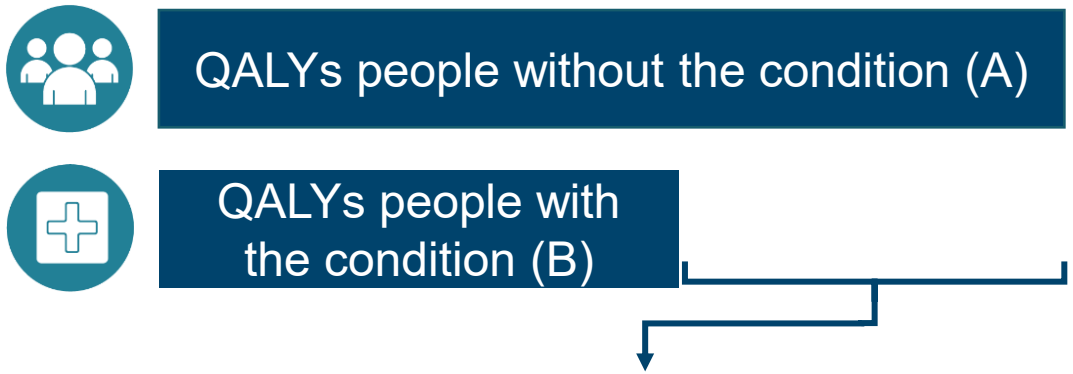
- Included all relevant items from TA975: SA20–SA23, SA38, SA39.
- Revised weighted cost of £48,153 (lower than company's).

Which costs should be used for stem cell transplant modelling?

Abbreviations: SCT, stem cell transplant; TA, technology appraisal

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

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Pirtobrutinib vs IdelaR	Modelled as cost-utility analysis	EAG consider of limited relevance to NHS practice
Pirtobrutinib vs BSC	No cost effectiveness results provided	Modelled as cost-utility analysis
Pirtobrutinib vs VenR	Modelled as cost comparison	Modelled as cost comparison
Pirtobrutinib vs cBTKis	No cost effectiveness results provided	Modelled as cost comparison
Post-progression utility values	Based on Holzner 2004 (0.60)	From baseline utility from dual-exposed population in BRUIN CLL-321 trial
Calculation of SCT cost	Stem Cell Harvesting Cost: • Base case: weighted cost of £5,992. Allogenic SCT Cost: • Reported cost: £61,328.	Stem Cell Harvesting Cost: • Recalculated cost: £1,495 Allogenic SCT Cost: • Revised weighted cost: £48,153

Abbreviations: BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; IdelaR, idelalisib plus rituximab; SCT, stem cell transplant; VenR, venetoclax plus rituximab

Cost effectiveness results

Confidential discounts for comparators – ICERs in Part 2 slides

ICER ranges presented below

Summary:

- Company base case is higher than £30,000 per QALY gained for all comparisons provided in all populations:
  - Post-cBTKi population, post-cBTKi population unsuitable for SoC and dual-exposed population
  - Pirtobrutininb vs IdelaR, VenR, cBTKis and BSC

Scenario analyses:

- No scenario gives cost effectiveness estimates within £20,000 to £30,000 per QALY
- Pirtobrutinib is not cost-saving in any of the cost comparisons

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Abbreviations: BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; ICER, incremental cost effectiveness ratio; IdelaR, idelalisib plus rituximab; QALY, quality adjusted life years; SoC, standard of care; VenR, venetoclax plus rituximab

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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Equality considerations and uncaptured benefits

- Equality considerations
  - Company, EAG and patient groups did not identify any equality issues
- Uncaptured benefits
  - Company:
    - noted that impact on caregiver quality of life was not captured, but provided no qualitative detail
    - highlighted that pirtobrutinib may reduce monitoring costs compared to venetoclax-containing regimens, offering a safety profile that avoids intensive hospitalisation and TLS-related monitoring
    - patient preference for orally administered treatments not captured in the economic analysis
  - EAG
    - difficult to assess the magnitude of any benefit from pirtobrutinib on caregiver quality of life due to lack of evidence
    - company only considered VenR in the original submission and included adverse events in the cost comparison analysis with pirtobrutinib
    - all comparator treatments (cBTKis and venetoclax) are also oral therapies, and any utility benefit from oral administration would likely be reflected in EQ-5D data from the BRUIN CLL-321 trial.

Abbreviations: EAG, external assessment group, EQ-5D, EuroQol- 5 Dimension; CLL, Chronic lymphocytic leukaemia; TLS, tumour lysis syndrome

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

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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Key Issues

Issue	Resolved?	ICER impact
No clinical evidence for relevant comparators	No – for discussion	Unknown – Potentially large
Cost comparison with VenR	No – for discussion	Unknown – Potentially large
No cost effectiveness results for comparisons of pirtobrutinib with cBTKi or BSC	No – for discussion	Unknown – Potentially large

Other issues

Issue	Resolved?	ICER impact
Post-progression utility values do not align with trial evidence	No – for discussion	Small
Incorrect calculation of cost of stem cell transplant	No – for discussion	Small

Abbreviations: BSC, best supportive care; cBTKi, covalent Bruton's tyrosine kinase inhibitor; ICER, incremental cost effectiveness ratio; VenR, venetoclax plus rituximab

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

Supplementary appendix

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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

Decision problem (1/3)

	Final scope	Company	EAG comments
Population	• Adults with CLL or SLL whose cancer has been previously treated with a BTKi	• Adults with R/R CLL whose cancer has been previously treated with a BTKi • Consider SLL and CLL are interchangeable terms • In line with UK licensed indication for pirtobrutinib	• Excluding SLL is appropriate • 91.2% of BRUIN CLL-321 trial patients had CLL → reflects the clinical effectiveness of CLL patients • EAG clinical advice: all patients who received ≥1 prior treatments would be considered to have R/R CLL
Subgroups	• Adults with CLL or SLL who have had at least two prior lines of therapy including a BTKi and BCL2i	Identified subpopulations: 1. SoC-suitable: Previously treated with a cBTKi; eligible for BCL2i and/or cBTKi 2. SoC-unsuitable: Previously treated with a cBTKi; not eligible for BCL2i and/or cBTKi 3. Dual-exposed: Previously treated with both a cBTKi and a BCL2i	• Company only presented clinical and cost effectiveness evidence for dual-exposed subpopulation • Company couldn't identify BRUIN CLL-321 patients by SoC suitability, so couldn't present evidence separately for these subgroups

Abbreviations: BR, bendamustine with rituximab; CLL, chronic lymphocytic leukaemia; DoR, duration of response; EFS, event-free survival; IdelaR, idelalisib plus rituximab; IRC, independent review committee; 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

Decision problem (2/3)

	Comparators
Final scope	• Zanubrutinib • Acalabrutinib • Ibrutinib • Venetoclax (if disease has progressed after a B-cell receptor pathway inhibitor) • Venetoclax with rituximab • Idelalisib with rituximab
Company	• Presented evidence for pirtobrutinib vs IdelaR • VenR was considered relevant comparator for SoC-eligible and dual-exposed patients • ITC for pirtobrutinib vs VenR was not feasible

Abbreviations: BCR, B-cell receptor; BTKi, Bruton's tyrosine kinase inhibitor; IdelaR, idelalisib with rituximab; ITC, indirect treatment comparison; SoC, standard of care; VenR, venetoclax with rituximab

Decision problem (3/3)

	Comparators
EAG comments	**1. Patients with R/R CLL previously treated with a cBTKi and suitable for SoC** ○ VenR ○ cBTKi (if prior discontinuation due to intolerance) Clinical advice: • BCL2i suitable for most; only unsuitable with poor renal function • VenR is the most relevant and commonly used • Ven-mono is rarely used and not relevant **2. Patients with R/R CLL previously treated with a cBTKi and unsuitable for SoC** ○ IdelaR ○ BSC Clinical advice: • BCL2i unsuitable only for small group (poor renal function) • IdelaR rarely used due to toxicity • IdelaR and BSC are main options when SoC unsuitable, and no other active treatments available **3. Dual-exposed patients (previously treated with both a cBTKi and BCL2i)** ○ VenR (if relapse after completing venetoclax) ○ cBTKi (if prior intolerance or relapse post-VenI without refractoriness) ○ IdelaR ○ BSC Clinical advice: • Rechallenge with venetoclax or cBTKi is appropriate if not refractory • VenR preferred over Ven-mono (which is rarely used) • BSC only relevant for dual-refractory patients

Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; BSC, best supportive care; CLL, chronic lymphocytic leukaemia; cBTKi, covalent Bruton's tyrosine kinase inhibitor; IdelaR, idelalisib with rituximab; R/R, relapsed or refractory; SoC, standard of care; Ven-mono, venetoclax monotherapy; VenR, venetoclax with rituximab

Trials included in the feasibility assessment

8 trials were included in the feasibility assessment but ITC was not appropriate

Trial name	Population	Intervention	Comparator	Key notes
BRUIN CLL-321	R/R CLL or SLL patients, previously treated with BTKi	Pirtobrutinib	Investigator's choice (IdelaR or BR)	• Multinational • Included CLL and SLL
ALPINE	R/R CLL or SLL patients ≥18 years	Ibrutinib	Zanubrutinib	• Multinational • Included CLL and SLL • Recruited primarily white populations
ASCEND	Previously treated CLL patients ≥18 years	Acalabrutinib	Investigator's choice (IdelaR or BR)	• Multinational
ELEVATE RR	Previously treated patients with ≥18 years of age or older; diagnosis of CLL	Acalabrutinib	Zanubrutinib	• Multinational
MURANO	R/R patients with CLL ≥18 years that required therapy; received one to three previous treatments (including at least one chemotherapy-containing regimen)	VenR	BR	• Multinational
NCT02007044	Previously treated CLL/SLL patients or untreated patients with 17p deletion (del17p) or TP53 mutation were also permitted	Ibrutinib + rituximab	Ibrutinib	• Multinational • US • Included CLL and SLL
DUO	R/R CLL or SLL patients who are BTKi naïve	Ofatumumab	Duvelisib	• Multinational • Included CLL and SLL
RESONATE	CLL/SLL patients who received at least one prior therapy	Ibrutinib	Ofatumumab	• Multinational • Included CLL and SLL • Recruited primarily white populations

Link back to main slide

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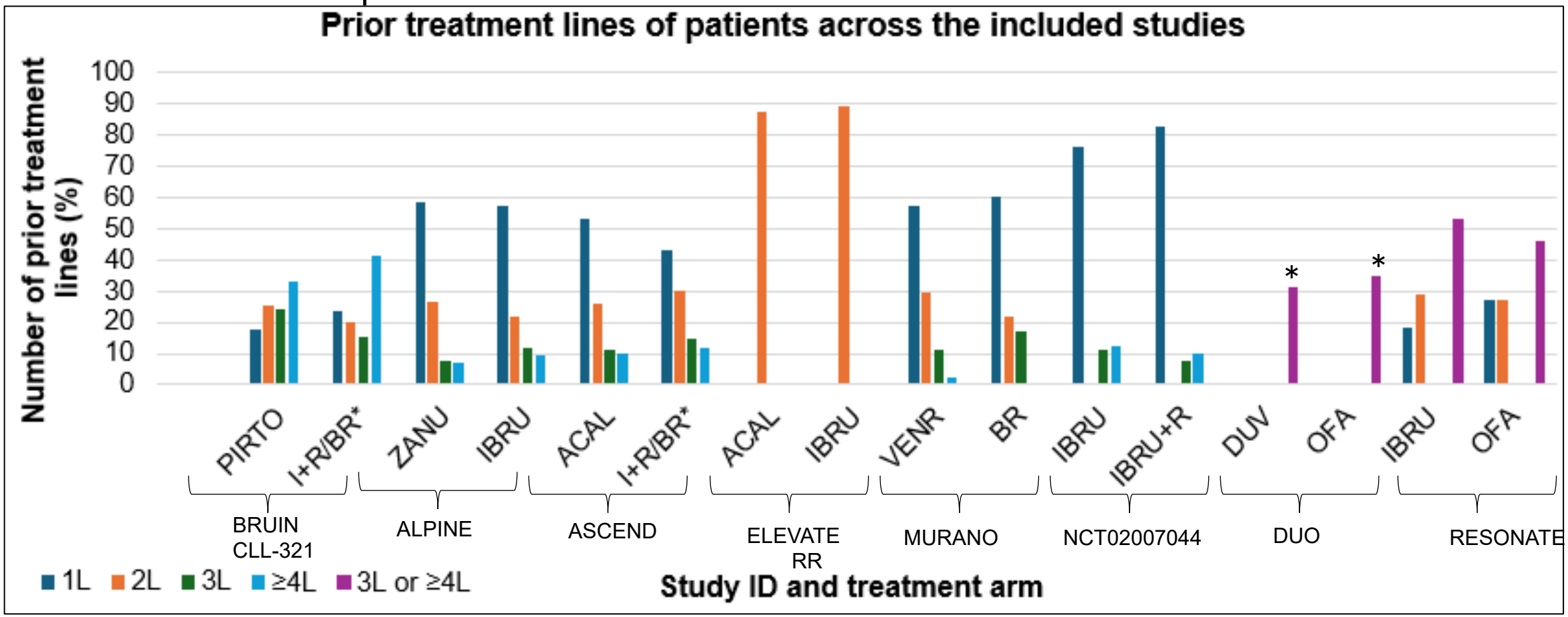
Abbreviations: BR, bendamustine in combination with rituximab; CLL, chronic lymphocytic leukaemia; IdelaR, idelalisib in combination with rituximab; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma; VenR, venetoclax in combination with rituximab

Key issue: No clinical evidence for relevant comparators

Prior treatment lines of patients across the included studies



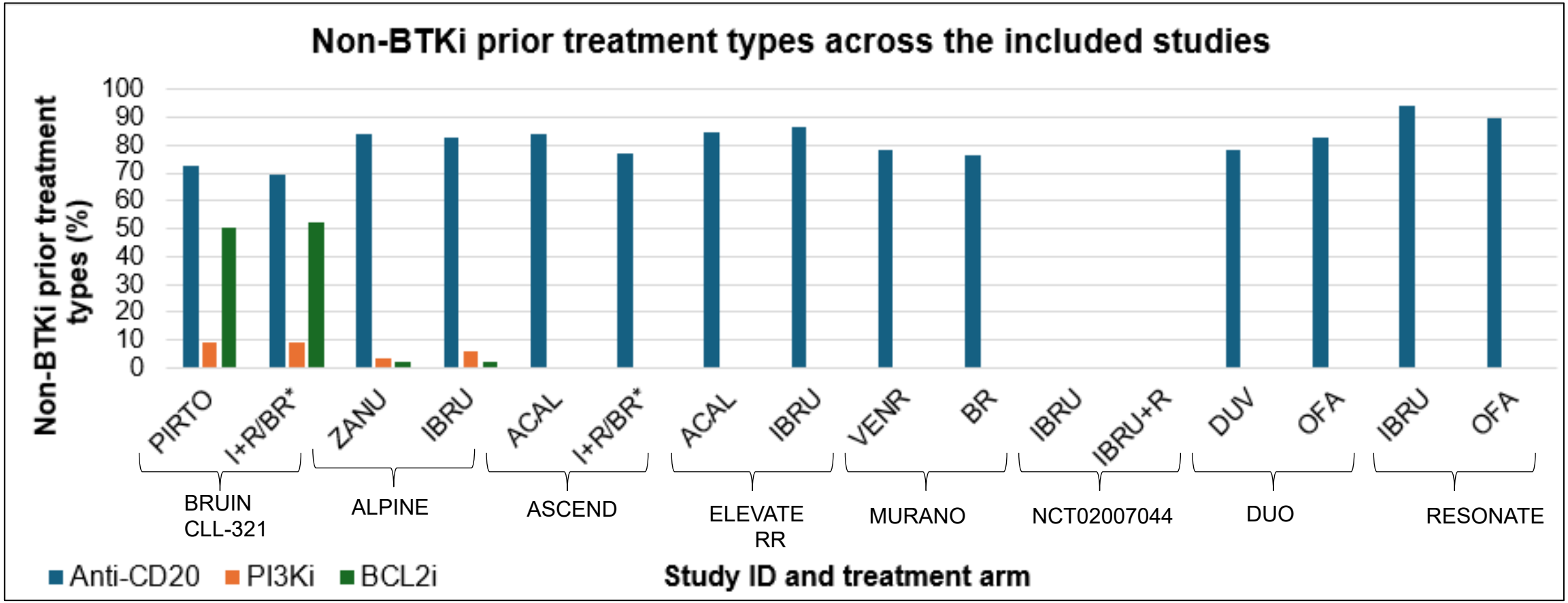
*Indicates the investigator's choice between I+R or BR. †Percentages re-calculated from DEF based on relapsed patient sub-group, not overall CLL population recruited in this study (including previously untreated patients).

Link to main slide

Abbreviations: 1L: first line; 2L: second line; 3L: third line; 4L: fourth line; ACAL: acalabrutinib; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton tyrosine kinase inhibitors; I: idelalisib; IBRU; ibrutinib; PI3K: phosphoinositide 3 kinase inhibitors; PIRTO: pirtobrutinib; R: rituximab; VEN: venetoclax; ZANU: zanubrutinib

Key issue: No clinical evidence for relevant comparators

Non-BTKi prior treatment types across the included studies

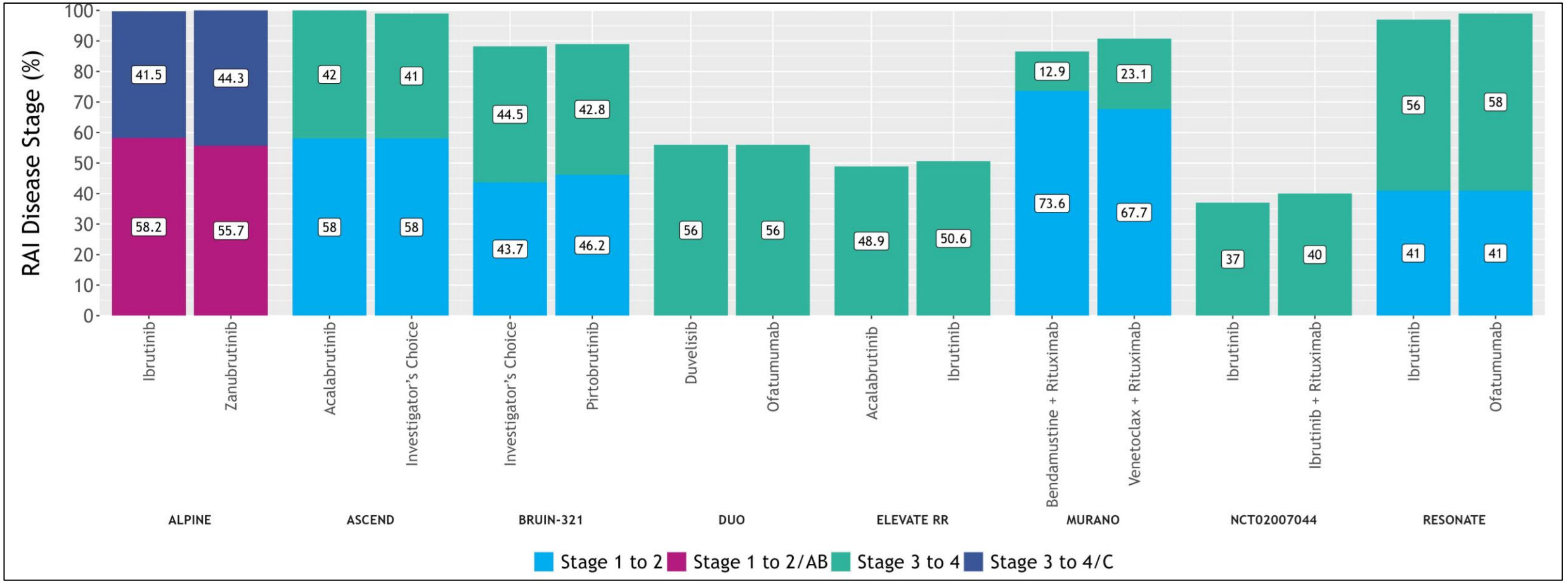


Link to main slide

Abbreviations: 1L: first line; 2L: second line; 3L: third line; 4L: fourth line; ACAL: acalabrutinib; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton tyrosine kinase inhibitors; I: idelalisib; IBRU; ibrutinib; PI3K: phosphoinositide 3 kinase inhibitors; PIRTO: pirtobrutinib; R: rituximab; VEN: venetoclax; ZANU: zanubrutinib

Key issue: No clinical evidence for relevant comparators (1/2)

Percentage disease stage breakdown of patients across the included studies



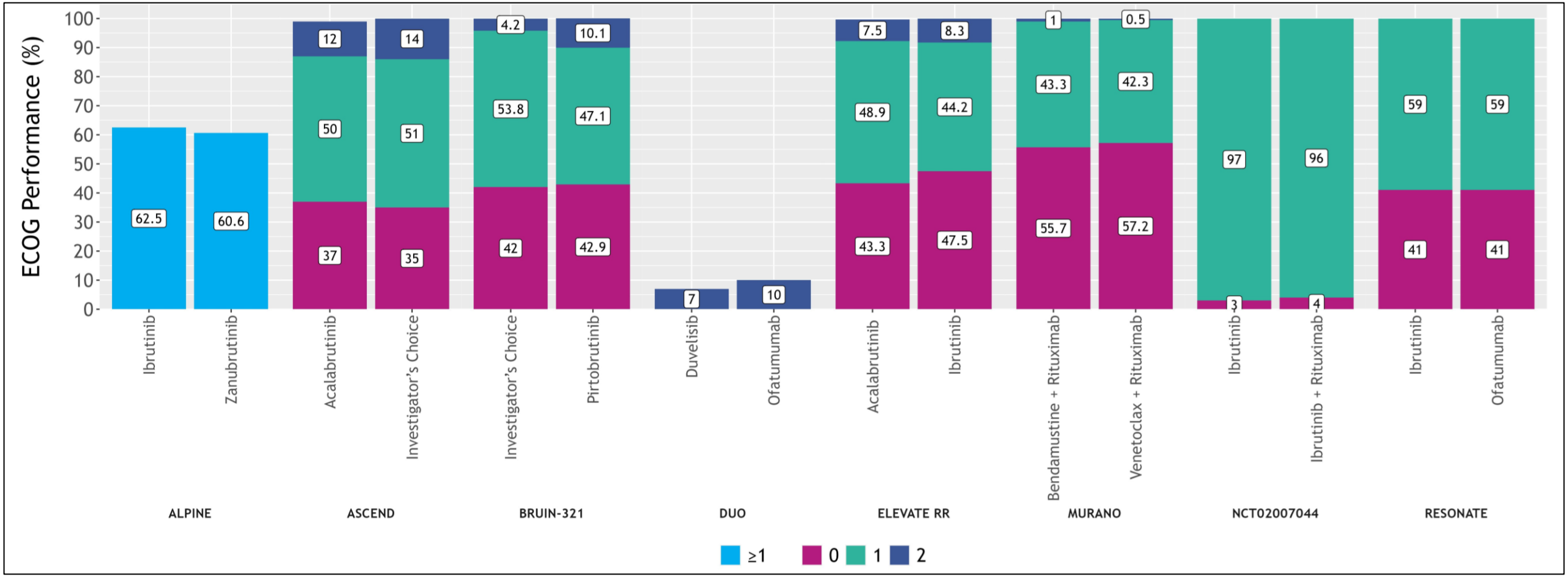
- Disease staging for BRUIN CLL-321 was grouped for similarity assessment across all studies.
- Rai stage at diagnosis was unknown for remaining patients in the MURANO study.
- NCT02007044 included both previously treated and untreated patients, but baseline characteristics were only reported for the overall population.

Link to main slide

Abbreviations: R/R: relapsed or refractory

Key issue: No clinical evidence for relevant comparators (2/2)

Percentage ECOG PS breakdown of patients across the included studies



- Outcome data is available for the R/R subgroup in NCT02007044.
- The trial included both previously treated and untreated patients (86% in the ibrutinib arm, 88% in the ibrutinib + rituximab arm).
- Baseline characteristics were reported only for the overall population.

Link to main slide

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Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; R/R: relapsed or refractory.