Single Technology Appraisal

Pirtobrutinib for treating relapsed or refractory chronic lymphocytic leukaemia after a BTK inhibitor [ID6269]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pirtobrutinib for treating relapsed or refractory chronic lymphocytic leukaemia after a BTK inhibitor [ID6269]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from** Eli Lilly & Company**:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Joint submission: Chronic Lymphocytic Leukaemia Support Association, Blood Cancer UK, Leukaemia Care, Lymphoma Action and Leukaemia UK – authored by patient expert, Jackie Martin, and endorsed by patient expert, Dorothy Chivers

4. **Expert personal perspectives** from:
   a. Catherine Parbutt – clinical expert, nominated by British Oncology Pharmacy Association (BOPA)
   b. Dorothy Chivers – patient expert, nominated by Chronic Lymphocytic Leukaemia Support Association, Blood Cancer UK, Leukaemia Care, Lymphoma Action, and Leukaemia UK

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRIG)

6. **External Assessment Report – factual accuracy check**

7. **Additional company evidence post first appraisal committee meeting**
   a. Additional comparative efficacy analysis
   b. Updated cost comparison and cost-effectiveness results appendix
   c. Appendix for the committee

8. **External Assessment Group critique of additional company evidence post first appraisal committee meeting**
   a. Critique of additional evidence
   b. Critique of appendix for committee

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia after 1 or more BTK inhibitors [ID6269]

Company evidence submission

June 2025

File name	Version	Contains confidential information	Date
[ID6269] Pirtobrutinib in CLL_NICE_Company Submission [CON].docx	V1.2	No	11th August 2025

Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Definition
ACAL	Acalabrutinib
AE	Adverse Event
AESI	Adverse Event of Special Interest
AFT	Accelerated Failure Time
AIC	Akaike's Information Criteria
AlloSCT	Allogeneic Stem Cell Transplant
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
AS	Age Standardised
AST	Aspartate Aminotransferase
BCL2i	B-Cell Lymphoma 2 Inhibitor
BCR	B-Cell Receptor
BCRi	B-Cell Receptor Inhibitor
BCRP	Breast Cancer Resistance Protein
BFI	Brief Fatigue Inventory
BIC	Bayesian Information Criterion
BID	Twice Daily
BNF	British National Formulary
BOR	Best Overall Response
BR	Bendamustine + Rituximab
BSA	Body Surface Area
BSC	Best Supportive Care
BSH	British Society Of Haematology
BTK	Bruton Tyrosine Kinase
BTKI	Bruton Tyrosine Kinase Inhibitor
cBTKi	Covalent Bruton Tyrosine Kinase Inhibitor
CD	Cluster Of Differentiation
CHMP	Committee For Medicinal Products For Human Use
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
CIT	Chemoimmunotherapy
Clb	Chlorambucil
CLL	Chronic Lymphocytic Leukemia
CMH	Cochran-Mantel-Haenszel (Statistical Method)
CNS	Central Nervous System
CON	Confidential
COVID	Coronavirus Disease 2019
CRF	Case Report Form
CRi	Complete Response With Incomplete Hematologic Recovery

CSR	Clinical Study Report
CYP	Cytochrome P450 Enzyme Family
DAE	Discontinuation Due To AE
DCO	Data Cut-Off
DEF	Data Extraction File
DLBCL	Diffuse Large B-Cell Lymphoma
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
DPD	Discontinuation Due To Progressive Disease
DSA	Deterministic Sensitivity Analysis
DSU	Decision Support Unit
DUV	Duvelisib
ECDRP	European Cancer Drug Response Program
ECOG	Eastern Cooperative Oncology Group (Performance Status)
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC	European Organisation For Research And Treatment Of Cancer
EOT	End Of Treatment
EQ	Equivalence
ESMO	European Society For Medical Oncology
ESS	Effective Sample Size
FA	Feasability Assessment
FACT	Functional Assessment Of Cancer Therapy
FCR	Fludarabine, Cyclophosphamide, Rituximab
FDA	Food And Drug Administration (US)
FISH	Fluorescence In Situ Hybridization
GCLLSG	German Cll Study Group
GFR	Glomerular Filtration Rate
GHS	Global Health Status
GnRH	Gonadotropin-Releasing Hormone
GP	General Practitioner
HCRU	Healthcare Resource Utilisation
Hgb	Haemoglobin
HR	Hazard Ratio
HRQoL	Health-Related Quality Of Life
HSCT	Hematopoietic Stem Cell Transplantation
HTA	Health Technology Assessment
IBRU	Ibrutinib
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IdelaR	Idelalisib Plus Rituximab
IGHV	Immunoglobulin Heavy Variable

IMID	Immune-Mediated Inflammatory Disease
INV	Investigator
IPCW	Inverse Probability Censoring Weighting
IPD	Individual Patient Data
IPI	International Prognostic Index
IRC	Independent Review Committee
IRP	International Recognition Procedure
IRR	Incidence Rate Ratio
ITC	Indirect Treatment Comparison
ITT	Intention-To-Treat
IV	Intravenous
iwCLL	International Workshop On Chronic Lymphocytic Leukaemia
IWRS	Interactive Web Response System
KM	Kaplan-Meier (Survival Analysis)
LH	Luteinising Hormone
LTFU	Loss To Follow-Up
LYG	Life-Years Gained
MAIC	Matching-Adjusted Indirect Comparison
MDS	Myelodysplastic Syndromes
MHRA	Medicines And Healthcare Products Regulatory Agency (UK)
MIMS	Monthly Index Of Medical Specialties
MIT	Massachusetts Institute Of Technology
MMRM	Mixed Model For Repeated Measures
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NCT	National Clinical Trial
NE	Not Evaluated
NED	No Evidence Of Disease
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NICE	National Institute For Care And Excellence
NMA	Network Meta-Analysis
NMB	Net Monetary Benefit
NMR	Nuclear Magnetic Resonance
nPR	Nodular partial response
NR	Not Reported
NRSI	Non-Randomised Study Intervention
OFA	Ofatumumab
ONS	Office for National Statistics
ORR	Overall Response Rate
OS	Overall Survival

PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PD	Progressive Disease
PF	Progression Free
PFS	Progression-Free Survival
PI3Ki	Phosphoinositide 3-kinase inhibitors
PICO	Population, Intervention, Comparison, Outcome
PIRTO	Piritobrutinib
PLCG2	Phospholipase C Gamma 2
PO	By Mouth / Oral
PPS	Post-Progression Survival
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned Survival Model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PYE	Patient Years at Risk
Q12W	Once Every 12 Weeks
Q24W	Once Every 24 Weeks
Q2W	Once Every 2 Weeks
Q4W	Once Every 4 Weeks
QALY	Quality-Adjusted Life Year
QD	Once Daily
QLQ	Quality of Life Questionnaire
RBC	Red Blood Cell
RCT	Randomised Controlled Trial
ROBINS	Risk Of Bias In Non-Randomised Studies
RPSFTM	Rank Preserving Structural Failure Time Model
SAE	Serious Adverse Event
SC	Subcutaneous
SCHARR	Sheffield Centre for Health and Related Research
SCT	Stem Cell Transplant
SD	Standard Deviation
SE	Standard Error
SERM	Selective Estrogen Receptor Modulator
SFU	Safety Follow-Up
SLL	Small Lymphocytic Lymphoma
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SoC	Standard of Care

TA	Technology Appraisal
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLS	Tumor Lysis Syndrome
TSD	Technical Support Document
TTD	Time to Treatment Discontinuation
TTNT	Time to Next Treatment
TTW	Time to Worsening
UK	United Kingdom
US	United States
VenI	Venetoclax + Ibrutinib
VenO	Venetoclax + Obinutuzumab
VenR	Venetoclax + Rituximab
WBC	White Blood Cell
WTP	Willingness-To-Pay

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The objective of this appraisal is to determine the clinical and cost-effectiveness of pirtobrutinib within its anticipated marketing authorisation in the UK for the treatment of adults with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi). Aligned with the primary population investigated in the pivotal BRUIN CLL-321 trial, pirtobrutinib is positioned across its full anticipated licence population in the UK, in this appraisal.

Of note, the full licence population is addressed in this submission through the use of three sub-populations, which differ in terms of relevant comparators and available direct and indirect evidence. These are defined in this submission as follows:

- Adults with CLL who have previously been treated with a covalent BTKi (cBTKi) i.e., a **post-cBTKi population, but can receive current standard of care (SoC)**
- Adults with CLL who have previously been treated with a cBTKi but are currently unsuitable for a BCL2i or another cBTKi, i.e., a **post-cBTKi population, but cannot receive current SoC**
- Adults with CLL who have previously been exposed to a cBTKi *and* BCL2i (either sequentially or in combination) i.e., the **dual-exposed population**

The rationale for the use of these sub-populations, and the considerations within each group of patients, are detailed in the sections below. Details on the positioning of pirtobrutinib and the relevant comparators within these sub-populations are discussed further in Section 1.3.3.3.

The decision problem addressed within this submission, including a description of any deviations from the NICE reference case and/or final scope, are outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with CLL or SLL whose cancer has been previously treated with a BTK inhibitor	Adults with R/R CLL who have been previously treated with a BTKi. This encompasses the following sub-populations: • Adults with CLL who have previously been treated with a covalent BTKi (cBTKi) i.e., a **post-cBTKi population, but can receive current** standard of care (**SoC**) • Adults with CLL who have previously been treated with a cBTKi but are currently unsuitable for a BCL2i or another cBTKi, i.e., a **post-cBTKi population, but cannot receive current SoC** • Adults with CLL who have previously been exposed to a cBTKi and BCL2i (either sequentially or in combination) i.e., the **dual-exposed population**	The anticipated license wording for pirtobrutinib in the UK is for "the treatment of adults with relapsed or refractory CLL who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)." Therefore, the decision problem addressed in this submission does not include patients who are diagnosed with small lymphocytic lymphoma (SLL). Additionally, as per its anticipated licence, patients are only eligible for treatment with pirtobrutinib if they underwent at least one prior line of treatment with a BTKi (e.g., zanubrutinib, acalabrutinib, ibrutinib). Therefore, in line with its licence and as requested in the NICE final scope, pirtobrutinib is positioned in this submission as a treatment for patients with CLL who have previously had at least one BTKi i.e., the overall post-cBTKi population. As presented in the adjacent cell, the decision problem is addressed by considering three sub-populations of the overall post-BTKi population. Further details on the rationale on defining these sub-populations and the relevant comparators within are discussed in Section 1.3.3.3.
Intervention	Pirtobrutinib	Pirtobrutinib	NA - in line with NICE final scope

Comparator(s)	• Zanubrutinib • Acalabrutinib • Ibrutinib • Venetoclax (if disease has progressed after a B-cell receptor pathway inhibitor) • Venetoclax with rituximab • Idelalisib with rituximab • Best supportive care	**Adults with CLL who have previously been treated with a cBTKi (post-cBTKi population, but can receive current SoC):** • Idelalisib in combination with rituximab **Adults with CLL who have previously been treated with a cBTKi but are currently unsuitable for a BCL2i or another cBTKi (post-cBTKi population, but cannot receive current SoC):** • Idelalisib in combination with rituximab **Adults with CLL who have previously been exposed to a cBTKi and BCL2i (either sequentially or in combination) (dual-exposed population):** • Idelalisib in combination with rituximab	Venetoclax-monotherapy (Ven-mono) was not considered standard of care in the UK by clinical experts consulted for this submission, and therefore it is not considered a relevant comparator to pirtobrutinib in this submission. Venetoclax with rituximab (VenR) is considered SoC for the group of patients who have previously been treated with a cBTKi. There is, however, a proportion of patients who cannot receive current SoC due to the presence of comorbidities or patient preference (discussed further in Section 1.3.3.2 and Section 1.3.3.3). For these patients idelalisib in combination with rituximab (IdelaR) is the only relevant comparator. Conversely, VenR may be considered as a treatment option for post-cBTKi patients who can receive current SoC. However, based on the feasibility assessment (FA) conducted for this submission, it was not considered feasible to conduct any indirect treatment comparisons (ITC) for pirtobrutinib versus VenR using the present evidence base (see Section 2.10 for further details). As such, comparisons against VenR are not included in this submission for post-cBTKi patients with R/R CLL, who can receive SoC; economic analyses for pirtobrutinib versus IdelaR, are considered the only proxy for effectiveness in this population. Covalent BTKi are considered SoC for patients with R/R CLL, including for patients previously treated with an

			alternative cBTKi. As such they represent a potential comparator to pirtobrutinib in the post-cBTKi population for patients who can receive current SoC. However, UK clinical experts were unlikely to consider cBTKi rechallenge in patients with clear evidence of disease progression as it is a hallmark of the development of cBTKi resistance mutations (discussed further in Section 1.3.3.2). Of note, the majority of patients randomised in BRUIN CLL-321 had discontinued prior cBTKi therapy due to progressed disease (see baseline characteristics, Section 2.3.2) and therefore would not be expected to be re-treated with cBTKi in UK clinical practice, in line with UK clinical expert opinion. Furthermore, Lilly acknowledge the presence of a group of patients who discontinue cBTKi due to intolerance or adverse events, and therefore may be eligible for re-treatment with an alternative cBTKi, as per BSH guidelines. However, the proportion of these eligible patients is anticipated to be very low in clinical practice, in line with the observed baseline disease and treatment characteristics of patients randomised to BRUIN CLL-321, wherein the majority of patients who had discontinued cBTKi treatment prior to randomisation had done so due to progression/refractoriness as opposed to intolerance. Comparative data on the effectiveness and safety of pirtobrutinib versus cBTKi in this population are also not available or generable through ITC, as

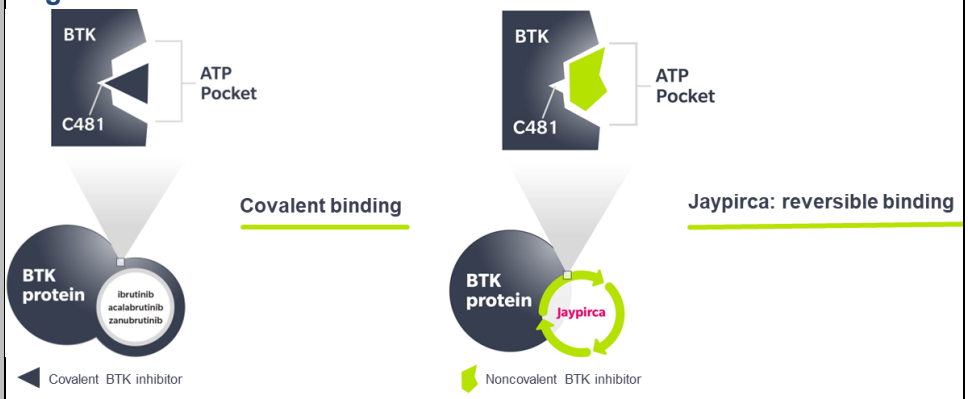
			confirmed through a robust FA conducted for this submission. Given the above, cBTKi are not considered a relevant comparator to pirtobrutinib, and are therefore not addressed in the decision problem in this submission. Further rationale for the selection of the comparators addressed in this submission are presented in Section 1.3.3.3.
Outcomes	• Overall survival • Progression-free survival • Response rate • Time to next treatment • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Time to next treatment • Time to worsening • Adverse effects of treatment • Health-related quality of life	In addition to the outcomes requested in the NICE final scope, this submission also includes data on patient-reported time to worsening outcomes, as obtained in BRUIN CLL-321.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	The economic analysis was conducted In line with the NICE reference case	NA - in line with NICE final scope

	The availability of biosimilar and generic products should be taken into account		
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	NA - in line with NICE final scope	NA - in line with NICE final scope

Abbreviations: BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton's tyrosine kinase inhibitor; BSH: British Society for Haematology; cBTKi: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; FA: feasibility assessment; FDA: Food and Drug Administration; ITC: indirect treatment comparison; NA: not applicable; NICE: National Institute of Health and Care Excellence; NHS: National Health Service; PI3K: phosphoinositide 3-kinase; SLL: small lymphocytic lymphoma.
Source: National Institute for Health Care and Excellence. [ID6269].[1]

1.2 *Description of the technology being evaluated*

Table 2: Technology being evaluated

UK approved name and brand name	Pirtobrutinib (Jaypirca®)
Mechanism of action	Pirtobrutinib is the first, non-covalent BTKi that inhibits B-cell receptor (BCR) signalling via highly selective, reversible binding to the ATP pocket of the BTK protein, without needing to bind to the BTK C481 residue (Figure 1).[2, 3] BTK is a signalling protein of the B-cell antigen receptor and cytokine receptor pathways.[4] In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.[4] Pirtobrutinib binds to both wild type BTK and BTK harbouring C481S mutations, inhibiting BTK-mediated B-cell CD69 expression and malignant B-cell proliferation.[5] **Figure 1: Pirtobrutinib mechanism of action**  **Abbreviations:** ATP; adenosine triphosphate; BTKi: Bruton tyrosine kinase inhibitors; C481; cysteine 481.
Marketing authorisation/CE mark status	An application for marketing authorisation in the UK was submitted to the Medicines and Healthcare Products Regulatory Procedure (MHRA) through the International Recognition Procedure (IRP) on [redacted]. Marketing authorisation in the UK is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pirtobrutinib is anticipated to be licensed for the treatment of [redacted].
Method of administration and dosage	Pirtobrutinib is administered orally once daily at a dosage of 200 mg.[6]
Additional tests or investigations	No additional tests are required
List price and average cost of a course of treatment	The anticipated list price for the formulations and pack sizes for pirtobrutinib are provided below: • [redacted] • [redacted]

	At list price, the cost of a 28-day cycle of pirtobrutinib, based on the [redacted], is [redacted]
Patient access scheme (if applicable)	A simple PAS is planned for pirtobrutinib which will be communicated with PASLU once details are confirmed.

Abbreviations: ATP: adenosine triphosphate; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; CHMP: Committee for Medicinal Products for Human Use; CLL: chronic lymphocytic leukaemia; EC: European Commission; ECDRP: EC Decision Reliance Procedure; EMA: European Medicines Agency; MHRA: Medicines and Healthcare Products Regulatory Agency; SmPC: Summary of Product Characteristics; SLL: small lymphocytic lymphoma.

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease Overview

CLL is the most common type of leukaemia and is characterised by the overproduction of cluster of differentiation 5+ ($CD5^+$) B lymphocytes, a type of white blood cell.[7] The aetiology of CLL is unknown, but is it thought to arise due to damage to one or more genes that control blood cell development.[8] As a result, the $CD5^+$ B lymphocytes mature but are rendered dysfunctional; reducing the patients capability to fight infections. The dysfunctional B cells accumulate in the blood, bone marrow, and other organs.[9] CLL is the most frequently diagnosed type of leukaemia in adults, affecting predominantly elderly individuals, with 40% of all new CLL cases in the UK being diagnosed in people aged 75 or over.[10-13] Approximately 4,000 people are diagnosed with CLL in the UK every year.[14]

Clinical presentation of CLL is highly variable, ranging from asymptomatic, indolent disease that may never require therapy to rapidly progressive disease that can lead to progressive lymphocytosis, cytopenia, lymphadenopathy, hepatosplenomegaly, B symptoms (i.e., weight loss, night sweats, and fever), fatigue, recurrent infections, or autoimmune complications.[15]

1.3.1.1 Clinical presentation, staging and diagnosis

A diagnosis of CLL requires the presence of ≥5 × 10^9/L monoclonal $CD5^+$ B lymphocytes in the peripheral blood, sustained for at least three months, as per guidelines defined at the 2018 International Workshop on Chronic Lymphocytic Leukaemia (iwCLL).[16, 17]

A high proportion of patients with CLL, 74%, do not exhibit symptoms at the time of diagnosis; the presence of CLL is often diagnosed following routine blood tests.[18-20] In those patients presenting with symptomatic disease, symptoms are initially mild and progress slowly.[20] Symptoms of CLL include swollen lymph glands or abdominal discomfort from an enlarged spleen, weight loss, infections that will not cease, tiredness, anaemia and bone pain.[20]

At diagnosis, the clinical stage of the disease is defined to gauge disease progression and to aid development of an appropriate treatment plan for the diagnosed patient. Two major clinical systems are used globally to stage CLL; the Binet staging system (predominantly in Europe) and the Rai staging system (predominantly in the US).[21] The Binet staging system (shown in Table 3) involves measuring the patients' platelet count, peripheral blood haemoglobin levels, and the number of areas of lymphoid enlargement, to stage the disease (from A to C), with Stage C representing the most progressed disease; patients diagnosed with Stage C disease are associated with the lowest median duration of survival post-diagnosis.[17] Areas examined for lymphoid enlargement include the head and neck, axilla, groin, spleen and liver.[19, 21]

Table 3: Summary of the Binet staging system for CLL

Stage	Characteristics	Median survival
Binet A	• Haemoglobin ≥10g/dL • Platelet count ≥100x10^9/L • <3 areas of lymphoid tissue enlargement	>10 years

Binet B	• Haemoglobin ≥10g/dL • Platelet count ≥100x10^9/L • ≥3 areas of lymphoid tissue enlargement	7 to 9 years
Binet C	• Haemoglobin <10g/dL • Thrombocytopenia (platelets <100,000/mm^3) • Any number of areas of lymphoid tissue enlargement	1.5 to 5 years

Abbreviations: CLL: chronic lymphocytic leukaemia.
Source: Leukaemia & Lymphoma Society,[22] and Sagatys *et al.* (2012).[17]

Furthermore, additional prognostic information can be gained from markers such as immunoglobulin heavy-chain variable region gene *(IGHV)* mutational status, serum β_2-microglobulin and the presence to chromosomal alterations.[7, 16] Such prognostic information can be utilised to inform the most appropriate treatment response.

Notably, approximately 80% of patients with CLL carry at least one of four common chromosomal alterations: a deletion in the short arm of chromosome 17 i.e., del(17p), deletions in the long arm of chromosome 13 or 11 (del[13q] and del[11q], respectively), or trisomy 12.[7] These chromosomal alterations are associated with a loss of proteins inhibiting apoptosis and may lead to unfavourable prognoses.[7]

In particular, the presence of del(17p) is associated with the loss of the tumour-suppressor *TP53* gene, which codes for the *TP53* protein that regulates cell division and prevents the proliferation of cells with damaged DNA.[7] Additionally, between 30–40% of *TP53* mutations are known to occur in the absence of del(17p). However, irrespective of the cause of the loss of *TP53*, people with *TP53* aberrations, either through direct *TP53* mutation or by del(17p), are referred to as having 'high-risk' CLL.[16] People with 'high-risk' CLL are not considered suitable for certain treatments of CLL, including the chemoimmunotherapies (CIT) fludarabine, cyclophosphamide, and rituximab (FCR) and bendamustine combined with rituximab (BR) (see Section 1.3.3 for details).[23]

In 2016, the CLL International Prognostic Index (CLL-IPI) was introduced to enable more targeted management of CLL.[24] This index, shown in Table 4, categorises patients into prognostic risk groups utilising genetic, biochemical and clinical parameters. Five independent prognostic factors were identified and assigned a risk score:

- *TP53* deleted or mutated (4 points)
- Unmutated IGHV (2 points)
- Serum β_2-microglobulin, concentration >3.5 mg/L (2 points)
- Rai Stage I - V or Binet Stage B - C (1 point)
- Patient age >65 years (1 point)

Patients categorised as lower-risk based on the generated risk score would not require immediate treatment. In contrast patients classified as very high risk would be recommended to receive treatment through targeted therapeutic agents (e.g., BTKi or BCL2i) or in clinical trials, rather than systemic CITs (see Section 1.3.3 for further details).[25]

Table 4: CLL-IPI risk score and treatment recommendations

CLL-IPI Category	Risk Score	Treatment Recommendations
Low Risk	0-1	Do not treat
Intermediate Risk	2-3	Do not treat unless the disease is highly symptomatic
High Risk	4-6	Treat unless the patient is asymptomatic
Very High Risk	7-10	If the decision is made to treat, use novel agents or treatment in a clinical trial rather than chemotherapy

Abbreviations: CLL: chronic lymphocytic leukaemia; IPI: International Prognostic Index.
Source: Leukaemia & Lymphoma Society.[22]

1.3.1.2 Epidemiology

CLL incidence rates have increased by 17% in the UK over the past 20 years, with CLL accounting for 1% of all new cancer cases in the UK in 2017–2019.[14, 26] Men account for 63% of all CLL cases in the UK, and have a worse disease prognosis than women.[14, 26] CLL primarily impacts an elderly population, with incidence rates being the highest in people aged 85 to 89.[14] Though CLL is the most frequently diagnosed type of leukaemia in adults, it is considered a rare disease in the UK, with an age-standardised incidence rate of 6.3 per 100,000 people.[27] Incidence rates for male and female persons in England and Wales between 2017 and 2019 are shown in Table 5.

Table 5: CLL incidence and AS incidence rates in England, Wales and the UK, 2017–2019

	England	Wales	UK
Number of new cases per year*	3,426	142	3,952
AS incidence rates per 100,000 people			
Female	4.5	3.2	4.3
Male	8.9	5.8	8.6
Persons	6.5	4.3	6.3

Footnote: *Based on mid-year 2023 population estimates from the ONS. UK estimates for new cases per year include patients in Scotland.
Abbreviations: AS: age standardised; CLL: chronic lymphocytic leukaemia; ONS: Office for National Statistics; UK: United Kingdom.
Source: Cancer Research UK. CLL statistics.[14]

In the UK, there are around 976 CLL-related deaths every year, with mortality rates being the highest in people aged over 90 years.[14] Approximately 79% of all CLL deaths occurred in people aged 75 and above during 2017 to 2019 (Table 6).[14]

Table 6: CLL mortality rates in England, Wales and the UK, 2017–2019

	England	Wales	UK
Number of deaths per year	931	51	976

AS incidence rates per 100,000 people			
Female	1.0	1.0	1.0
Male	2.3	2.2	2.3
Persons	1.6	1.5	1.5

Abbreviations: AS: age standardised; CLL: chronic lymphocytic leukaemia; UK: United Kingdom.
Source: Cancer Research UK. CLL statistics.[14]

1.3.2 Disease Burden

1.3.2.1 Impact on health-related quality of life

Initiating treatment in the earlier stages of CLL, when symptoms are not exhibited, has not been shown to have any added benefit. [28] In a meta-analysis of a series of randomised trials, the effects on overall survival (OS) of immediate versus deferred CIT for early stage CLL, or as a first-line treatment for progressed disease, found that there was no statistically significant difference in survival.[28] Many patients therefore live a long time with the disease prior to treatment, remaining in the 'Watch and Wait' treatment stage, undergoing regular check-ups to monitor progression. In 2024, an estimated 13,000 people were on the 'Watch and Wait' list in the UK, with half of these patients expressing feelings of increased concern and anxiety since diagnosis, with one in eight feeling constantly depressed or anxious.[29-31] For elderly patients, who constitute the majority of the CLL population, regular GP visits for check-ups can be challenging due to mobility limitations and proximity to their local healthcare providers.[29]

Patients with CLL experience substantially worse health-related quality of life (HRQoL) in terms of fatigue, anxiety, physical functioning, social functioning, depression, sleep disturbance and pain.[20, 27, 32] The severity of fatigue is higher in CLL patients compared to published population norms and worsens as the disease progresses.[33] An international survey (n=1,482) reported statistically significant higher levels of fatigue, in 80% of respondents, than the general population (mean Brief Fatigue Inventory [BFI] scores of 2.8 vs 2.2; p <0.001).[33] Mean BFI scores for low-risk, intermediate-risk and high-risk CLL patients were 2.2, 2.6 and 3.6 respectively.[33] Emotional wellbeing FACT-General (FACT-G) scores were also significantly lower for patients with CLL compared to that of the general population (p<0.001), highlighting the psychological burden of CLL.[33]

As CLL progresses, it can have an increasingly negative impact on patients' families and carers HRQoL, as the patients' ability to remain independent decreases.[34]

Choice of treatment has a large impact on a patient's HRQoL, especially in those with R/R CLL, which predominantly affects an elderly population. These patients have limited effective targeted treatment options available. Clinical expert opinion elicited for this submission emphasised that patient QoL is a critical consideration, as the ease of treatment significantly influences patient preferences and satisfaction.[35] Many of these patients have at least one comorbidity; common comorbidities – including secondary malignancies, cardiovascular, and respiratory diseases, and metabolic disorders – often result in patients taking a median of two prescription medications daily at the time of diagnosis.[36] These factors collectively impact overall health status and daily functioning, further highlighting how comorbidities and treatment burden can profoundly affect QoL in this patient population.

Elderly patients may exhibit reduced fitness or impaired organ function, which, combined with comorbidities, can compromise their ability to tolerate certain therapies, such as BCL2i or PI3Ki therapy. Patients with R/R CLL who have previously received BTKi therapy may struggle with the intensive treatment requirements associated with BCL2i, including the dose escalation process, therefore subsequent treatment with BCL2i may not be advised.[35] Furthermore, PI3Ki therapy can lead to an increased risk of severe infections, immune-mediated toxicities, and treatment-related deaths, which outweigh the benefits in this already vulnerable population.[27] This uncertainty of subsequent treatments can lead to feelings of anxiety due to uncertainty as to whether another treatment will be available if the treatment is not well-tolerated.[37]

1.3.2.2 Symptom burden

In Youron *et al.* (2020), the treatment-naïve population reported inferior patient reported outcomes (PRO) in physical condition (mean: 16.2 vs 11.8), pain (mean: 6.3 vs 2.9), nausea/vomiting (mean: 7.9 vs 2.1), appetite loss (mean: 6.3 vs 2.9), constipation (mean: 15.8 vs 1.3), and diarrhoea (mean: 3.1 vs 0) than the general population.[38] The CLL8 trial (n=817; treatment-naïve population study conducted at 190 centres across 11 countries [Australia, Austria, Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, New Zealand and Spain]) further corroborates these findings where significantly poorer baseline scores were highlighted for all items of the EORTC-QLQ-C30, except for pain, compared to the general population ($p<0.0010$).[39, 40]

Infection is a major cause of morbidity and mortality in patients with CLL, as due to an increased number of abnormal white blood cells, patients are more susceptible to infection.[20, 41] Infections occur at least once during treatment in more than 50% patients and contribute to 30% to 50% of deaths in patients with CLL.[42] There is conflicting evidence on the relationship of severe infections and treatment received. Patients with heavily pre-treated fludarabine-refractory CLL have high susceptibility to developing serious infections;[33] a similar risk was also observed in patients treated with ibrutinib (N=263).[43] This risk can be reduced by treatment with more novel therapies, though the risk of infection remains high; between 10–30% for patients treated with BCL2i or novel BTKi.[44]

CLL patients are prone to a number of further complications due to the disease itself, or treatment, such as Richter's transformation (occurs in 2–10% of patients), tumour lysis syndrome (TLS; caused by the broken-down cancer cells and results in kidney failure), and are at an increased risk of developing secondary cancers (such as acute myeloid leukaemia [AML] and myelodysplastic syndromes [MDS]).[11, 25] Elderly patients often face increased symptom burden and treatment related challenges as the majority of patients who present to their GP with a CLL diagnosis, are taking a median of two prescription medications per day, as a result of a diverse variety of comorbidities.[36]

The five-year relative survival rates of patients diagnosed with CLL in England range from 95% for patients <60 years, to 65% for those >80 years, shown in Table 7.

Table 7: Five-year survival rates for CLL in England in 2022

	<60 years	60 to 69 years	70 to 79 years	≥80 years
5-year survival rate (%)	95	90.8	83.6	69.4

Abbreviations: CLL: chronic lymphocytic leukaemia.
Source: Haematological Malignancy Research Network: Survival. Chronic lymphocytic leukaemia.[45]

Survival rates are dependent on disease stage, patient age and the presence or absence of del(17p) and/or *TP53* mutations. Patients diagnosed with 'high-risk' CLL (Binet Stage C) have a reduced survival rate whereas those diagnosed with 'lower-risk' CLL (Binet Stage A) have minimal reduction in overall survival rates compared, as shown in Table 8.

Table 8: Proportion of patients surviving 1-, 3- and 5-years by Binet stage

Binet Stage	1-year survival (%)	3-year survival (%)	5-year survival (%)
A	97.6	93.9	88.7
B	97.2	89.6	79.9
C	77.8	66.1	58.4

Source: Haematological Malignancy Research Network: Survival. Chronic lymphocytic leukaemia.[45]

1.3.2.3 Economic burden

The long-term, progressive, and relapsing nature of CLL, is associated with substantial economic burden. A retrospective chart review, conducted in the UK (17 sites), Spain (18 sites), and Italy (16 sites) investigated the economic burden of CLL patients who initiated treatment between 2011 to 2012.[46] Patients in the UK had the highest percentage (89.4%) of having two or more comorbidities, and the highest rate of patient hospitalisation.[46] Notably, all patients were prescribed then-standard CIT.[46] Patients utilised outpatient services and laboratory monitoring, with hospitalisation costs being the largest expense in the UK, Spain and, Italy at €10,291, €3,284 and €1,312 respectively.[46] Outpatient care represented the second-highest category of costs.[46]

Recent data on the economic burden of CLL are limited from the UK perspective. However, data from studies conducted (following the development of BTKi), in Europe and North America, are supportive of an increased burden on healthcare systems from treating CLL.[47] In particular the average cost to treating prevalent CLL patients in Germany was estimated at €4,946 per year from the payer's perspective and €7,910 per year from a societal perspective (N=4,198), with inpatient hospital stays and the costs of treatment acquisition being the main cost drivers of the disease.[47] In a retrospective study of US claims data of patients who were previously treated with a covalent BTKi (N=166) or both a covalent BTKi and BCL2i (N=20), the health care resource utilisation (HCRU) and costs associated with treating CLL were investigated. The costs associated with outpatient visits, emergency room visits, and inpatient visits were higher in the post-cBTKi population, whereas the drug cost was higher in the dual-exposed population.

Table 9: Health care costs associated with patients with R/R CLL

Cost category	Post-cBTKi population	Dual-exposed population
All outpatient	$1,339	$1,370
Emergency room	$85	$0
Inpatient	$4,066	$2,787
Drug	$9,632	$12,978

Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; cBTKi: covalent BTKi; CLL: chronic lymphocytic leukaemia.
Source: Priyadarshini *et. al* (2023).[48]

1.3.3 Clinical pathway of care

For managing early-stage CLL, in asymptomatic patients at Binet Stage A or B, the 2022 guidelines from the British Society for Haematology (BSH), and the iwCLL recommend a 'Watch and Wait' strategy.[25, 49] Likewise, the European Society for Medical Oncology (ESMO) also recommends against the need for front-line treatment in patients with asymptomatic CLL as there is no confirmed benefit to survival for initiating treatment in these patients.[50] Blood cell counts and clinical examinations are recommended every three months during the first year, then every three to 12 months thereafter until a progression event is identified.[25, 49, 51] The majority of these patients may never require treatment during their lifetime.[52]

Upon progression to an active disease state, patients can benefit from initiating first-line treatment. For optimal first-line treatment, the presence of high-risk mutations, fitness level and age is considered. Of note, there are no standardised age cutoffs where patients with CLL are considered to be ‘older’ or ‘younger’; CLL is predominantly a disease of the elderly. However, the clinical care pathway in treatment guidelines often differ for patients younger or older than 65, with clinical experts in the UK suggestive of differences in care prescribed for patients younger or older than 70.[25, 35, 49]

Screening for 'high-risk' CLL is advised, characterised by presence del(17p) or *TP53* mutations, prior to each treatment line. Additionally, *IGHV* mutation analysis is recommended to identify patients who are 'fit and young' and therefore have the potential to achieve long-term remission with CITs i.e., FCR. *IGHV* mutation analyses which identify patients who are ‘fit and older’ may also achieve durable responses with a 12-month fixed-duration regimen of the BCL2i, venetoclax, in combination with obinutuzumab (VenO).[25] As an alternative option, patients who are fit may also be considered suitable for treatment with venetoclax in combination with ibrutinib (VenI), should they present with high-risk CLL.[25]

Table 10 summarises the NICE guidance for first-line treatments in adults with CLL, and Figure 2 summarises the clinical pathway of care in the UK for adults with untreated and R/R CLL based on a combination of published NICE guidance, BSH treatment guidelines and UK clinical expert opinion.[25, 35]

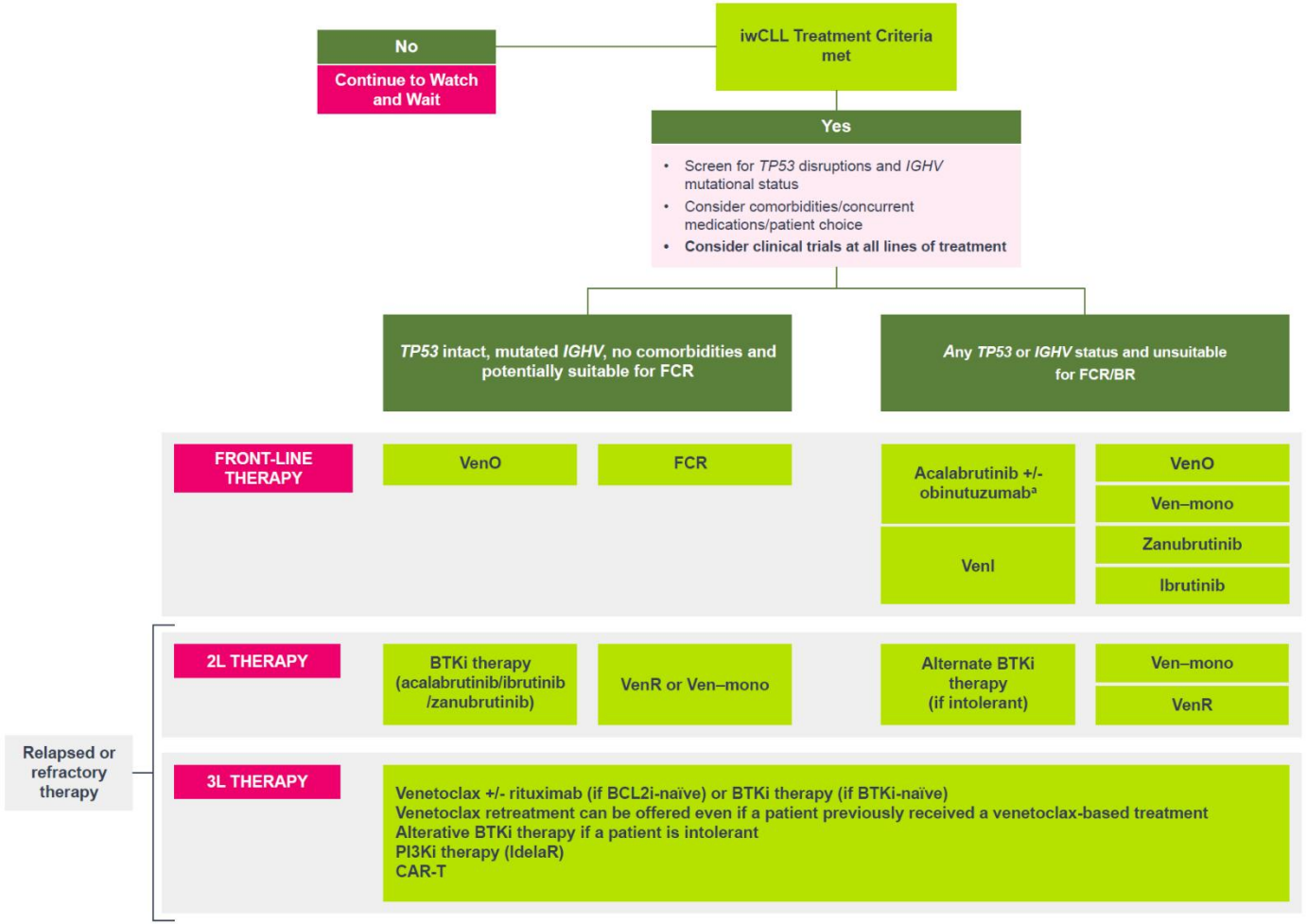
Table 10: Treatments recommended for previously untreated CLL (NICE technology appraisals)

Treatment	NICE recommendation	Date published	Regimen
Zanubrutinib (TA931)	• People with no 17p deletion or *TP53* mutation and FCR or BR is unsuitable • People with a 17p deletion or *TP53* mutation	22 November 2023	Continuous regimen with zanubrutinib (oral) administered until disease progression or unacceptable toxicity[53]
VenI (TA891)	People with untreated CLL	31 May 2023	Fixed duration regimen with ibrutinib (oral) and venetoclax (oral), for a total of 15 cycles of ibrutinib and 12 cycles of venetoclax[54]
Venetoclax monotherapy (TA796)	People with a 17p deletion or *TP53* mutation, or whose disease has progressed after a BCL2i	15 June 2022	Fixed duration regimen with venetoclax (oral)[54]
Acalabrutinib (TA689)	• People with no 17p deletion or *TP53* mutation and FCR or BR is unsuitable • People with a 17p deletion or *TP53* mutation	21 April 2021	Continuous regimen with acalabrutinib (oral) administered until disease progression or unacceptable toxicity[55]
VenO (TA663)	• People for whom fludarabine-based therapy or bendamustine-based therapy is suitable • People with no 17p deletion or *TP53* mutation and FCR or BR is unsuitable • People with a 17p deletion or *TP53* mutation	9 December 2020	Fixed duration regimen with venetoclax (oral) and obinutuzumab (IV), for a total of 12 cycles[54]
Ibrutinib (TA429)	People who are high-risk (del17p/*TP53* mutation) or in patients for whom CIT is unsuitable	25 January 2017	Continuous regimen with ibrutinib (oral) administered until disease progression or unacceptable toxicity[56]
Idelalisib with rituximab (TA359)	People with a 17p deletion or *TP53* mutation	28 October 2015	Continuous regimen with idelalisib (oral) administered until disease progression or unacceptable toxicity,[57] in combination rituximab (IV)[58]
O-Clb (TA343)	People for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable	2 June 2015	Fixed duration regimen with chlorambucil (oral) and obinutuzumab IV)[59, 60]
BR (TA216)	People for whom fludarabine combination chemotherapy is not appropriate	23 February 2011	Fixed duration regimen with bendamustine (IV), in combination with rituximab (IV)[58]

FCR (TA174)	People for whom fludarabine in combination with cyclophosphamide is considered appropriate	22 July 2009	Fixed duration regimen with rituximab (IV) and fludarabine and cyclophosphamide (both IV or oral)[61]

Abbreviations: BCL2i: B-cell lymphoma 2 inhibitor; BR: bendamustine with rituximab; CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukaemia; del17p: deletion of chromosome 17p; FCR: fludarabine and cyclophosphamide with rituximab; IV: intravenous; NICE: National Institute for Health and Care Excellence; O-Clb: obinutuzumab in combination with chlorambucil; TA: technology appraisal; TP53: tumour protein p53 gene; VenI: venetoclax in combination with ibrutinib; VenO: venetoclax in combination with obinutuzumab.
Sources: Eli Lilly. Data on File. Clinical Validation Meeting Minutes;[35] 2. National Institute for Health Care and Excellence. [TA174]; [TA216]; [TA663]; [TA891]; [TA343]; [TA931]; [TA689]; [TA359]; [TA429]; [TA796].[27, 31, 37, 62-68]

Figure 2: The clinical pathway of care treatment algorithm for CLL in the UK



[a] Combination of acalabrutinib with obinutuzumab has not yet been recommended by NICE in the UK. **Abbreviations:** 2L: second-line; 3L: third-line; BCL2i: B-cell lymphoma 2 inhibitor; BR: bendamustine in combination with rituximab; BSH: British Society for Haematology; BTKi: Bruton's tyrosine kinase inhibitor; CAR-T: chimeric antigen receptor T-cells; CIT: chemoimmunotherapy; FCR: fludarabine in combination with cyclophosphamide and rituximab; IdelaR: idelalisib in combination with rituximab; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; NICE: National Institute for Health and Care Excellence; VenI: venetoclax in combination with ibrutinib; Ven–mono: venetoclax monotherapy; VenO: venetoclax in combination with obinutuzumab; VenR: venetoclax in combination with rituximab. **Source:** Adapted from Walewska et al. (2022).[25]

1.3.3.1 Current treatments in adults with R/R CLL who have had at least one previous therapy

Disease relapse alone is not a criterion to restart therapy unless the disease is symptomatic.[16] The 2022 BSH guidelines, ESMO guidelines and iwCLL recommend managing those who relapse in the absence of active disease, with a 'Watch and Wait' approach.[16, 25, 49] Upon progression to active disease, for those with relapsed/refractory (R/R) CLL, it is important to consider:

- The number and type of previous therapies
- The intensity of previous therapies (such as intensive CIT therapies)
- The duration of response to previous therapies
- Whether the patient has 'high-risk' CLL (del[17p]/*TP53* mutations)
- The number of patient comorbidities

Current licensed therapies in R/R CLL are BTKi, BCL2i and phosphoinositide 3-kinase inhibitors (PI3Ki).[25] After at least one cycle of CIT, BTKi, PI3Ki and BCL2i, alone or in combination with anti-CD20 antibodies, comprise standard treatment options for relapsed CLL, regardless of whether *TP53* is disrupted or intact.[25]

Decisions by NICE, 2022 BSH guidelines, ESMO and iwCLL inform the clinical pathway of care in the UK. A summary of the NICE guidance for patients with R/R CLL are presented in Table 11.[25, 27, 37, 49, 66-69]

Table 11: Current NICE guidance in adults with R/R CLL

Therapy line	Intervention Class	Intervention	Conditions of use
Treated CLL	BTKi	Zanubrutinib [TA931]	For those with R/R CLL
		Acalabrutinib [TA689]	For people who have had at least one previous therapy
		Ibrutinib [T429]	For people who have had at least one previous therapy
	BCL2i	Venetoclax monotherapy [TA796]	For people with a 17p deletion or *TP53* mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor or, For people without a 17p deletion or *TP53* mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor.
		Venetoclax with rituximab [TA561]	For people who have had at least one previous therapy
	PI3Ki	Idelalisib, in combination with rituximab [TA359]	For people whose disease has been treated but has relapsed within 24 months

Abbreviations: BCL2i: B-cell lymphoma 2 inhibitors; BTKi: Bruton tyrosine kinase inhibitors; CLL: chronic lymphocytic leukaemia; PI3Ki: phosphoinositide 3-kinase inhibitors; TA: technology appraisal; TP53: tumour protein p53 gene.
Sources: Eli Lilly. Data on File. Clinical Validation Meeting Minutes;[35] 2. National Institute for Health Care and Excellence. [TA174]; [TA216]; [TA663]; [TA891]; [TA343]; [TA931]; [TA689]; [TA359]; [TA429]; [TA796].[27, 31, 37, 62-68]

Sequencing of therapies for R/R CLL is recommended by the 2022 BSH guidelines and the ESMO guidelines, however, there is little data available on the ideal sequencing strategy when patients relapse following targeted agents.[25, 49] The treatment sequence suggested by the BSH is presented in Table 12.

Table 12: Treatment sequencing options for patients with relapsed CLL

Relapsed therapy	Suggested sequence
BTKi	BCL2i or PI3Ki[a]
PI3Ki	BTKi or BCL2i
BCL2i/BTKi	PI3Ki or AlloSCT
BCL2i/BTKi/PI3Ki	AlloSCT
Venetoclax Obinutuzumab	BTKi or Venetoclax with Rituximab[b] or PI3Ki[a]
Venetoclax monotherapy	BTKi or PI3Ki[a]
Venetoclax with Rituximab	BTKi or venetoclax monotherapy or PI3Ki[a]

[a]BTKi or BCL2i are the preferred options in those naïve to those classes. [b]Only in cases where the patient has not relapsed whilst on venetoclax combination treatment, and where patients have had at least 12 months in remission.
Abbreviations: AlloSCT: allogeneic stem cell transplant; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton's tyrosine kinase inhibitor; PI3Ki: phosphoinositide 3-kinase inhibitor.
Source: 2022 BSH guidelines.[25]

The BSH guidelines recommends, if a patient relapses on a targeted agent, treatment should be continued for as long as the patient derives clinical benefit until the subsequent targeted therapy is available, as there is a risk of rapid progression once therapy is discontinued.[25, 35] This approach of treating beyond relapse was supported by UK clinical experts who noted that patients may often wish to continue on targeted treatments to maintain the clinical benefit for as long as possible.

For patients with R/R CLL, the treatment sequence suggested within the ESMO guidelines broadly align with that recommended by the BSH. However, following an interim guideline update in 2024, ESMO recommend patients be considered for treatment with a non-covalent BTKi e.g., pirtobrutinib, following relapse or refractoriness to a cBTKi.[50] This recommendation was made in the context of pirtobrutinib having demonstrated a tolerable and efficacious profile in the Phase 2 BRUIN trial.[2]

1.3.3.2 Limitations of current treatments and unmet need

Limitations of current treatments for patients with R/R CLL

Despite there being several treatment options for patients with CLL, current therapies present several limitations and shortcomings which contribute to substantial patient burden. Adverse events (AE) associated with treatment include anaemia which can lead to fatigue, neutropenia leading to infection and thrombocytopenia which is associated with bruising.[64]

CIT, previously the standard first-line treatment for CLL prior to the introduction of the then novel BCL2i and covalent BTKi, poses potential toxicities to the liver, kidneys, heart, lungs, nervous system, or other organ systems.[16] As a result, CIT may need to be discontinued after a fixed duration treatment and therefore may not be the preferred treatment choice by many patients.[9, 16] Richter's transformation has also been reported in approximately 2% to 10% of patients treated with CIT, wherewith the disease becomes highly aggressive and prognosis is dismal;[70, 71] median survival of patients with Richter's transformation is 12 months.[72] Patients with del(17p) or *TP53* mutations appear relatively resistant to standard chemotherapy regimens using alkylating drugs and/or purine analogues.[16]

Clinical experts in the UK were consulted for their views on the relevance of CIT in UK clinical practice. Experts unanimously agreed that CIT is primarily regarded as a historical reference point in R/R CLL, used mainly to inform decisions regarding treatment suitability.[35] It was acknowledged that CIT is soon to be phased out of treatment guidelines.[35]

Fixed-duration venetoclax treatments (a type of BCL2i) are usually given in combination with therapies administered using intravenous (IV) infusions, necessitating regular in-person appointments.[73] This can be challenging for patients who are deemed frail and elderly, or due to socioeconomic factors including the need for transport to clinics which may not be in close proximity to their residence. Treatment with venetoclax also necessitates an intensive schedule of care and monitoring, particularly during venetoclax dose escalation; this is often difficult for these patients to adhere to.[35] An international cohort of 342 venetoclax-treated patients, outside of clinical trials, compared the efficacy and safety in patients ≥75 years compared to those <75 years, when treated with venetoclax monotherapy, and found that older patients discontinued therapy more frequently due to toxicity.[74]

Similar concerns with access to venetoclax were cited by UK clinical experts approached in support of this submission.[35] Clinical experts were in alignment that the intense monitoring requirements of venetoclax therapy, meant that treatment with venetoclax-containing regimens were more easily facilitated in larger NHS trusts where the necessary monitoring facilities were readily available. In smaller trusts the inpatient monitoring requirements for venetoclax treatment could result in competition for the limited number of hospital bed spaces, with decisions needing to be made on patient priority.[35] Despite these considerations clinical experts acknowledged that if a venetoclax-containing regimen was the most appropriate treatment for a patient, they would usually be able to access it. However, all clinical experts signalled the need for alternative treatments that do not have such monitoring requirements. Should such a tolerable and efficacious alternative be available for these patients, clinicians would consider prescribing these ahead of venetoclax-containing regimens for eligible patients.[35]

PI3Ki have been associated with a higher risk of infection and associated death.[27] Patients on IdelaR have been reported to experience several severe adverse events (SAE), including diarrhoea/colitis, which has been reported to continue with a median onset of more than six months of therapy.[75] Acquired resistance and intolerance due to AEs may have contributed to treatment discontinuation among these patients.[75] Drug interruption and steroid therapy are required for rapid resolution, and following this many patients may be reluctant to resume treatment.[75]

The rituximab portion of IdelaR therapy is also administered intravenously, and therefore similar considerations of patient access to those discussed for the fixed-duration venetoclax treatments are applicable to treatment with IdelaR. For added context, IV treatment (or infusions) require

inpatient admission or visits to outpatient healthcare facilities for administration. In addition to the socioeconomic barriers to access discussed earlier, the insertion of the IV needle may be associated with added discomfort or anxiety. In a literature review conducted by Eek *et al.* (2016), undertaken to evaluate patient preferences regarding treatment modalities, it was found that patients receiving cancer therapies reported a clear preference for oral treatments over IV options.[76] Patients perceive oral administration positively, citing attributes such as the ability to receive treatment at home, increased convenience and a lower likelihood of contraindications and AEs associated with IV or infusion-based therapies.[76] These factors collectively contribute to a perceived improvement to patient QoL for those on oral treatment regimens.

Relatedly, BTKi are all administered orally, thereby avoiding the socioeconomic barriers and impediments to QoL associated with fixed-duration venetoclax treatments or IdelaR. However, while BTKi treatment reduces CLL symptoms and improves patient HRQoL, the tolerability and AE profile is highly dependent on the generation of drug being used. For example, treatment with ibrutinib – a first generation BTKi – is linked with increased susceptibility to cardiovascular complications such as atrial fibrillation or hypertension, owing to a less selective mechanism of action.[77] Discontinuation due to cardiovascular AEs are therefore commonplace following treatment with ibrutinib.[77] Second generation BTKi such as zanubrutinib and acalabrutinib are more selective in their mechanism of action and therefore linked with fewer treatment-emergent cardiovascular events.[77] However, intolerance to second-generation BTKi have also been reported, with clinical experts suggesting that between 20 – 30% of patients treated with a second-generation BTKi may discontinue due to AEs. When also considering the proportion of patients who progress on BTKi treatment, this figure for discontinuation may be greater than 50%.[78, 79]

It is important to note that progression on BTKi treatment is often a hallmark of BTKi resistance, mediated by mutations in the BTK protein at cysteine position 481 (C481), affecting the covalent binding of BTKi and by activating mutations in the BTK downstream target, *PLCG2*.[80] The development of resistance or intolerance to existing BTKi therapies underscores the urgent need for new, efficacious treatments with improved safety profiles, particularly for patients who have tried at least one BTKi or BCL2i, or those who cannot tolerate current options. As noted by clinical experts approached for comment in this submission, non-covalent BTKi, such as pirtobrutinib, are therefore crucial for overcoming resistance mediated by BTK mutation at C481, offering these patients an additional treatment option.[80]

Unmet need in a dual-exposed population

Patients with R/R disease who progress after covalent BTKi therapy face a significant clinical challenge, with limited effective treatment options and generally poor outcomes.[81] Prognosis is especially poor for those who become refractory to both BTKi and BCL2 inhibitors, highlighting a major unmet need for new therapies.[82] In a retrospective chart review study, conducted from 2021 to 2023, in patients with CLL who were R/R to BTKi and received BCL2i response rates to subsequent treatments were low, with only 23.5% achieving a complete or partial response after failing both drug classes.[82] Disease progression and Richter transformation were common (84% and 21%, respectively), and most deaths were a result of disease progression.[82]

Clinical expert opinion sought for this submission emphasised that there is a key unmet need for more efficacious treatment options in CLL patients who are dual-exposed.[35] One of the major challenges is the lack of available options in this population. Currently, the standard of care in this context is not clearly defined, especially for patients with R/R CLL who fail treatment with

both BTKi and BCL2i therapy. Although guidelines recommend PI3K inhibitors as an option – and some recommend clinical trials – PI3Kis are associated with resistance over time and both are associated with safety concerns, which further complicate their use.[25, 49] Additionally, these agents are associated with significant toxicity profiles, including immune-related AEs, infections, and hepatotoxicity, which increase safety concerns and often lead to treatment discontinuation.[75] Similar concerns on the safety profile of PI3Kis were also raised by UK clinical experts approached for this submission,[35] who would opt for more tolerable alternatives over PI3Ki for dual-exposed patients, were these to be available in the UK.

Furthermore, there is a proportion of patients who may be treated with VenI as a first-line therapy for their CLL (see Figure 2 and Table 10, above). These patients are dual-exposed to BCL2i and cBTKi in combination, as opposed to sequentially. Treatment sequencing for patients who progress on VenI are not established in the UK, neither within the BSH treatment guidelines, nor in standard UK clinical practice. Therefore, UK clinical experts were of the opinion that there remains a substantial unmet medical need for effective, well-tolerated therapies in this dual-exposed population.[35]

In the pivotal BRUIN CLL-321 trial, pirtobrutinib demonstrated efficacy and a more favourable safety profile in patients with R/R CLL who were previously treated with a covalent BTKi, compared to its most relevant comparator (IdelaR).[83] Notably, the pivotal BRUIN CLL-321 trial demonstrated that pirtobrutinib significantly improves progression-free survival and delays the need for subsequent therapy within a heavily pre-treated, high-risk, patient population (see Section 2.6 for details).[6]

Unmet need in the post-covalent BTKi subpopulations

Post-cBTKi population, but cannot receive current SoC

For patients previously treated with covalent BTKi, BSH and ESMO guidelines recommend venetoclax-based therapies as the next line of treatment.[25] However, there is a subset of this population, for whom venetoclax is contraindicated or currently unsuitable (discussed below), resulting in reliance on suboptimal treatment options (e.g., PI3Ki's).

UK clinical experts stated that patient-unsuitability for venetoclax is influenced by a number of factors, such as past therapies, level of frailty and comorbidities, disease burden and patient choice. Should any of these circumstances change and venetoclax be deemed the best option for these patients, previously unsuitable patients may ultimately be treated with a venetoclax-containing regimen. While suitability to venetoclax may change over the course of the disease evolution for individual patients, the clinical experts consider there to be an unmet need in patients with R/R CLL who have previously received a BTKi therapy, and are currently unsuitable for treatment with venetoclax, based on the factors discussed earlier.

There are several factors which can make patients unsuitable for venetoclax therapy, that were raised by clinical experts consulted for this submission:[35]

- **Disease-related factors:** Individuals with measurable lymph nodes larger than 10 cm in diameter, lymphocyte counts exceeding 25 × 10^9/L and lymph nodes between 5–10 cm, or lymphocyte counts above 100 × 10^9/L are at a higher risk of TLS.
- **Treatment-related factors**: Intense prophylaxis with rehydration and rasburicase therapy, alongside continuous inpatient monitoring is advised for patients receiving venetoclax who are

at risk of TLS.[84] However, some patients cannot tolerate the large fluid volumes due to other health issues.

- **Patient-related factors:** Individuals with compromised organ function or other health issues, such as impaired renal function (eGFR <30 mL/min), or heart failure, are significantly more likely to develop TLS.[35, 54] Combined with a very high risk of TLS, and insufficient organ function to maintain hydration during treatment, the TLS risk may outweigh the therapeutic benefits typically associated with venetoclax.[35]

UK clinical experts therefore unanimously agreed that there is an unmet need for additional treatment options for patients who have received prior treatment with covalent BTKi but cannot receive current BCL2i.[73] They noted a preference for pirtobrutinib therapy in this sub-population due to the observed PFS benefit in venetoclax-naïve patients (presented in Section 2.6) compared to those with prior venetoclax exposure. In the pivotal BRUIN CLL-321 trial, patients were stratified by venetoclax exposure, with around 50% being venetoclax-naïve, and the median TTNT was longer in these patients compared to those with prior venetoclax exposure. However, despite the associated risks discussed here, the clinicians noted that due to the limited availability of effective treatment options in later lines of therapy, most clinicians would be unlikely to exclude the use of BCL2i therapies completely.[35]

Additionally, as per the guidelines published by the BSH and ESMO, rechallenge with an alternative BTKi is an option should initial discontinuation in patients with R/R CLL be due to AEs or intolerance rather than refractoriness.[25] Usually this would entail switching from first-generation BTKi (e.g., ibrutinib) to second-generation BTKi (e.g., acalabrutinib or zanubrutinib). However, UK clinical experts were unlikely to consider cBTKi rechallenge in patients with clear evidence of disease progression as it is a hallmark of the development of cBTKi resistance mutations.[35]

Therefore, given the above, there is a clear unmet need for efficacious and tolerable alternatives to current SoC (BCL2i and cBTKi) for patients who have previously received cBTKi, but cannot receive current SoC.

Post-cBTKi population, but can receive current SoC

As presented in Table 12, treatment sequencing guidelines published by the BSH recommend the use of BCL2i following relapse or disease refractory to treatment with covalent BTKi, should a patient be naïve to BCL2i therapy. This treatment sequence is supported by UK clinical experts, and suggests continuing BTK inhibition with BTKi agents, such as pirtobrutinib, to maximise benefits of this effective mechanism before transitioning to a BCL2i, such as venetoclax once the BTK pathway is exhausted. However, there are a number of limitations to treatment with venetoclax that may preclude its use in eligible patients, key amongst which is patient preference, including for treatments with a familiar mode of administration (oral versus IV).[35]

Additional limitations of BCL2i have been discussed in prior sections of this submission, however, the presence of these limitations highlight the unmet need for tolerable and efficacious alternatives to BCL2i in these patients. As noted earlier, clinical experts consulted for this submission also signalled their support for any suitable alternatives to venetoclax in this subset of patients, and may prefer to prescribe these over venetoclax to bypass the barriers to access discussed above.[35]

There is also a small proportion of patients who initiate R/R treatment with BTKi, but discontinue due to the emergence of AEs or intolerance to treatment. Clinical experts estimate that this applied to ~20% of patients treated with a BTKi in UK clinical practice.[35] This estimate is broadly in line with studies of patients with R/R CLL treated with a BTKi.[85]

However, clinical experts note that certain AEs e.g., cardiovascular events, while more common with ibrutinib have also been reported with greater frequency in patients treated with acalabrutinib or zanubrutinib.[35] As such, clinical experts are of the opinion that there remains an unmet need for more tolerable alternatives to acalabrutinib or zanubrutinib for patients who discontinue BTKi treatment due to these AEs, and who may also be at a heightened risk of experiencing these AEs should they be rechallenged with BTKi.[35]

1.3.3.3 Proposed placement of pirtobrutinib

The proposed placement of pirtobrutinib is shown in Figure 3. In line with its anticipated marketing authorisation (see Section 1.1), pirtobrutinib is positioned after patients relapse or become refractory to covalent BTKi therapy. For ease of reference this is referred to as the overall post-covalent BTKi population in this submission.

Within this population, Lilly acknowledge the presence of three distinct subsets of patients, each with unmet needs that are anticipated to be addressed by the introduction of pirtobrutinib. The limitations to the available treatment options within these subsets and the respective unmet needs have been discussed in Section 1.3.3.2.

In the following sections, the proposed position of pirtobrutinib within these subsets are discussed, including the comparators being addressed in this submission, and the rationale for these decisions. A summary of the positioning and the relevant comparators addressed in each sub-population are presented in Table 1.

Dual-exposed population

As per the BSH and ESMO guidelines for CLL, treatment sequencing is advised following relapse or refractoriness to treatment.[25, 49] Patients who progress on BTKi or BCL2i at first-line are typically treated with BCL2i or BTKi, respectively, at second-line.[25]

For patients who relapse or become refractory to covalent BTKi and subsequently receive treatment with a BCL2i-containing regimen, it is anticipated that patients would be treated with pirtobrutinib after receiving treatment with these two therapies. This is in line with the interim update to the ESMO treatment guidelines which are supportive of the use of non-covalent BTKi in this dual-exposed population.[49] For the proportion of patients in whom treatment is initiated with a BCL2i and covalent BTKi combination regimen, pirtobrutinib is also positioned as a treatment option for this group of patients. These two populations define the dual-exposed population discussed in this submission.

It is anticipated that treatment with pirtobrutinib in the dual-exposed population would be as an alternative to IdelaR, the only relevant comparator therapy in this sub-population, based on treatment sequencing guidelines by the BSH, ESMO and aligned with UK clinical expert opinion.[25, 35, 49]

Robust comparative evidence for pirtobrutinib versus IdelaR are available from the pivotal BRUIN CLL-321 trial discussed in Section 2 of this submission.

It should be noted that treatment guidelines by the BSH are supportive of the use of venetoclax-monotherapy (Ven-mono) as a third-line treatment following relapse on a BTKi, and subsequently fixed-duration venetoclax therapy.[25] However, UK clinical experts were unanimous in their opinion that Ven-mono should not be considered standard of care in the dual-exposed populations due to the lack of any prospective studies assessing its efficacy in these indications. Therefore, Ven-mono is not considered a relevant comparator in the dual-exposed population.[35]

Additionally, BSH guidelines also recommend the use of venetoclax with rituximab (VenR) at third-line, but only if a patient is BCL2i-naïve after receiving two previous lines of therapy.[25, 69] As, by definition, the dual-exposed population includes patients who were exposed to at least one previous line of BCL2i therapy, VenR would not be a suitable option for these patients, and therefore is not considered a relevant comparator to pirtobrutinib in the dual-exposed population.

Finally, while the BSH guidelines are supportive of the use of an alternative covalent BTKi after discontinuation of a previous covalent BTKi, this is only considered in patients who stopped treatment with the prior BTKi due to intolerance or safety concerns.[25] Clinical expert opinion obtained for this submission were in alignment with this treatment sequence and agreed that following relapse or refractoriness to a covalent BTKi, patients would not be rechallenged with other covalent BTKi.[35] As such, covalent BTKi are not considered to be relevant comparators to pirtobrutinib in the UK in those who are covalent BTKi-refractory.

Post-cBTKi population, but cannot receive current SoC

In line with treatment guidelines published by the BSH and ESMO, the treatment pathway for patients with CLL is highly individualised and includes considerations for symptom presentation, patient fitness, the presence or absence of genetic mutations, patient suitability to treatments and any previous treatments received i.e., whether they are R/R to any treatments in the pathway (as discussed in Section 1.3.3).[25]

Treatment sequencing guidelines (Table 12) recommend that patients who relapse on treatment to a cBTKi (at first-line) should be treated with BCL2i (venetoclax) before treatment with any other class of therapies e.g., PI3Ki (idelalisib).[25] Clinical expert opinion obtained by Lilly in support of this submission is indicative of a population of patients for whom BCL2i are not currently suitable.[35] Details of this population and the clinical expert opinion received are discussed in Section 1.3.3.2. It is anticipated that patients who relapse or become refractory to treatment with a cBTKi, and are currently unsuitable for BCL2i, would receive pirtobrutinib as a second-line therapy following its introduction in the UK.

As an alternative to BCL2i, some patients in the UK may be considered for re-treatment with an alternative cBTKi following initial discontinuation, as suggested in the BSH and ESMO treatment guidelines. However, it is important to note that these recommendations are limited to the small minority of patients who discontinue due to AEs or intolerance, rather than refractoriness. For most patients with R/R CLL, discontinuation from cBTKi is due to refractoriness; this is line with observed baseline treatment data for patients randomised to BRUIN CLL-321 and with UK clinical expert opinion. Therefore, these patients would not be suitable for re-treatment with cBTKi.

Given the above, for patients who cannot currently receive SoC, PI3Ki are the only available treatment option at second-line, after previous relapse or refractoriness to cBTKi. This position was validated with UK clinical experts who were in alignment, and agreed on the necessity of pirtobrutinib within this population.[35] As discussed earlier, high quality evidence comparing pirtobrutinib to IdelaR, in post-cBTKi patients, yet to be treated with BCL2i, are available from the pivotal BRUIN CLL-321 trial; these are reported in detail in Section 2.

Post-cBTKi population, but can receive current SoC

Clinical experts also expressed support for the use of pirtobrutinib as an alternative choice to BCL2i in patients with R/R CLL who were previously treated with a BTKi and are otherwise suitable for treatment with current SoC (BCL2i and BTKi).[35]

Clinical experts noted that treatment with venetoclax-containing regimens were intensive with the potential for serious side effects e.g., TLS.[35] Consequently, even when eligible for venetoclax, some patients and clinicians may prefer to avoid venetoclax-containing regimens in favour of alternative options (see Section 1.3.3.2).[35]

An additional consideration in this population is patient access to BCL2i. As discussed earlier, treatment with venetoclax is intensive; patients at high risk of TLS often require inpatient monitoring during initiation as prophylaxis. Clinical experts indicate that such inpatient monitoring is typically available at larger NHS trusts.[35] While this does not necessarily limit access to venetoclax for those with the greatest need, it can impact clinician preferences, with many clinicians expressing a desire for alternative therapies with fewer logistical barriers.[35]

Additionally, as noted earlier, patients may also be considered for re-treatment with an alternative BTKi, following discontinuation of a previous cBTKi due to the emergence of AEs or intolerance, but not refractoriness.[25]

Given these factors, pirtobrutinib is also positioned as a second-line therapy in the broader post-cBTKi population, for those who are suitable for current SoC, to address the unmet need in this sub-population.

Based on the treatment guidelines published by the BSH and ESMO the potential comparators of relevance in this sub-population include:

- IdelaR
- VenR
- Ven-mono
- Zanubrutinib
- Acalabrutinib
- Ibrutinib

Comparative efficacy between pirtobrutinib and IdelaR are available from BRUIN CLL-321. However, there is an absence of randomised controlled trials (RCT) comparing the efficacy and safety of treatment with pirtobrutinib to VenR, Ven-mono and the cBTKi. A robust feasibility assessment was therefore conducted to assess whether indirect treatment comparisons (ITC)

could be conducted to generate comparative efficacy estimates between these treatments (please refer to Section 2.10 for further details).

No relevant studies in the post-cBTKi population were identified for inclusion in the feasibility assessment, except for BRUIN CLL-321, the pivotal trial for pirtobrutinib comparing its efficacy and safety to treatment with Investigator choice of IdelaR and BR, in patients with post-BTKi R/R CLL. Therefore, the feasibility assessment was expanded to include all RCTs in R/R CLL, regardless of past exposure to BTKi.

However, the feasibility assessment (detailed in Section 2.10) identified considerable heterogeneity in treatment effect modifiers and prognostic markers across the included studies, especially with regards to prior treatment. Of note, prior treatment with a B-cell receptor (BCR) kinase inhibitor, e.g., BTKi, was identified as an important treatment effect modifier in R/R CLL.[86-89] Hence, combining studies with heterogeneous prior treatment regimens using the published clinical evidence of the potential comparators to pirtobrutinib, within any form of an ITC (with or without adjustment for other patient characteristics) was considered to result in an analysis favouring treatments studied in patients with less aggressive risk features and without exposure to a prior BTKi. Conducting an ITC with this degree of heterogeneity would result in uncertainty around the treatment effects and the conclusions drawn from such an analysis would be unreliable.

Alternative ITC methods were explored including a multi-level network meta-regression (ML-NMR) and a matched adjusted indirect comparison (MAIC) however, these options were also discounted as neither method can fully compensate for substantial differences in the trial populations. Therefore, ITCs for pirtobrutinib versus VenR, Ven-mono or the cBTKi were not conducted.

To address this evidence gap, clinical experts were consulted on the relevance of VenR, Ven-mono or cBTKi as comparators to pirtobrutinib in the post-cBTKi, suitable for current SoC population. As noted earlier, UK clinical experts stated that Ven-mono was not considered standard of care in the UK, in any of the sub-populations discussed in this submission. Therefore, it is also not considered a relevant comparator in the post-cBTKi population who can receive current SoC.[35]

Conversely, clinicians did consider VenR to be a relevant comparator to pirtobrutinib in the this population, in line with its NICE recommendation for use in R/R CLL (TA561).[69] However, all consulted clinicians acknowledged the difficulties in conducting any meaningful comparisons between these treatments due to the significant heterogeneity between the respective clinical trial populations.[35]

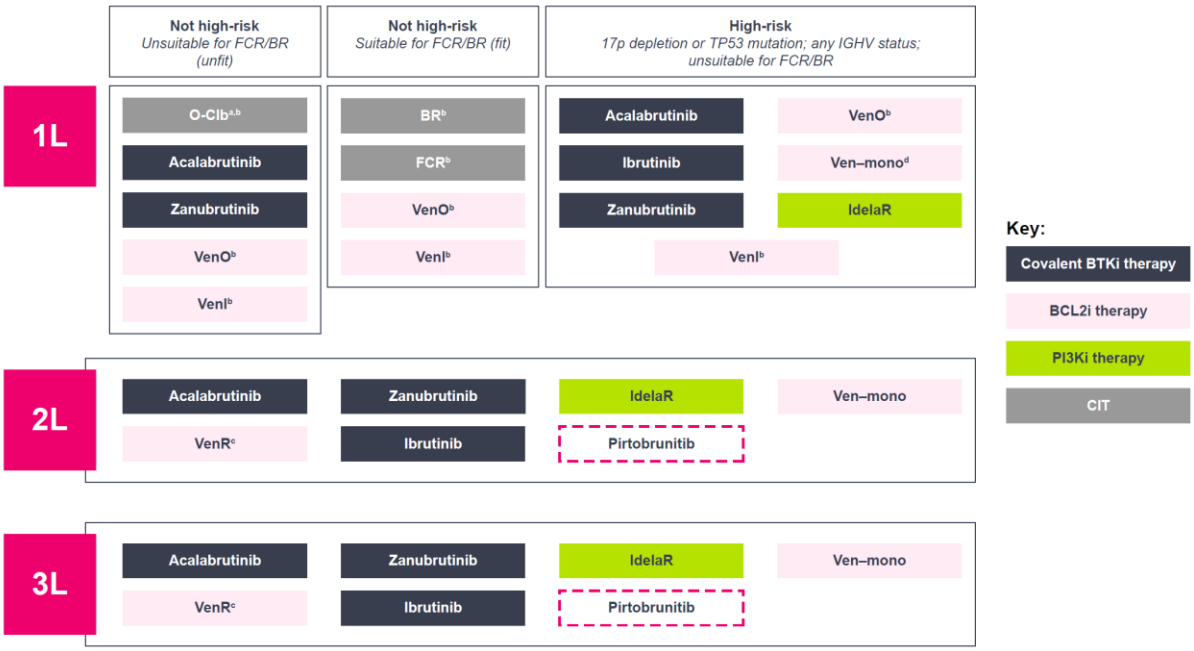
Given the above, Lilly acknowledge the relevance of VenR as a comparator to pirtobrutinib in this sub-population, however are unable to conduct meaningful comparative efficacy analyses, and by association, any meaningful economic analyses versus VenR in this submission, based on the available clinical evidence at this point in time.

With regard to the cBTKi, it is understood that only a small proportion of patients would be eligible for re-treatment with an alternative BTKi. This is due to the fact that in the majority of patients – as observed in BRUIN CLL-321 – patients discontinue prior cBTKi therapy due to refractoriness rather than intolerance. As discussed previously, comparative data on the effectiveness and safety of pirtobrutinib versus cBTKi in this population are also not available or

generable through ITC, as confirmed through the feasibility assessment conducted for this submission.

Given the above, cBTKi are not considered a relevant comparator to pirtobrutinib, and are therefore not addressed in the decision problem in this submission.

Figure 3: The expected positioning of pirtobrutinib in the clinical care pathway



Footnotes: [a] As per the 2022 BSH CLL guidelines, chlorambucil-based CIT is no longer recommended. [b] Therapies used for a fixed duration. [c] Rituximab is stopped after cycle 6 in VenR. [d] Only a first line therapy option for TP53-disrupted patients who are ineligible for a BTKi therapy.
Abbreviations: 1L: first-line; 2L: second-line; 3L: third-line; BCL2i: B-cell lymphoma 2 inhibitor; BR: bendamustine in combination with rituximab; BSH: British Society for Haematology; BTKi: Bruton's tyrosine kinase inhibitor; CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; IdelaR: idelalisib in combination with rituximab; O-Clb: obinutuzumab in combination with chlorambucil; TLS: tumour lysis syndrome; VenI: venetoclax in combination with ibrutinib; Ven–mono: venetoclax monotherapy; VenO: venetoclax in combination with obinutuzumab; VenR: venetoclax in combination with rituximab.
Source: Adapted from Walewska et al. (2022).[25]

1.4 Equality considerations

There are no identified equality considerations to the use of pirtobrutinib for CLL in patients who have previously had at least one BTKi.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A *de novo* systematic literature review (SLR) was originally conducted on 26th September 2023 (original SLR). An update search was conducted in February 2025 (update SLR) to identify any new evidence for the comparators of interest that had been published since September 2023.

The SLRs were conducted to identify all relevant clinical evidence evaluating treatments for patients with R/R CLL, given the limited data specifically available in those previously treated with a cBTKi, with the aim to inform comparative evidence for pirtobrutinib. In the original SLR (26th September 2023), a total of 4,985 unique records were identified after de-duplication, with 2,038 full-text records identifies for eligibility. Overall, 604 records presenting data on 380 clinical trials (reporting 191 unique trials in R/R CLL), and 224 observational studies were included in the SLR. Of the 191 unique trials identified in R/R CLL, 44 were comparative studies, with 25 RCTs identified. The update SLR (19th February 2025), identified a total of 2,704 records, with 1,776 eligible for full-text screening. Overall, 472 clinical trials (209 unique records in R/R CLL), and 311 observational studies were included in the SLR.

Full details of the original and update SLR, including the search strategy, study selection process and detailed results are presented in Appendix B.

2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified two unique trials in patients with R/R CLL, one RCT and one non-randomised study of interventions (NRSI). The RCT is the BRUIN CLL-321 study, and the NRSI is a Phase II trial of the investigational BTKi agent TL-895 (NCT02825836).[90] However, the BRUIN CLL-321 study is the only relevant study of interest for pirtobrutinib, with direct relevance to the decision problem of this appraisal.

The pivotal BRUIN CLL-321 trial provides the main body of evidence for this appraisal, used to support the marketing authorisation application for pirtobrutinib in adults with R/R CLL who have been previously treated with a BTKi. Details of the BRUIN CLL-321 trial presented in this submission are based on data reported within the clinical study reports (CSRs) included within the submission reference pack.[91] A summary of the clinical evidence from BRUIN CLL-321 is presented in Table 13.

The BRUIN CLL-321 trial supports the full licensed indication of pirtobrutinib and aligns with the population specified within the NICE scope for this appraisal; patients with R/R CLL who have previously had at least one BTKi.

Table 13: Clinical effectiveness evidence

Study	BRUIN CLL-321 (NCT04666038)[91, 92]
Study design	A Phase 3, global, multicentre, randomised (1:1), open-label study comparing pirtobrutinib as continuous monotherapy to either idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) in CLL patients who have been treated with a covalent BTKi, approved or investigational

Population	Adults aged 18 years or older with a confirmed diagnosis of CLL as defined by iwCLL 2018 criteria:[16] • B-cells co-expressing CD5 together with at least one B-cell antigen (CD19, CD20, CD23) and either κ or λ light-chain restricted • The presence of ≥5 × 10^9/L monoclonal $CD5^+$ B lymphocytes in the peripheral blood • Prolymphocytes compromise ≤55% of blood lymphocytes Patients must have a requirement for therapy consistent with iwCLL 2018 criteria for initiation of therapy, known 17p depletion status and have previously been treated with a covalent BTKi. Patients may have received an unlimited number of lines of prior therapy		
Intervention(s)	Pirtobrutinib 200 mg (oral) once daily (QD) in 28-day continuous cycles		
Comparator(s)	Investigator's choice of: **IdelaR:** Idelalisib • 150 mg (oral) BID in 28-day continuous cycles Rituximab • 375 mg/m^2 on Cycle 1 Day 1 (C1D1) and then 500 mg/m^2 (IV) Q2W for four infusions and Q4W for three infusions **BR:** Bendamustine • 70 mg/m^2 (IV) on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6 Rituximab • 375 mg/m^2 on C1D1 and then 500 mg/m^2 (IV) on Day 1 of each 28-day cycle, Cycles 2 to 6		
Indicate if study supports application for marketing authorisation	Yes	**Indicate if study used in the economic model**	Yes
Reported outcomes specified in the decision problem	The outcome measures used in this submission include: • Progression-Free Survival (PFS) • Overall Survival (OS) • Time to Next Treatment (TTNT) • Event-Free Survival (EFS) • Overall Response Rate (ORR) • Duration of Response (DOR) • Adverse Events (AEs) • Patient-Reported Outcomes (PROs) • Health-Related Quality of Life (HRQoL)		

Abbreviations: AEs: adverse events; BID: twice daily; BR: bendamustine plus rituximab; BTKi: Bruton tyrosine kinase inhibitor; C1D1: Cycle 1 Day 1; CLL: chronic lymphocytic leukaemia; DOR: duration of response; EFS: event-free survival; HRQoL: health-related quality of life; IdelaR: idelalisib plus rituximab; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; IV: intravenous; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PROs: patient-reported outcomes; QD: once daily; Q2W: every two weeks; Q4W: every four weeks; SLL: small lymphocytic lymphoma; TTNT: time to next treatment.
Source: Eli Lilly (Data on File);[93] BRUIN CLL-321 CSR.[91]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial design and methodology

The BRUIN CLL-321 trial is a Phase 3, open-label, randomised trial, conducted to evaluate the clinical efficacy and safety of pirtobrutinib in patients with BTKi pre-treated CLL. BRUIN CLL-321 compares pirtobrutinib as continuous monotherapy to Investigator choice of either IdelaR or BR. Further details of BRUIN CLL-321 are discussed below.

Trial design

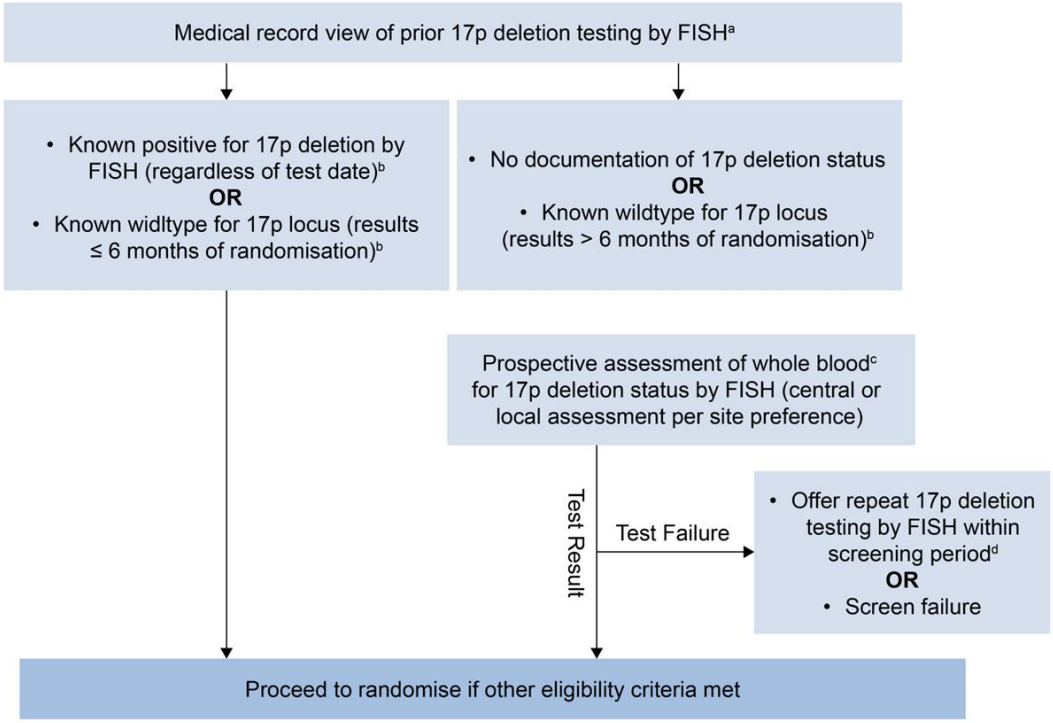
BRUIN CLL-321 is an international trial, conducted at 232 centres globally, with 13 sites in the UK. Screening assessments were required to be completed within 28 days of the first dose of study treatment. Screening results within three days of Cycle 1 Day 1 (C1D1) were acceptable as C1D1 results.

Eligibility was determined as shown in Table 14. Eligible patients were randomised 1:1 to either the pirtobrutinib arm or the comparator arm (Investigator's choice of IdelaR or BR) based on stratification factors of del(17p) presence (Figure 4), and receipt of prior venetoclax treatment (yes or no). During screening, patients who had been previously treated with IdelaR or BR and had either documented progressed disease (PD), or could not tolerate the regimen, were not retreated with the same regimen. Patients who were randomly assigned to IdelaR or BR, were eligible to cross over to the pirtobrutinib arm (the crossover population; please refer to Section 2.4.1) if they met the following criteria during the study:

- Independent Review Committee (IRC)-confirmed PD according to iwCLL 2018 guidelines
- Met treatment eligibility criteria, as per iwCLL2018 guidelines
- No receipt of any other anticancer systemic therapy from the time discontinued the control treatment
- Met inclusion and exclusion criteria detailed in Table 14

Patients who discontinued treatment for toxicity were still eligible for evaluation for cross over at the time of IRC-confirmed PD.

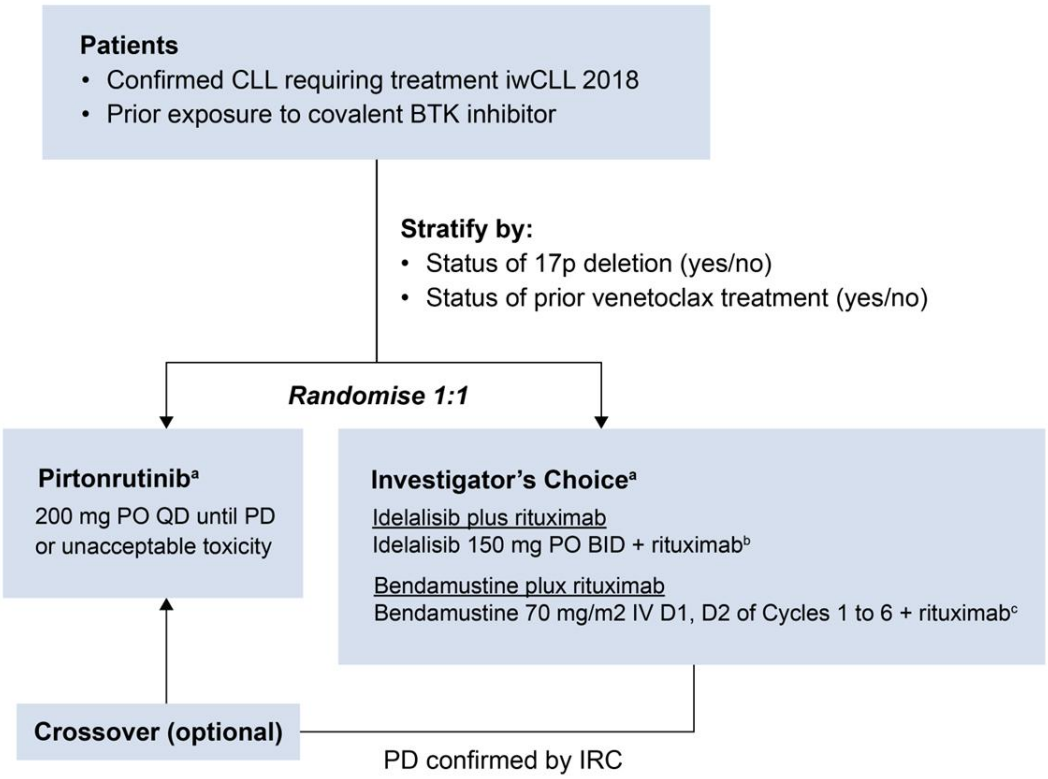
Figure 4: Schema for 17p depletion stratification



Abbreviations: FISH: fluorescence in situ hybridisation.
Source: Eli Lilly (Data on File). BRUIN CLL-321 BRUIN CLL-321 Study Protocol.[93]

BRUIN CLL-321 was designed as a multinational study. The comparator arms were designed to align with the global standard-of-care (SoC) for the patients with R/R CLL previously treated with a BTKi, based on considerations during the trial design phase prior to recruitment in 2021, and in consultation with key regulatory bodies including the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). As per the eligibility criteria discussed in Table 14, patients were permitted to be randomised in BRUIN CLL-321 after prior BCL2i-based therapy to enable subgroup evaluations in patients who had failed both BTKi and BCL2i therapy (the dual-exposed population within this submission). The study schema of BRUIN CLL-321 is shown in Figure 5.

Figure 5: Study schema of the BRUIN CLL-321 trial



Abbreviations: BID: twice daily; BTK: Bruton tyrosine kinase; CLL: chronic lymphocytic leukaemia; D1: Day 1; D2: Day 2; IRC: independent review committee; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; PD: progressed disease; PO: orally; QD: once daily.
Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR.[91]

Trial methodology

Patients randomised to pirtobrutinib, received continued pirtobrutinib dosing in 28-day cycles until discontinuation criteria were met. Discontinuation criteria included disease progression, death, lost to follow-up or withdrawal of consent. Patients were allowed to continue pirtobrutinib beyond PD, if the patient was tolerating study treatment and deriving ongoing clinical benefit, in the opinion of the Investigator.

If patients were randomised to the comparator arm, Investigators preselected which patients would receive IdelaR or BR. Treatment selection was based on region of enrolment (based on local approval/authorisation). Patients randomised to IdelaR received rituximab for a total of eight infusions and continuous oral idelalisib until discontinuation criteria were met. Patients assigned to BR received up to six cycles of both agents and then were followed until progression, death, lost to follow-up, or withdrawal of consent.

Patients who discontinued treatment for any reason other than PD, death, loss to follow-up, or withdrawal of consent were followed for tumour assessment until PD, regardless of whether the patient received a new anticancer therapy. Upon PD, all patients were placed on long-term follow-up every three months until death, loss to follow-up, or consent withdrawal. A summary of the methodology for the BRUIN CLL-321 is presented in Table 14.

Available data cut-offs

The primary endpoint of the BRUIN CLL-321 trial was IRC-accessed progression-free survival (PFS), which was assessed at the primary analysis (29th August 2023), alongside secondary endpoints overall survival (OS), Investigator-accessed PFS, overall response rate (ORR) and best overall response (BOR), duration of response (DOR), event-free survival (EFS), time to next treatment (TTNT) and safety. The median follow-up was 8.31 months for the pirtobrutinib arm and 6.05 for the Investigator's choice of IdelaR or BR arm. Longer term follow-up of the primary, secondary and safety analyses were performed on 12th February 2024 and the 29th August 2024. Data from the latest follow up analysis (29th August 2024) have been included within this appraisal, to ensure data maturity and to provide a more comprehensive assessment of long-term outcomes, durability of response, and safety profiles, thus providing more robust evidence. At this follow-up analysis (29th August 2024), the median follow-up was 19.35 and 17.74 months for the pirtobrutinib and comparator arms, respectively.

Table 14: Summary of BRUIN CLL-321 trial methodology

Trial name	**BRUIN CLL-321 (NCT04666038)[91, 92]**
Location	The study was conducted in 232 investigational study sites in Australia, Austria, Belgium, Canada, China, Croatia, Czechia, France, Germany, Hungary, Ireland, Israel, Italy, Japan, the Republic of Korea, Poland, Russian Federation, Singapore, Spain, Switzerland, Taiwan, Turkey, the United Kingdom and the United States
Trial design	A Phase 3, global, multicentre, randomised (1:1), open-label study comparing pirtobrutinib as continuous monotherapy to either IdelaR or BR in CLL patients who have been treated with a covalent BTKi

Eligibility criteria for patients	A summary of the key inclusion and exclusion criteria is provided below. Full details of the eligibility criteria are presented in Appendix B.1
	Inclusion criteria:
	• Confirmed diagnosis of CLL as defined by iwCLL 2018 criteria:[16]
	  ○ B-cells co-expressing CD5 together with at least one B-cell antigen (CD19, CD20, CD23) and either κ or λ light-chain restricted
	  ○ The presence of $\geqslant 5 \times 10^9$/L monoclonal $CD5^+$ B lymphocytes in the peripheral blood
	  ○ Prolymphocytes may comprise $\leqslant$55% of blood lymphocytes
	• Requirement for therapy consistent with iwCLL 2018 criteria for initiation of therapy
	• Known 17p deletion status by FISH
	• Previously treated with a covalent BTKi, either alone or in combination with other agents. Patients may have received an unlimited number of lines of prior therapy
	• Eastern Cooperative Oncology Group (ECOG) 0 to 2
	• Adequate organ function, met during the Screening Period
	• Washout periods prior to C1D1 of the following:
	  ○ Targeted agents or cytotoxic chemotherapy: five half-lives or two weeks, whichever is shorter
	  ○ Anticancer therapeutic monoclonal antibodies: four weeks; patients who cross over are not required to observe this washout period prior to starting crossover treatment
	  ○ Palliative limited field radiation: seven days
	  ○ Broad field radiation ($\geqslant$ 30% of bone marrow or whole brain radiotherapy): 28 days
	• Prior treatment-related AEs must have recovered to Grade ≤ 1
	Exclusion criteria:
	• Known or suspected Richter's transformation to diffuse large B-cell lymphoma (DLBCL), prolymphocytic leukaemia, or

	Hodgkin's lymphoma at any time preceding enrolment • Prior exposure to noncovalent (reversible) BTK inhibitor • Known or suspected history of central nervous system (CNS) involvement by CLL • Patients who experienced a major bleeding event on a prior BTKi • Active second malignancy • Major surgery, within four weeks of planned start of study treatment • History of ongoing drug-induced liver injury, primary biliary cirrhosis and/or extrahepatic obstruction caused by cholelithiasis, and cirrhosis of the liver • History of allogeneic or autologous SCT or CAR-T therapy within the past 60 days
Study drugs	**Intervention – Pirtobrutinib** • 200 mg oral QD in 28-day continuous cycles **Comparator – IdelaR** • Idelalisib: 150 mg IV BID in 28-day continuous cycles • Rituximab: 375 mg/m^2 on Cycle 1 Day 1 (C1D1) and then 500 mg/m^2 (IV) Q2W for four infusions and Q4W for three infusions **Comparator – BR** • Bendamustine: 70 mg/m^2 (IV) on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6 • Rituximab: 375 mg/m^2 on C1D1 and then 500 mg/m^2 (IV) on Day 1 of each 28-day cycle, Cycles 2 to 6

Permitted and prohibited concomitant medication	**Permitted**
	• **Hormonal Therapies**: Oral contraceptives, hormone-replacement therapy, and osteoporosis treatments (e.g., denosumab, bisphosphonates)
	• **Supportive Medications:**
	  ○ Hematopoietic growth factors
	  ○ RBCs and platelet transfusions
	  ○ Anti-emetics
	  ○ Analgesics
	  ○ Antidiarrheals
	  ○ Electrolyte repletion
	• **Glucocorticoids**: Prednisone or equivalent (≤ 20 mg per day, ideally for ~14 days)
	• **Cancer Hormonal Therapies**: Prostate cancer treatments (e.g., GnRH or LH-RH agonists) and breast cancer treatments (e.g., aromatase inhibitors, SERMs)
	• **Local Treatment**: Palliative radiation therapy for nodal disease is allowed if the patient is not clinically or radiographically progressing
	Prohibited
	• **CYP3A4 Interactions with Idelalisib**: Avoid strong inhibitors/inducers, including herbal products like St. John's wort, and foods like grapefruit, Seville oranges, and star fruit. Use moderate inhibitors/inducers cautiously
	• **Pirtobrutinib**: Avoid with sensitive P-gp, CYP2C8, or BCRP substrates to prevent increased risk of adverse reactions
	• **Bendamustine**: Avoid CYP1A2 inhibitors to prevent decreased drug efficacy
	• **Live-Virus Vaccines**: Should not be administered during treatment, especially with rituximab, unless B-cell levels normalise
	• **Idelalisib and Hepatotoxic Drugs**: Concurrent use should be avoided

Primary endpoint	PFS per iwCLL 2018 criteria, IRC assessment
Key secondary endpoint	OS assessed at the time of data cutoff via a descriptive interim analysis after the analysis of IRC-assessed PFS
Other secondary endpoints	**Secondary outcomes** • PFS[a] as assessed by Investigator per iwCLL 2018 criteria • TTNT by investigator assessment • EFS by investigator assessment • ORR by IRC and investigator assessment

	• DOR by IRC and investigator assessment • PROs of TTW of CLL-related symptoms and physical functioning **Safety** • SAEs, AEs, deaths and clinical laboratory abnormalities
Exploratory endpoints	**Exploratory endpoints** • Assessment of the use of medical resources including hospitalisations and emergency department visits, transfusions, and growth factor support according to treatment arm • Evaluation of PROs of the pirtobrutinib arm compared to the Investigator's choice of IdelaR or BR arms, measured by the EORTC QLQ-C30 and EQ-5D-5L The full range of exploratory outcomes are available in the CSR included within the reference pack
Pre-specified subgroups	Pre-specified subgroup analyses were conducted for the primary and key secondary endpoints only. Subgroup variables included: • Age (< 65 years versus ≥ 65 years, < 75 years versus ≥ 75 years, and < 85 years versus ≥ 85 years) • Sex (male versus female) • Race (White, Asian, Black or African American, other) • Region (North America, Europe, Asia, Australia) • Histology (CLL versus SLL) • Rai stage (0-II versus III-IV) • ECOG performance status at Baseline (0-1, 2) • Prior lines of systemic therapies (1, 2, 3, ≥ 4) • Receipt of prior BCL2 treatment (yes, no) • Receipt of prior venetoclax treatment (yes, no; per Interactive Web Response System [IWRS]) • Most recent prior anticancer therapy including covalent BTKi (yes, no) • Reason for discontinuation from the most recent prior covalent BTKi (PD versus • toxicity versus other) • Bulky disease (<5 cm versus ≥ 5 cm, < 10 cm versus ≥ 10 cm) • β2 microglobulin (mg/L) group at Baseline (≤ 3.5 mg/L, > 3.5 mg/L) • Cytogenetic features (FISH panel, biomarker central laboratory): presence or absence of 17p deletion; presence or absence of 11q deletion • High risk features (biomarker central laboratory): ○ IGHV (mutated, unmutated)

	○ Complex karyotype (yes, no) ○ TP53 mutation (yes, no) ○ TP53 mutation and/or deletion of 17p (yes, no) ○ TP53 mutation and deletion of 17p (yes, no) ○ TP53 mutation without deletion of 17p (yes, no) ○ TP53 mutation, deletion of 17p, or unmutated IGHV (yes, no) • Intended comparator (IdelaR, BR)
Duration of study and follow-up	The study is ongoing, with the first patient enrolled to the study on 9th March 2021. At the follow-up analysis (29th August 2024), the median duration of follow up for PFS was 19.35 months and 17.74 months for the pirtobrutinib arm and the Investigator's choice of IdelaR or BR arms, respectively Patients continued pirtobrutinib dosing in 28-day cycles until discontinuation criteria were met. Upon, PD, all patients were placed on LTFU every three months until death, loss to follow-up, or consent withdrawal The safety follow-up (SFU) assessments were performed as part of the EOT if the latter was performed 28 days (+7 days) after final dose of the last cycle. For patients on continuous pirtobrutinib or IdelaR, at the decision to discontinue study treatment, the EOT visit was required within seven days of stopping treatment. A SFU visit 28 days (+7 days) after the EOT, if the EOT occurred for AEs For patients who crossed over, the SFU visit was not required if pirtobrutinib treatment was initiated less than 28 days after the final dose of IdelaR or BR

Footnotes: [a]IRC assessments were the principal data source for PFS, ORR, and DOR. Supplemental analyses based on Investigator assessments are provided.
Abbreviations: AE: adverse event; BCL2: B-cell lymphoma 2; BID: twice daily; BR: bendamustine plus rituximab; CAR-T: chimeric antigen receptor T-cell therapy; C1D1: Cycle 1, Day 1; covalent BTKi: covalent Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; CNS: central nervous system; CSR: clinical study report; DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; EOT: end of treatment; FISH: fluorescence in situ hybridisation; GnRH: gonadotropin-releasing hormone; IdelaR: idelalisib plus rituximab; IRC: independent review committee; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; IV: intravenous; IWRS: Interactive Web Response System; LH-RH: luteinising hormone-releasing hormone; LTFU: long-term follow-up; ORR: overall response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PRO: patient-reported outcome; QD: once daily; Q2W: every two weeks; Q4W: every four weeks; SAE: serious adverse event; SCT: stem cell transplant; SERMs: selective oestrogen receptor modulators; SFU: safety follow-up; SLL: small lymphocytic lymphoma; TTNT: time to next treatment; TTW: time to worsening.
Sources: Eli Lilly (Data on File). BRUIN CLL-321 CSR;[91] Eli Lilly (Data on File). BRUIN CLL-321 BRUIN CLL-321 Study Protocol.[93]

2.3.2 Baseline Characteristics

2.3.2.1 ITT population

A summary of baseline characteristics of patients in BRUIN CLL-321 are presented in Table 15. The demographics of the intention-to-treat (ITT) population (defined in Table 19) aligned broadly with R/R CLL populations in the UK, as validated by consultation with UK clinical experts for this submission.[35] Patients in BRUIN CLL-321 likely represent a high-risk subset of patients, compared with the overall R/R CLL population, particularly because many of these patients received front-line therapies such as CITs before the widespread use of BTKi. Consequently, the observed efficacy outcomes are likely conservative, as they reflect a more challenging patient group with a poorer prognosis.

As shown by Table 15, demographics were balanced for the majority of patients in the pirtobrutinib and IdelaR or BR arms. Of the ITT population, 69.7% were male in both arms, the majority were white, with 82.4% in the pirtobrutinib arm and 79.8% in the comparator arm. Non-Hispanic individuals accounted for 89.9% and 90.8% in the pirtobrutinib and comparator arms respectively. Additionally, 58.9% in the pirtobrutinib arm and 67.2% in the comparator arm were aged 65 or older. The median age of patients was 66.0 and 68.0 respectively in the pirtobrutinib and IdelaR or BR arms.

Differences were observed as fewer patients were enrolled in the North America region in the pirtobrutinib arm (20.2%) than in the Investigator's choice of IdelaR or BR arm (32.8%), more patients were enrolled in the Europe region in the pirtobrutinib arm (63.9%) compared to in the Investigator's choice of IdelaR or BR arm (52.9%); fewer patients aged 65 years or older were enrolled in the pirtobrutinib arm (58.8%) than in the Investigator's choice of IdelaR or BR arm (67.2%). More patients in Europe were treated with IdelaR (65.9%) than BR (24.3%), while in Asia patients were predominantly treated with BR (37.8%) compared to IdelaR (1.2%), due to the lack of approval of IdelaR in Asian countries.

Baseline disease characteristics of the ITT population were broadly representative of patients with CLL in a real-world setting who have received prior BTKi therapy. Notably, the BRUIN CLL-321 trial included a more heavily pre-treated patient population, with a median of three prior therapies (ranging from one to 13). Nearly a quarter had received greater than four previous therapies, and 70% had previously received CIT (Table 17). More than half presented with del(17p) and/or TP53 mutation, complex karyotype and unmutated IGHV, and presented with a RAI stage greater than II – factors linked to more aggressive disease and suboptimal outcomes.

As shown in Table 16, the majority of baseline disease characteristics were similar across the study arms. In the pirtobrutinib arm 18.5% of patients were classified as Rai Stage I, 27.7% Rai Stage II, 6.7% Rai Stage III and 36.1% Rai Stage IV. Conversely, in the Investigator's choice of IdelaR or BR arm, 21.0% of patients were classified as Rai Stage I, 22.7% Rai Stage II, 17.6% Rai Stage III, and 26.9% Rai Stage IV.

Prior covalent BTKi therapy was received by 100% of patients in the pirtobrutinib and IdelaR or BR arms, with one line of prior covalent BTKi therapy received by 85.7% and 84.9% respectively in the pirtobrutinib and IdelaR or BR arms. Across both arms, the median number of lines of systemic therapy received was three. The majority of patients in both the pirtobrutinib and comparator arms discontinued prior covalent BTKi due to PD, with only a small proportion

discontinuing due to toxicity. The percentage of patients who received prior venetoclax was the same in both study arms (50.4% in each arm). The prior treatment history of patients enrolled in BRUIN CLL-321 are shown in Table 19.

Table 15: Summary of baseline patient demographics for patients in the BRUIN CLL-321 trial (ITT population)

	Pirtobrutinib (N=119)	IdelaR or BR (N=119)	IdelaR (N=82)
Age, years			
Mean (SD)	66.90 (9.32)	67.00 (8.52)	67.6 (8.52)
Median	66.0	68.0	68.0
Range	42.0 – 90.0	42.0 – 85.0	42.0 – 82.0
Age group, n (%)			
<50 years	3 (2.5)	4 (3.4)	3 (3.7)
≥50 and <65 years	46 (38.7)	35 (29.4)	20 (24.4)
≥65 and <75 years	41 (34.5)	57 (47.9)	38 (46.3)
≥75 and <85 years	27 (22.7)	22 (18.5)	21 (25.6)
≥85 years	2 (1.7)	1 (0.8)	0
Sex, n (%)			
Female	36 (30.03)	36 (30.3)	27 (32.9)
Male	83 (69.7)	83 (69.7)	55 (67.1)
Ethnic group, n (%)			
Hispanic or Latino	6 (5.0)	4 (3.4)	4 (4.9)
Not Hispanic or Latino	107 (89.9)	108 (90.8)	72 (87.8)
Not Reported	4 (3.4)	7 (5.9)	6 (7.3)
Unknown	2 (1.7)	0 (0)	0 (0)
Race, n (%)			
Asian	14 (11.8)	15 (12.6)	1 (1.2)
Black or African American	1 (0.8)	5 (4.2)	3 (3.7)
White	98 (82.4)	95 (79.8)	74 (90.2)
Not Reported	5 (4.2)	4 (3.4)	4 (4.9)
Unknown	0	0	0
Region, n (%)			
North America	24 (20.2)	39 (32.8)	26 (31.7)
Europe	76 (63.9)	63 (52.9)	54 (65.9)
Asia	14 (11.8)	15 (12.6)	1 (1.2)
Australia	5 (4.2)	2 (1.7)	1 (1.2)
Body weight (kg)			
Mean (SD)	77.57 (16.275)	79.14 (18.098)	80.67 (18.894)
Median	76.00	76.20	79.00
Range	47.40 – 127.90	39.50 – 134.99	39.50 – 134.99
Height (cm)			
Mean (SD)	170.07 (9.149)	171.52 (10.571)	172.46 (10.928)

Median	170.00	172.00	173.00
Range	151.00 – 190.50	148.00 – 198.00	148.00 – 198.00
Body surface area (m^2)			
Mean (SD)	1.90 (0.224)	1.93 (0.257)	1.96 (0.269)
Median	1.88	1.90	1.97
Range	1.42 – 2.53	1.31 – 2.60	1.31 – 2.60

Abbreviations: CLL: chronic lymphocytic leukaemia; ITT: intention-to-treat; N: total number of participants; SD: standard deviation.
Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR. Table 14.1.4.1.[91]

Table 16: Summary of baseline disease characteristics for patients in the BRUIN CLL-321 trial (ITT population)

Duration of disease (months)			
Mean (SD)	123.50 (63.993)	120.64 (58.578)	127.19 (56.616)
Median (Q1, Q3)	118.70 (73.30,170.02)	120.87 (80.30,154.51)	123.79 (87.95,161.22)
Range	16.76 – 300.22	8.05 – 323.52	23.29 – 272.99
Histology, n (%)			
CLL	109 (91.6)	108 (90.8)	76 (92.7)
SLL	10 (8.4)	11 (9.2)	6 (7.3)
ECOG PS, n (%)			
0	51 (42.9)	50 (42.0)	34 (41.5)
1	56 (47.1)	64 (53.8)	43 (52.4)
2	12 (10.1)	5 (4.2)	5 (6.1)
Rai Stage, n (%)			
Stage 0	7 (5.9)	8 (6.7)	7 (8.5)
Stage I	22 (18.5)	25 (21.0)	17 (20.7)
Stage II	33 (27.7)	27 (22.7)	20 (24.4)
Stage III	8 (6.7)	21 (17.6)	16 (19.5)
Stage IV	43 (36.1)	32 (26.9)	17 (20.7)
Missing	6 (5.0)	6 (5.0)	5 (6.1)
Bulky disease, n (%)			
Patients with measurable target lesion (lymph node)	115 (96.6)	112 (94.1)	78 (95.1)
<5cm	67 (56.3)	54 (45.4)	35 (42.7)
≥5cm	48 (40.3)	58 (48.7)	43 (52.4)
<10cm	100 (84.0)	93 (78.2)	65 (79.3)
≥10cm	15 (12.6)	19 (16.0)	13 (15.9)
No measurable target lesion at baseline	4 (3.4)	7 (5.9)	4 (4.9)
Missing	0	0	0
ß$_2$ microglobulin (mg/L) at baseline, n (%)			
≤ 3.5	27 (22.7)	39 (32.8)	27 (32.9)
> 3.5	89 (74.8)	77 (64.7)	53 (64.6)

Missing/Unknown	3 (2.5)	3 (2.5)	2 (2.4)
Cytogenetic features (FISH panel, biomarker laboratory), n (%)			
17p deletion presence	39 (32.8)	43 (36.1)	34 (41.5)
Yes	72 (60.5)	69 (58.0)	43 (52.4)
No	8 (6.7)	7 (5.9)	5 (6.1)
Missing/Unknown	39 (32.8)	43 (36.1)	34 (41.5)
11q deletion presence, n (%)			
Yes	19 (16.0)	25 (21.0)	15 (18.3)
No	82 (68.9)	74 (62.2)	62 (75.6)
Missing/Unknown	18 (15.1)	20 (16.8)	5 (6.1)
High risk features (biomarker central laboratory), n(%)			
IGHV Mutation Status			
Mutated	7 (5.9)	19 (16.0)	13 (15.9)
Unmutated	90 (75.6)	74 (62.2)	59 (72.0)
Missing/Unknown	22 (18.5)	26 (21.8)	10 (12.2)
Complex karyotype, n (%)			
Yes	53 (44.5)	44 (37.0)	36 (43.9)
No	21 (17.6)	31 (26.1)	20 (24.4)
Missing/Unknown	45 (37.8)	44 (37.0)	26 (31.7)
***TP53* mutation status, n (%)**			
Yes	33 (27.7)	26 (21.8)	23 (28.0)
No	55 (46.2)	55 (46.2)	40 (48.8)
Missing/Unknown	31 (26.1)	38 (31.9)	19 (23.2)
***TP53* mutation and/or del(17p), n (%)**			
Yes	50 (42.0)	51 (42.9)	40 (48.8)
No	38 (31.9)	37 (31.1)	27 (32.9)
Missing/Unknown	31 (26.1)	31 (26.1)	15 (18.3)
***TP53* mutation and del(17p), n (%)**			
Yes	22 (18.5)	18 (15.1)	17 (20.7)
No	89 (74.8)	87 (73.1)	56 (68.3)
Missing/Unknown	8 (6.7)	14 (11.8)	9 (11.0)
***TP53* mutation without del(17p), n (%)**			
Yes	10 (8.4)	7 (5.9)	5 (6.1)
No	77 (64.7)	73 (61.3)	57 (69.5)
Missing/Unknown	32 (26.9)	39 (32.8)	20 (24.4)
***TP53* mutation, del(17p) or unmutated *IGHV*, n (%)**			
Yes	93 (78.2)	84 (70.6)	64 (78.0)
No	5 (4.2)	9 (7.6)	5 (6.1)
Missing/Unknown	21 (17.6)	26 (21.8)	13 (15.9)

Cytopenia at Baseline			
Neutropenia - absolute neutrophil count (ANC) <1.5 x 10^9/L	11 (9.2)	10 (8.4)	5 (6.1)
Anaemia - Hgb <11 g/dL	33 (27.7)	30 (25.2)	23 (28.0)
Thrombocytopenia - platelet counts <100 x 10^9/L	42 (35.3)	37 (31.1)	28 (34.1)
Any of the above	62 (52.1)	55 (46.2)	39 (47.6)

Abbreviations: ANC: absolute neutrophil count; CLL: chronic lymphocytic leukaemia; del(17p): deletion of the short arm of chromosome 17; FISH: fluorescence in situ hybridisation; Hgb: haemoglobin; IGHV: immunoglobulin heavy chain variable region; ITT: intention-to-treat; SD: standard deviation; TP53: tumour protein p53.
Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR. Table 14.1.4.2.[91]

Table 17: Prior therapies of patients in the BRUIN CLL-321 trial (ITT population)

	Pirtobrutinib (N=119)	IdelaR or BR (N=119)	IdelaR (N=82)
Prior systemic therapies, n (%)			
Prior covalent BTKi	119 (100)	119 (100)	82 (100)
Acalabrutinib	17 (14.3)	20 (16.8)	14 (17.1)
Ibrutinib	100 (84.0)	106 (89.1)	74 (90.2)
Zanubrutinib	9 (7.6)	7 (5.9)	2 (2.4)
Other	5 (4.2)	3 (2.5)	1 (1.2)
Prior venetoclax	60 (50.4)	60 (50.4)	48 (58.5)
Prior BCL2i	60 (50.4)	62 (52.1)	48 (58.5)
Prior chemotherapy	81 (68.1)	83 (69.7)	58 (70.7)
Prior anti-CD20 antibody	86 (72.3)	83 (69.7)	59 (72.0)
Prior PI3k agent	11 (9.2)	11 (9.2)	3 (3.7)
Prior IMID/immunomodulator	2 (1.7)	3 (2.5)	2 (2.4)
Prior stem cell transplant therapy	3 (2.5)	1 (0.8)	1 (1.2)
Auto-SCT	1 (0.8)	0 (0)	0 (0)
Allo-SCT	2 (1.7)	1 (0.8)	1 (1.2)
Prior other systemic therapy	6 (5.0)	9 (7.6)	5 (6.1)
Number of lines of prior systemic therapy			
Mean (SD)	3.1 (1.87)	3.4 (2.23)	3.4 (2.25)
Median	3.0	3.0	3.0
Q1, Q3	2.0, 4.0	2.0, 5.0	2.0, 5.0
Min, Max	1.0, 13.0	1.0, 11.0	1.0, 11.0
1	21 (17.6)	28 (23.5)	18 (22.0)
2	30 (25.2)	24 (20.2)	16 (19.5)
3	29 (24.4)	18 (15.1)	13 (15.9)
≥4	39 (32.8)	49 (41.2)	35 (42.7)

Number of lines where prior covalent BTKi was used			
Mean (SD)	1.2 (0.41)	1.2 (0.49)	1.2 (0.47)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 1.0
Min, Max	1.0, 3.0	1.0, 3.0	1.0, 3.0
1	102 (85.7)	101 (84.9)	70 (85.4)
2	15 (12.6)	13 (10.9)	9 (11.0)
3	2 (1.7)	5 (4.2)	3 (3.7)
Number of lines of prior BCL2i, n			
Mean (SD)	0.6 (0.62)	0.6 (0.60)	0.6 (0.58)
Median	1.0	1.0	1.0
Q1, Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0
Min, Max	0.0, 2.0	0.0, 2.0	0.0, 2.0
0	59 (49.6)	57 (47.9)	34 (41.5)
1	52 (43.7)	55 (46.2)	44 (53.7)
2	8 (6.7)	7 (5.9)	4 (4.9)
Reason for discontinuation from the most recent covalent BTKi, n (%)			
PD	81 (68.1)	85 (71.4)	61 (74.4)
Toxicity	16 (13.4)	18 (15.1)	11 (13.4)
Other Reason for Discontinuation	22 (18.5)	13 (10.9)	9 (11.0)
Missing	0	3 (2.5)	1 (1.2)
Reason for discontinuation from any prior covalent BTKi, n (%)			
PD	83 (69.7)	86 (72.3)	61 (74.4)
Toxicity	17 (14.3)	19 (16.0)	12 (14.6)
Other Reason for Discontinuation	19 (16.0)	12 (10.1)	8 (9.8)
Missing	0	2 (1.7)	1 (1.2)
Intolerance to any prior covalent BTKi, n (%)			
Yes	20 (16.8)	26 (21.8)	17 (20.7)
No	99 (83.2)	91 (76.5)	64 (78.0)
Missing	0	2 (1.7)	1 (1.2)
Relapsed/refractory to most recent prior covalent BTKi, n (%)			
Yes	104 (87.4)	107 (89.9)	77 (93.9)
No	15 (12.6)	12 (10.1)	5 (6.1)
Relapsed/refractory to any prior covalent BTKi, n (%)			
Yes	105 (88.2)	108 (90.8)	77 (93.9)
No	14 (11.8)	11 (9.2)	5 (6.1)
Reason for discontinuation from the most recent venetoclax, n (%)			
PD	35 (29.4)	43 (36.1)	35 (42.7)
Toxicity	1 (0.8)	4 (3.4)	3 (3.7)
Patient Choice	1 (0.8)	0	0

Other Reason For Discontinuation	8 (6.7)	6 (5.0)	5 (6.1)
Reason for discontinuation from any prior venetoclax, n (%)			
PD	36 (30.3)	43 (36.1)	35 (42.7)
Toxicity	1 (0.8)	4 (3.4)	3 (3.7)
Patient Choice	1 (0.8)	0	0
Other Reason For Discontinuation	7 (5.9)	6 (5.0)	5 (6.1)

Abbreviations: BCL2i: B-cell lymphoma 2 inhibitor; covalent BTKi: covalent Bruton tyrosine kinase inhibitor; IMID: immunomodulatory drug; PD: progressed disease; PI3K: phosphoinositide 3-kinase; SCT: stem cell transplant; SD: standard deviation.
Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR. Table 14.1.4.4.[91]

2.3.2.2 Dual-exposed population

A summary of baseline characteristics for patients, in BRUIN CLL-321, who have received two prior treatments, including at least one cBTKi, is presented in Table 18.

Table 18: Summary of baseline patient demographics for patients in the BRUIN CLL-321 trial (Dual-exposed population)

	Pirtobrutinib (N=60)	IdelaR or BR (N=62)	IdelaR (N=48)
Age, years			
Mean (SD)	66.90 (9.44)	66.6 (9.12)	67.1 (9.22)
Median	67.0	67.0	68.0
Range	44.0 – 90.0	42.0 – 85.0	42.0 – 80.0
Age group, n (%)			
<50 years	1 (1.7)	2 (3.2)	2 (4.2)
≥50 and <65 years	22 (36.7)	22 (35.5)	16 (33.3)
≥65 and <75 years	24 (40.0)	24 (38.7)	17 (35.4)
≥75 and <85 years	11 (18.3)	13 (21.0)	13 (27.1)
≥85 years	2 (3.3)	1 (1.6)	0
Sex, n (%)			
Female	18 (30.0)	22 (35.5)	18 (37.5)
Male	42 (70.0)	40 (64.5)	30 (62.5)
Ethnic group, n (%)			
Hispanic or Latino	3 (5.0)	3 (4.8)	3 (6.3)
Not Hispanic or Latino	54 (90.0)	53 (85.5)	39 (81.3)
Not Reported	1 (1.7)	6 (9.7)	6 (12.5)
Unknown	2 (3.3)	0	0
Race, n (%)			
Asian	2 (3.3)	3 (4.8)	0
Black or African American	1 (1.7)	3 (4.8)	2 (4.2)
White	54 (90.0)	52 (83.9)	42 (87.5)
Not Reported	2 (3.3)	4 (6.5)	4 (8.3)
Unknown	1 (1.7)	0	0

Region, n (%)			
North America	13 (21.7)	21 (33.9)	16 (33.3)
Europe	40 (66.7)	36 (58.1)	31 (64.6)
Asia	2 (3.3)	3 (4.8)	0
Australia	5 (8.3)	2 (3.2)	1 (2.1)
Body weight (kg)			
Mean (SD)	78.36 (17.659)	79.99 (20.208)	80.63 (20.408)
Median	76.60	77.00	80.75
Range	47.40 - 127.90	39.50 - 134.99	39.50 - 134.99
Height (cm)			
Mean (SD)	171.08 (9.667)	172.25 (11.038)	172.64 (11.542)
Median	171.95	172.50	173.45
Range	151.00 - 190.50	155.00 - 198.00	155.00 - 198.00
Body surface area (m^2)			
Mean (SD)	1.91 (0.244)	1.94 (0.282)	1.95 (0.287)
Median	1.90	1.93	1.98
Range	1.42 - 2.53	1.31 - 2.60	1.31 - 2.60

Abbreviations: CLL: chronic lymphocytic leukaemia; ITT: intention-to-treat; N: total number of participants; SD: standard deviation.
Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR. Table 14.1.4.1.[91]

2.3.3 Patient Disposition

A total of 238 patients underwent randomisation, with 119 patients randomised to the pirtobrutinib arm and 119 patients to the Investigator's choice of IdelaR or BR arm. At the time of the primary analysis (29th August 2023), 79 (66.4%) patients in the pirtobrutinib arm and 35 (29.4%) patients in the Investigator's choice of IdelaR or BR arm were still receiving study treatment. Moreover, as of the follow-up analysis (29th August 2024), 46 (38.7%) patients were still receiving pirtobrutinib and five (4.2%) were still being treated in the Investigator's choice of IdelaR or BR arm (five treated with IdelaR and zero with BR). In addition, a total of 29 out of 50 (58.0%) patients (initially receiving IdelaR or BR) in crossover were still receiving pirtobrutinib treatment after crossing over (after IRC confirmed PD).

At the time of the follow-up analysis (29th August 2024), out of 66 patients eligible for crossover, 50 patients received pirtobrutinib, representing an effective crossover rate of 75.8%. This corresponded to approximately 55% of the total population randomised to the Investigator's choice of IdelaR or BR arm.

Treatment was discontinued in 70 (58.8%) patients randomised to pirtobrutinib and in 104 (87.4%) patients randomised to IdelaR or BR (72 patients and 32 patients, respectively). Most patients in the Investigator's choice of IdelaR or BR arm (87.4%) were off all study treatment, including 17 (14.3%) patients who had completed treatment, including two (2.4%) who had received IdelaR and 15 (40.5%) who had received BR. The patient flow diagram for BRUIN CLL-321 is presented in Appendix B.2.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical analyses were performed in two stages. At the primary analysis (29th August 2023), the primary endpoint (IRC-assessed PFS) was assessed in addition to secondary endpoints OS, PFS by Investigator assessment, ORR, DOR, EFS, TTNT and safety results. At the follow-up analysis (29th August 2024), updated efficacy and safety results and final OS analyses were conducted. Longer follow-up allowed for data to continue to mature for the IRC-assessed PFS and OS data.

2.4.1 Trial populations

The description and number of patients in each analysis population for the BRUIN CLL-321 trial is presented in Table 19. The ITT population were used in the analysis of patient disposition and demographics, and the primary and secondary efficacy endpoints and exploratory outcomes; the safety population was used for the safety-related analyses, and the crossover population were used for selected safety analyses.

Table 19: Trial populations used for the analysis of outcomes in BRUIN CLL-321

Population	Description	N		
		Pirtobrutinib	IdelaR	BR
Entered	All participants who signed informed consent	NR	NR	NR
ITT	All randomised patients. All analyses that used the ITT population included data only prior to cross over for IdelaR or BR patients, except for OS related analyses	119	82	37
Safety	All randomised patients who took at least one dose of study treatment. Analysis of safety data were based on the actual treatment a patient received on the first study treatment administration	116	77	32
Crossover	A subpopulation of patients included in the ITT population who were randomised to IdelaR or BR, and crossed over to receive at least one dose of pirtobrutinib	NA	37	13

Abbreviations: BR: bendamustine plus rituximab; IdelaR: idelalisib plus rituximab; ITT: intention-to-treat; N: total number of participants; OS: overall survival.
Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR.[91]

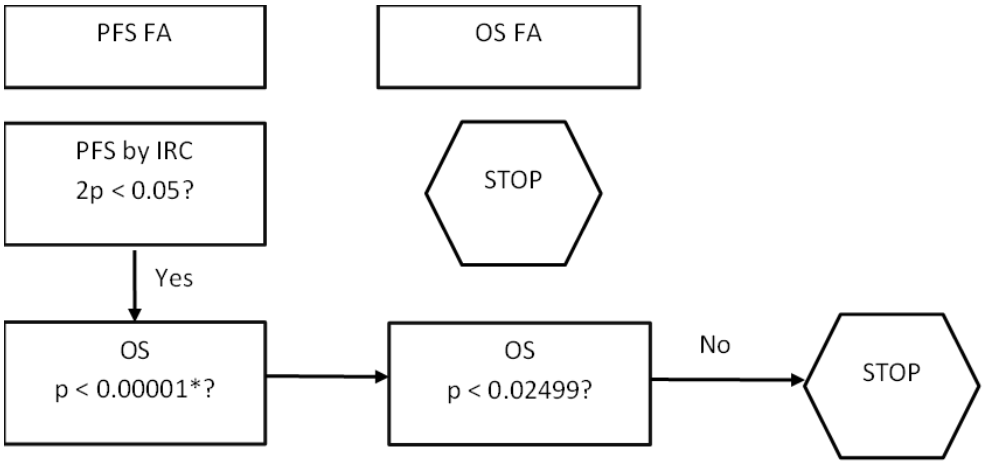
2.4.2 Statistical methods

2.4.2.1 Methodology

The statistical methods employed in the BRUIN CLL-321 trial are presented in Table 20.

Table 20: Statistical methods for the primary analysis of BRUIN CLL-321

Hypothesis objective	To test the hypothesis that treatment with pirtobrutinib as continuous monotherapy provides superior PFS (assessed by IRC) over treatment of IdelaR and BR in patients with covalent BTKi pre-treated CLL

Statistical analysis	Statistical comparisons for the primary efficacy endpoint and the key secondary endpoint were carried out in IRC-assessed PFS then, OS. Only if the test for IRC-assessed PFS was statistically significant were OS data tested inferentially for statistical significance **Primary Analysis** The IRC-accessed PFS was compared between treatment arms using a stratified logrank test, stratified by the two randomisation strata based on the IWRS data: del(17p) presence and receipt of prior venetoclax treatment. The corresponding hazard ratio (HR) between treatment arms was estimated using a stratified Cox regression model. PFS Kaplan-Meier (KM) survival curves, medians, and PFS rates at various time points with 95% confidence interval (CI) for each treatment arm were estimated using the KM method ***Sensitivity Analyses*** Several sensitivity analyses were conducted: • Repetition of the primary analysis for IRC-assessed PFS was performed, using an unstratified logrank test and an unstratified Cox regression model • Subjects with the use of any subsequent anticancer therapy prior to the first IRC confirmed PD or death due to any cause were not censored at the last adequate assessment prior to the start date of the subsequent anticancer therapy • IRC-assessed PD or death after two or more consecutively missed visits were included as a PFS event • Patients with important protocol deviations (IPDs) deemed to impact efficacy analysis were excluded **Key Secondary Analysis** A descriptive interim analysis of OS was conducted at the time of the IRC-accessed PFS final analysis. The one-sided p-value boundary for the final analysis of OS was equal to 0.02499. The final OS analysis was planned to occur approximately 12 months after the primary analysis of the PFS, or when approximately 70 OS events were observed, and the one-sided alpha at this analysis was to be 0.2498 ***Sensitivity Analyses*** A sensitivity analysis was conducted for OS. Patients in the crossover population were censored at the time of crossover **Figure 6: Statistical testing procedure for primary and key secondary efficacy endpoints**  **Footnotes:** FA: final analysis; IRC: independent review committee; OS: overall survival; PFS: progression-free survival; p: probability value. **Source:** Eli Lilly (Data on File). BRUIN CLL-321 Statistical Analysis Plan.[94]

	Supportive Secondary Efficacy Endpoints
	• **ORR** – The ORR, with 95% CI, was summarised for each treatment arm. ORR was compared between the pirtobrutinib and IdelaR or BR arms using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomisation strata
	• **PFS**, by Investigator assessment – PFS, by investigator assessment was analysed using the same methodology as for the PFS per IRC assessment
	• **DOR** – DOR was analysed for patients who achieved BOR of CR, CRi, nodular partial response (nPR) or partial response (PR). The DOR was evaluated by both the IRC and Investigator assessment
	• **EFS** – EFS analysis was similar to the primary analysis for IRC-accessed PFS
	• **TTNT** – TTNT analysis was similar to the primary analysis for IRC-accessed PFS
	• **PRO –** Changes from baseline were analysed using a mixed model for repeated measures (MMRM) for the following measures:
	  ○ CLL/SLL-related symptoms
	  ○ QLQ-C30 Physical function
	  ○ Expanded fatigue
	  ○ QLQ-C30 GHS/QoL
	PRO scores derived from the CLL-related symptoms, QLQ-C30 PF, Expanded Fatigue, GHS/QoL, and all other QLQ-C30 scales were described at baseline and each post-baseline visit by treatment arm and overall using descriptive statistics. Change from baseline to each post-baseline visit was also described by treatment arm and overall.

Sample size, power calculation	The sample size of this study was determined (under the assumption of 1:1 randomisation) to allow sufficient power for testing IRC-assessed PFS in an error-controlled fashion. For the IRC-assessed PFS, assuming a true HR of 0.5, 88 IRC-assessed PFS events were required to provide approximately 90% power at a 2-sided significance level of 5% to reject the null hypothesis (HR = 1.0) using the logrank test. The study was expected to enrol approximately 250 patients. The accrual period was assumed to be approximately 12 months, and the final analysis is expected to occur approximately 20 months after the first patient has been randomised.

Data management, patient withdrawals	**Clinical data management**
	Case report form data were captured via data entry by study centre personnel in a Sponsor database system. Data quality checks were applied using manual and/or electronic verification methods
	Patient withdrawals
	Data censoring conditions for PFS, OS, DOR, EFS, and TTNT were described as below.
	PFS, EFS and DOR
	PFS, EFS and DOR were right censored for patients who met one or more of the following:
	• Progression documented on or between scheduled visits on or before data cutoff
	  ○ Censored at the earliest date of disease assessment documenting disease progression
	• Treatment discontinuation due to unacceptable toxicity
	  ○ Censored at date of treatment discontinuation
	• Start of subsequent anticancer therapy
	  ○ Censored at date of initiation of subsequent anticancer therapy
	• Death without documented progression on or before data cutoff

	○ Censored at date of death • No documented progression or death on or before data cut off ○ Censored at date of last adequate disease assessment on or before data cutoff • Study discontinuation without documented progression or death ○ Censored at date of last adequate disease assessment on or before study discontinuation as reported on end of study case report form (CRF) • Documented progression or death after start of subsequent anticancer therapy ○ Censored at date of last adequate disease assessment prior to subsequent anticancer therapy • Subsequent anticancer therapy without documented progression or death ○ Censored at date of last adequate disease assessment prior to subsequent anticancer therapy • Documented progression or death immediately after two or more consecutively missed scheduled disease assessment visits ○ Censored at date of last adequate disease assessment prior to the consecutively missed visits • No adequate disease assessment at post-baseline ○ Censored at date of randomisation • No radiological tumour assessment at baseline ○ Censored at date of randomisation **OS** OS was right censored for patients who met one or more of the following: • Death on or before data cutoff date ○ Censored at date of death • Alive at data cutoff ○ Censored at date of data cutoff • Study discontinuation without death on or before data cutoff date ○ Censored at date of discontinuation from study participation as reported on end of study CRF • Unknown survival status at data cutoff ○ Censored at date patients last known to be alive **TTNT** TTNT was right censored for patients who met one or more of the following: • Start of subsequent anticancer therapy ○ Censored at date of initiation of subsequent anticancer therapy • Death on or before at data cutoff ○ Censored at date of death • Have not received next anticancer therapy including crossover therapy and are still alive on or before data cutoff ○ Censored at date of data cutoff • Unknown survival status at data cutoff ○ Censored at date patient last known to be alive

Abbreviations: BOR: best overall response; BR: bendamustine plus rituximab; CI: confidence interval; covalent BTKi: covalent Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; CMH: Cochran-Mantel-Haenszel; CR: complete response; CRF: case report form; CRi: complete response with incomplete hematologic recovery; del(17)p: deletion of the short arm of chromosome 17; DOR: duration of response; EFS: event-free survival; FA: final analysis; HR: hazard ratio; IdelaR: idelalisib plus rituximab; IPD: important protocol deviations; IRC: independent review committee; IWRS: Interactive Web Response System; KM: Kaplan-Meier; nPR: nodular partial response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; PRO: patient-reported outcome; QLQ-C30 GHS/QoL: Quality of Life Questionnaire-Core 30 Global Health Status/Quality of Life; TTNT: time to next treatment.
Source: Eli Lilly (Data on File). BRUIN CLL-321 Statistical Analysis Plan.[94]

2.4.2.2 Definitions for outcome measures

The timepoints of each endpoint analysis are outlined in Table 21. Initial analyses were conducted at the primary analysis, and the extended follow-up allowed for data maturation at the follow-up analysis.

Table 21: Date cut-off data for efficacy and safety analyses presented

Endpoint	Analysis performed at data cut-off	
	Primary analysis (29th August 2023)	Follow-up analysis (29th August 2024)
Primary		
IRC assessed-PFS	Yes	Yes (descriptive)
Secondary		
OS	Yes (interim)	Yes (final)
Investigator assessed-PFS	Yes	Yes (descriptive)
Investigator assessed-TTNT	Yes	Yes (descriptive)
Investigator assessed-EFS	Yes	Yes (descriptive)
IRC and Investigator assessed-ORR	Yes	Yes (descriptive)
IRC and Investigator assessed-DOR	Yes	Yes (descriptive)
Safety		
Safety	Yes	Yes

Abbreviations: IRC: independent review committee; PFS: progression-free survival; OS: overall survival; ORR: overall response rate; BOR: best overall response; EFS: event-free survival; TTNT: time to next treatment.
Source: Eli Lilly (Data on File). BRUIN CLL-321 Statistical Analysis Plan.[94]

Several outcomes were employed to explore the efficacy of pirtobrutinib for patients with BTKi pre-treated CLL. Definitions of these outcome measures are presented in Table 22.

Table 22: Definitions of the primary and key secondary endpoints

Outcome measure	Definition
IRC assessed-PFS	The time from randomisation until the occurrence of documented disease progression assessed by the IRC, per iwCLL 2018 criteria,[16] or death from any cause in the absence of documented PD Analysis was event driven, and the final analysis was conducted when approximately 88 events assessed by the IRC were observed, approximately 20 months after the first patient has been randomised

OS	The time from randomisation until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive
Investigator assessed-PFS	The time from randomisation until the occurrence of documented disease progression assessed by Investigator, per iwCLL 2018 criteria,[16] or death from any cause in the absence of documented PD
IRC and Investigator assessed-ORR and BOR	The number of patients who achieve a BOR of CR, CRi, nPR, PR at or before the initiation of subsequent anticancer therapy divided by the total number of patients randomised to each treatment arm. IRC-assessed best overall response is the best overall response recorded from the start of treatment until IRC-assessed PD, in the order of CR, CRi, nPR or PR, stable disease (SD), nonPD, PD, no evidence of disease (NED), or unknown
IRC and Investigator assessed-DOR	The time from the date of the first documented response until the first date of the documentation of PD per iwCLL 2018 criteria, or the date of death from any cause in the absence of documented PD
Investigator assessed-EFS	The time from randomisation to the first occurrence of: • Documented disease progression per iwCLL 2018 criteria as assessed by Investigator • Initiation of subsequent anticancer therapy for CLL • Unacceptable toxicity leading to treatment discontinuation as assessed by the Investigator • Death (due to any cause)
TTNT	The date of randomisation to the date of initiation of the subsequent anticancer therapy for CLL, therapy of pirtobrutinib for patients who crossed over, or death due to any cause, whichever occurs first. For patients who did not receive the next anticancer therapy and were still alive or lost to follow-up at the time of data analysis cutoff, TTNT was censored at the last date the patient was known to be alive

Abbreviations: BOR: best overall response; CLL: chronic lymphocytic leukaemia; CR: complete response; CRi: complete response with incomplete hematologic recovery; DOR: duration of response; EFS: event-free survival; IRC: independent review committee; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; NED: no evidence of disease; nPR: nodular partial response; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease.
Source: Eli Lilly (Data on File). BRUIN CLL-321 Statistical Analysis Plan.[94]

2.4.2.3 Sensitivity analyses of overall survival

As discussed in Section 2.3.1, patients who progressed on treatment with Investigator's choice of IdelaR or BR were allowed to crossover to the pirtobrutinib arm, provided they met the criteria for crossover described in Section 2.3. To assess the impact of patient crossover on the results from BRUIN CLL-321, a prespecified sensitivity analysis for OS was conducted at the timepoint of the primary analysis (28th August 2023 data-cut) and was conducted for censoring of patients who crossed over from the Investigator's choice of IdelaR or BR arm to the pirtobrutinib arm at the time of crossover. When it was noted that the final analysis of OS (29th August 2024 data cut) was confounded by patients who crossed over to the pirtobrutinib arm following progression on IdelaR or BR, several complex methodologies for analyses of OS were explored, to explore potential confounding in OS and to adjust for the bias introduced by crossover (further details on the treatment switching methodologies, along with comprehensive explanations of the most appropriate approaches, are presented in Section 3.3.2.2). A summary of the methods explored are presented below.

The NICE DSU 16 guidelines, updated in TSD24, outline several adjustment methods to consider when adjusting for treatment switching:[95]

- Simple adjustment methods such as:
    - Censoring switches at the point of switch
    - Excluding switches

These approaches are highly prone to selection bias as treatment switching is often associated with prognosis. Instead, crossover analyses were conducted in accordance with methods recommended by the NICE DSU guidelines, updated in TSD24, including:[95]

- The Rank Preserving Structural Failure Time Model (RPSFTM)
- The inverse probability censoring weighting (IPCW) method
- The two-stage accelerated failure time (AFT) method

RPSFTM

The RPSFTM method, described by Deng at al. (2023), represents a randomisation-based method for estimating counterfactual survival times (i.e., survival times that would have been observed in the absence of switching). A method referred to as g-estimation is used to estimate a time acceleration factor that can be applied to survival times in the control to create the counterfactual data. The RPSFTM allows for a treatment-switching adjustment assuming the control arm consisted of a single treatment. This method was deemed inappropriate to model treatment switching in the model (as discussed in Section 3.3.2.2).

IPCW method

The IPCW method accounted for the crossover effect by censoring crossover patients at the time of PD and reweighting the remaining patients in the control arm who had PD but did not crossover (Latimer *et al.* 2012; Latimer *et al.* 2013).[95, 96] The reweighting considered the predicted probability of crossover based on the most relevant baseline prognostic factors as well as the predicted probability of crossover among patients with PD based on the most relevant prognostic factors measured at PD (that is, second baseline covariates); if prognostic factors at PD were unavailable, baseline covariates could be used.

A number of known CLL/SLL prognostic factors were considered as covariates in this model. Using the random forest-based model selection approach, the following baseline covariates for all patients in the control arm or second baseline covariates for PD patients were included:

- **Baseline covariates**: number of prior lines of therapy (≤3 versus >3 lines), reason for discontinuation from most recent BTKi (due to PD versus not due to PD), beta-2 microglobulin (≤3.5 versus >3.5 mg/L)
- **Second baseline covariates for patients with PD**: reason for discontinuation from most recent BTKi (due to PD versus not due to PD), ECOG performance status (0 to 1 versus 2) at PD, bulky disease (<5 versus ≥5 mg/L) at baseline

In addition, PFS time was adjusted for in both the baseline covariate and second baseline covariate models

Two-stage AFT method

The Two-Stage AFT model estimated counter-factual survival for the control arm as if crossover had never occurred (Latimer *et al.* 2020).[97] This approach applied a "shrinking factor" to the survival time after crossover, which adjusted the OS outcomes in the control arm by scaling down survival times for crossover patients. The shrinking factor was estimated by comparing post-progression survival between the crossover and the non-crossover patients within the control arm, while accounting for strongly associated second baseline covariates. The second baseline covariates included in the model were:

- Reason for discontinuation from most recent BTKi (due to PD versus not due to PD)
- ECOG performance status (0 to 1 versus 2) at PD
- Bulky disease (<5 versus ≥5 cm) at baseline
- PFS time

These covariates ensured that the shrinking factor captured the influence of any clinical characteristics that were likely to affect survival after crossover.

The results from the sensitivity analyses of OS are reported in Section 2.6.4.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Included studies in the clinical SLR were assessed for quality using the Cochrane Risk of Bias Assessment for Randomised Trials Tool v2.0, and non-randomised trials via the Risk of Bias in Non-randomised studies – of Interventions (ROBINS-II) assessment tool. The results of these quality assessments are presented in Appendix B.3, and a summary of the quality assessment for the BRUIN CLL-321 trial, the sole clinical trial informing clinical evidence within this submission, is presented in Table 23.

Notably, open-label studies are prevalent in CLL as they allow for practical assessment of treatment effects without the need for placebo controls, which are ethically challenging in this patient population. Additionally, this design aligns with those of competitor trials.[98-101] Although crossover can introduce bias due to the introduction of deviations from intended interventions, the confounding in this study has been mitigated through statistical analyses, as presented in Sections 2.4.2.3 and 2.6.3, and notably confounding solely impacts OS results which has been accounted for when interpreting trial results from the BRUIN CLL-321 study.

Table 23: Quality assessment of BRUIN CLL-321 using the Cochrane tool

Question	BRUIN CLL-321 (NCT04666038)
Bias arising from randomisation process	Low
Bias due to deviations from intended interventions	Medium
Bias due to missing outcome data	Low
Bias in measurement of the outcome	Low
Bias in selection of the reported result	Low
Overall	Medium

Source: Eli Lilly (Data on File). Clinical SLR Report.[102]

2.6 Clinical effectiveness results of the relevant studies

As discussed in Section 2.3.1, the clinical effectiveness results of pirtobrutinib are informed by the primary and follow-up analyses. The data presented within this submission are informed by the follow-up analysis due to the availability of longer-term, mature data (median follow-up was 19.35 months in the pirtobrutinib arm compared to 17.74 months in the Investigator's choice of IdelaR or BR arm) from the follow-up analysis. As the primary endpoint was assessed at the primary analysis, these data for IRC assessed-PFS are also presented alongside data from the follow-up analysis.

2.6.1 Primary efficacy endpoint: IRC-accessed PFS

2.6.1.1 ITT population

Primary analysis (28th August 2023)

Pirtobrutinib monotherapy showed improvement in IRC-assessed PFS compared to the Investigator's choice of IdelaR or BR arm (hazard ratio [HR] = 0.58; 95% confidence interval [CI]: 0.38, 0.89; p = 0.0105; Table 24). The median PFS by IRC assessment for pirtobrutinib was [redacted] months ([redacted]) and for IdelaR or BR was [redacted] months ([redacted]). The median follow-up time for pirtobrutinib was [redacted] months ([redacted]) and for the Investigator's choice of IdelaR or BR arm was [redacted] months ([redacted]).

At six months, the Kaplan-Meier (KM) estimate for the probability of being progression-free by IRC assessment (presented in Figure 7) was [redacted] ([redacted]) for the pirtobrutinib arm and [redacted] ([redacted]) for the Investigator's choice of IdelaR or BR arm. At nine months, the probability of being progression-free was [redacted] ([redacted]) for the pirtobrutinib arm and [redacted] ([redacted]) for the Investigator's choice of IdelaR or BR arm. A KM plot of PFS based on IRC assessment is presented in Figure 7.

A number of sensitivity analyses were conducted to assess the robustness of the PFS results (as described in Table 20). Results from the preplanned sensitivity analyses of PFS based on IRC assessment were consistent and supported the primary efficacy PFS results (see Appendix J.3 for further details).

Table 24: PFS based on IRC assessment (ITT population)

	Pirtobrutinib (N=119)	IdelaR or BR (N=119)
Number of events, n (%)	[redacted]	[redacted]
PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Progression-free survival (months)[a]		
Median (95% CI)	[redacted]	[redacted]
min; max	[redacted]	[redacted]
Stratified analysis (versus the Investigator's choice of IdelaR or BR arm)[b]		
HR (95% CI)[c]	0.58 (0.38, 0.89)	
p-value[d]	0.0105	

	Pirtobrutinib (N=119)	IdelaR or BR (N=119)
Duration of follow-up (months)		
Median	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]

Footnotes: Quartiles and PFS rates, along with 95% CIs, were estimated using the Kaplan-Meier method. [a] For minimum and maximum, + indicates a censored observation. [b] Randomisation stratification factors per IWRS: del(17p) presence and prior venetoclax treatment. [c] Based on the stratified Cox proportional hazards model.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib plus rituximab; IRC: Independent Review Committee; ITT: intention-to-treat; IWRS: interactive web-response system; max: maximum; min: minimum; n: number of patients per category; N: number of patients in the population.
Source: Eli Lilly (Data on File). CSR. Table 14.2.1.1.[91]

Figure 7: Kaplan-Meier plot of PFS based on IRC assessment (ITT population, 28th August 2023 data cut)

Footnotes: [a] Based on the stratified Cox proportional hazards model with stratification factor 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 the pirtobrutinib arm versus the Investigator's choice of IdelaR or BR arm; descriptive analysis only.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; del(17p): deletion of the short arm of chromosome 17; HR: hazard ratio; IdelaR: idelalisib plus rituximab; IWRS: Interactive Web Response System.
Source: Eli Lilly (Data on File). CSR. Table 14.2.1.[91]

Follow-up analysis (29th August 2024)

Longer follow-up allowed for data to continue to mature for IRC-assessed PFS data (

Table 25). At the follow-up analysis, a statistically significant and clinically meaningful improvement in IRC-accessed PFS continued to be observed for pirtobrutinib monotherapy compared to IdelaR or BR.

The median follow-up time for IRC-assessed PFS was 19.35 months (95% CI: 16.66, 22.14) in the pirtobrutinib arm and was 17.74 months (95% CI: 13.93, 22.90) in the Investigator's choice of IdelaR or BR arm. Longer follow-up (from the primary analysis) allowed the PFS data to further mature and pirtobrutinib monotherapy continued to show a clinically meaningful benefit in IRC assessed PFS compared to IdelaR or BR with an HR of 0.536 (95% CI: 0.385, 0.746; Figure 8).

Treatment with pirtobrutinib prolonged IRC-assessed median PFS by 5.22 months compared to IdelaR or BR. Median PFS in the pirtobrutinib arm was 13.96 months (95% CI: 11.24, 16.56) as compared to 8.74 months (95% CI: 8.08, 10.38) in the Investigator's choice of IdelaR or BR arm.

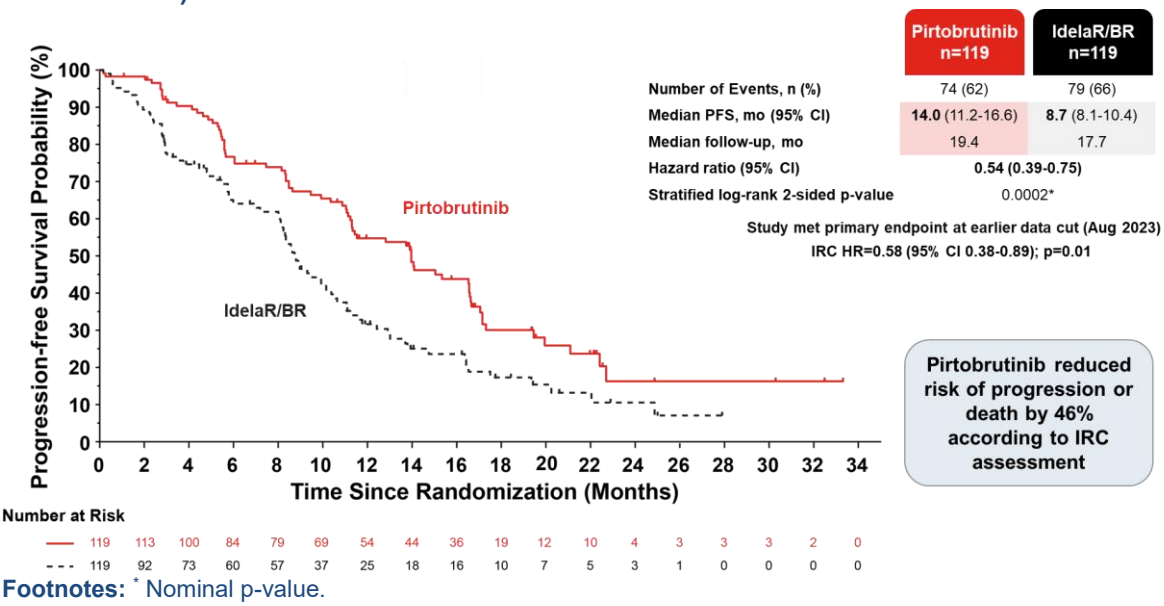
Sensitivity analyses of PFS by IRC were conducted as per the approach detailed in Table 20, and were supportive of the results of the primary efficacy analysis (see Appendix J.3 for further details).

Table 25: PFS based on IRC assessment (ITT population)

	Pirtobrutinib (N=119)	IdelaR or BR (N=119)
Number of events, n (%)	74 (62.2)	79 (66.4)
PD	60 (50.4)	66 (55.5)
Death	14 (11.8)	13 (10.9)
Censored, n (%)	[redacted]	[redacted]
Progression-free survival (months)[a]		
Median (95% CI)	13.96 (11.24, 16.56)	8.74 (8.08, 10.38)
min; max	[redacted]	[redacted]
Stratified analysis (versus the Investigator's choice of IdelaR or BR arm)[b]		
HR (95% CI)[c]	0.536 (0.385, 0.746)	
p-value[d]	0.0002	
Duration of follow-up (months)		
Median	19.35 (16.66, 22.14)	17.74 (13.93, 22.90)
25th, 75th percentiles	[redacted]	[redacted]

Footnotes: [a] For min and max, + indicates a censored observation. [b] Randomisation stratification factors per IWRS: del(17p) presence and prior venetoclax treatment. [c] Based on the stratified Cox proportional hazards model. [d] 2-sided p-value based on stratified log-rank test; descriptive analysis only.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib plus rituximab; IRC: Independent Review Committee; ITT: intention-to-treat; IWRS: interactive web-response system; max: maximum; min: minimum; n: number of patients per category; N: number of patients in the population.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 14.2.1.1.[103]

Figure 8: Kaplan-Meier plot of PFS based on IRC assessment (ITT population, 29th August 2024 data cut)



Footnotes: * Nominal p-value.

Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; IdelaR: idelalisib plus rituximab; ITT: intention-to-treat; INV: Investigator; mo: months; PFS: progression-free survival.
Source: Sharman et al. (2025).[104]

Subgroup analyses

Subgroup analyses of IRC-assessed PFS, at both the primary (29th August 2023) and follow-up (29th August 2024) analyses, showed a consistent treatment effect favouring pirtobrutinib in PFS across most subgroups, including, but not limited to, key subgroups defined by lines of prior systemic therapy, prior venetoclax treatment, reason for BTKi discontinuation, choice of comparator (IdelaR or BR), and the presence of high-risk prognostic factors such as unmutated *IGHV*, complex karyotype, and *TP53* mutation and/or deletion 17p. Please refer to Section 2.8.1 for further details on subgroup analyses.

2.6.1.2 Dual-exposed population

At the follow-up analysis, in those who had received prior treatment with both cBTKi and BCL2i therapy, the IRC-assessed PFS results showed clinically meaningful improvement for pirtobrutinib monotherapy compared to Investigator's choice of IdelaR or BR in PFS (HR: 0.539; 95% CI: 0.349, 0.831). Treatment with pirtobrutinib prolonged IRC-assessed median PFS by [redacted] months compared to IdelaR or BR (Table 26).

Table 26: PFS based on IRC assessment (Dual-exposed population)

	Pirtobrutinib (N=60)	IdelaR or BR (N=62)
Number of events, n	[redacted]	[redacted]
Progression-free survival (months)		
Median (95% CI)	[redacted]	[redacted]
Stratified analysis (versus the Investigator's choice of IdelaR or BR arm)		
HR (95% CI)	0.539 (0.349, 0.831)	

Footnotes: Median PFS was estimated using the Kaplan-Meier method. Hazard ratio and 95% CI (Wald) were estimated on the unstratified Cox model.
Abbreviations: CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib plus rituximab; N: total number of subjects in the population within the treatment group; n: number of patients in each subgroup.
Source: Eli Lilly (Data on File). CSR. Table 14.2.8.1.[91]

Figure 9: Kaplan-Meier plot of PFS based on IRC assessment (Dual-exposed population)

Footnotes: [a] Based on the unstratified Cox proportional hazards model, Arm A/Prior Ven Treatment: No vs Arm B/Prior Ven Treatment: Yes. [b] Based on the unstratified Cox proportional hazards model, Arm A/Prior Ven Treatment: Yes vs Arm B/Prior Ven Treatment: Yes.
Abbreviations: Arm A: Pirtobrutinib arm; Arm B: IdelaR or BR; HR: hazard ratio.
Source: Eli Lilly (Data on File). CSR. Figure 14.2.4.[91]

2.6.2 Secondary efficacy endpoint: Investigator-assessed PFS

2.6.2.1 ITT population

As a secondary endpoint, PFS assessed by the Investigator, is defined as the time from randomisation until the earlier occurrence of documented PD by Investigator or death without documented PD.

At the follow-up analysis, the PFS results based on Investigator assessments (Table 27; Figure 10) were consistent with the primary efficacy outcome, IRC-assessed PFS results, and showed clinically meaningful improvement for pirtobrutinib monotherapy compared to Investigator's choice of IdelaR or BR in PFS (HR: 0.48; 95% CI: 0.34, 0.67). Treatment with pirtobrutinib prolonged Investigator-assessed median PFS by 6.08 months compared to IdelaR or BR. Median PFS in the pirtobrutinib arm was 15.3 months (95% CI: 12.8, 19.9) and was 9.2 months (95% CI: 7.3, 10.6) in the IdelaR or BR arm.

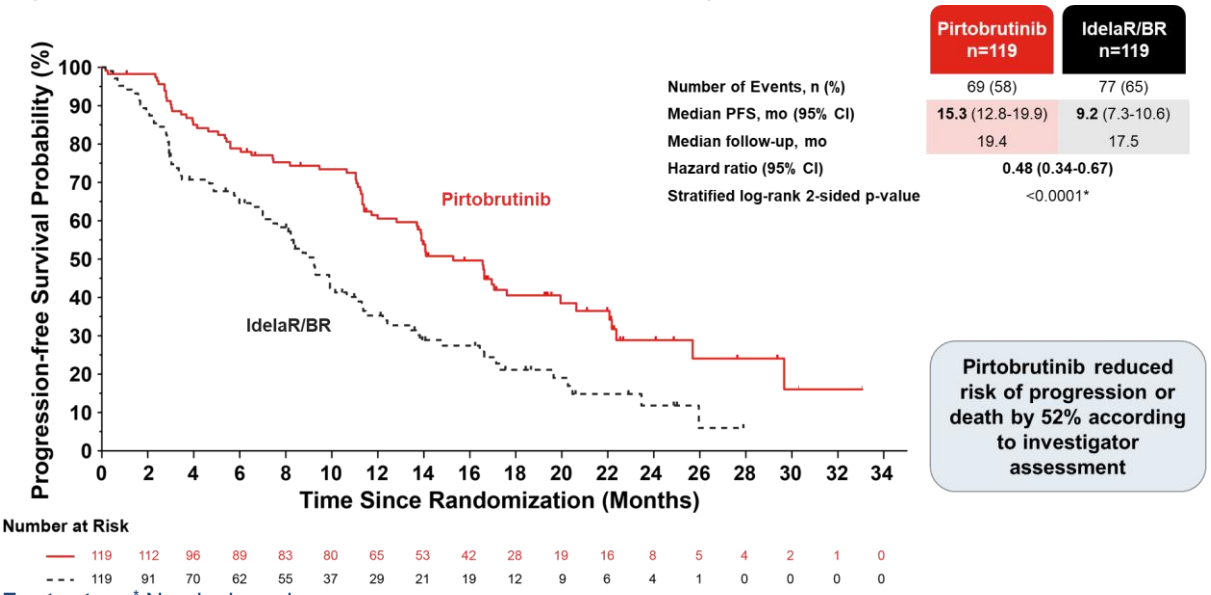
Table 27: PFS based on Investigator assessment (ITT population)

	Pirtobrutinib (N=119)	**IdelaR or BR (N=119)**
Number of events, n (%)	69 (58.0)	77 (64.7)
Progressive disease	57 (47.9)	66 (55.5)
Death	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Progression-free survival (months)[a]		
Median (95% CI)	15.3 (12.8, 19.9)	9.2 (7.3, 10.6)

min; max	[redacted]	[redacted]
Stratified analysis (versus the Investigator's choice of IdelaR or BR arm)[b]		
Hazard ratio (95% CI)[c]	0.475 (0.338, 0.669)	
p-value[d]	<0.0001	
Duration of follow-up (months)		
Median	19.4 (16.7, 22.0)	17.5 (13.9, 22.9)
25th, 75th percentiles	[redacted]	[redacted]

Footnotes: [a] For min and max, [+] indicates a censored observation. [b] Randomisation stratification factors per IWRS: del 17p presence and prior venetoclax treatment. [c] Based on the stratified Cox proportional hazards model. [d] 2-sided p-value based on stratified log-rank test.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; IdelaR: idelalisib plus rituximab; ITT: intention-to-treat; IWRS: interactive web-response system; max: maximum; min: minimum; n: number of patients per category; N: number of patients in the population.
Source: Eli Lilly (Data on File). CSR. Figure 14.2.1.2.[91]

Figure 10: Kaplan Meier plot of PFS based on Investigator Assessment (ITT population)



Footnotes: * Nominal p-value.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; IdelaR: idelalisib plus rituximab; ITT: intention-to-treat; INV: Investigator; mo: months; PFS: progression-free survival.
Source: Sharman et al. (2025).[104]

2.6.2.2 Dual-exposed population

At the follow-up analysis, in those who had received prior treatment with both cBTKi and BCL2i therapy, the Investigator-assessed PFS results showed clinically meaningful improvement for pirtobrutinib monotherapy compared to Investigator's choice of IdelaR or BR in PFS ([redacted]). Treatment with pirtobrutinib prolonged IRC-assessed median PFS by [redacted] months compared to IdelaR or BR (Table 28; Figure 11).

Table 28: PFS based on Investigator assessment (Dual-exposed population)

	Pirtobrutinib (N=60)	IdelaR or BR (N=62)
Number of events, n	[redacted]	[redacted]
Progression-free survival (months)		

	Pirtobrutinib (N=60)	IdelaR or BR (N=62)
Median (95% CI)	[redacted]	[redacted]
Stratified analysis (versus the Investigator's choice of IdelaR or BR arm)		
HR (95% CI)	[redacted]	

Footnotes: Median PFS was estimated using the Kaplan-Meier method. Hazard ratio and 95% CI (Wald) were estimated on the unstratified Cox model.
Abbreviations: CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib plus rituximab; N: total number of subjects in the population within the treatment group; n: number of patients in each subgroup.
Source: Eli Lilly (Data on File). CSR. Table 14.2.8.1.1.[91]

Figure 11: Kaplan Meier plot of PFS based on Investigator Assessment (ITT population)

Footnotes: [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 vs Arm B.
Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; Arm A: Pirtobrutinib; Arm B: IdelaR or BR.
Source: Eli Lilly (Data on File). CSR. Table 14.2.2.[91]

2.6.3 Secondary efficacy endpoints: IRC-assessed ORR and BOR

With the extended follow-up time from the primary analysis, ORR continued to mature until the follow-up analysis (29th August 2024). More patients achieved iwCLL responses, and ORR remained higher with pirtobrutinib monotherapy than for the Investigator's choice of IdelaR or BR arm, when assessed by IRC.

This improvement was seen in ORR of partial response (PR) or better, and of partial response with lymphocytosis (PR-L) or better. The IRC-assessed ORR of PR or better was greater for the pirtobrutinib arm (48.7%, 95% CI: 39.47, 58.07; Table 29) compared to the Investigator's choice of IdelaR or BR arm (38.7%, 95% CI: 29.87, 48.02; Table 29). Similar results were observed with disease control rate, where a continued improvement was seen for PR or better and stable disease (SD), and for PR-L or better.

Post hoc sensitivity analyses of IRC and Investigator-assessed ORR support increases in ORRs for both arms. Detailed descriptive results are presented in Appendix J.

Table 29: ORR and BOR based on IRC assessment (ITT population)

	Pirtobrutinib (N=119)	IdelaR or BR (N=119)
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
PR-L	[redacted]	[redacted]
SD	[redacted]	[redacted]
Non-PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
NA	[redacted]	[redacted]
ORR (ORR, PR or better)		
n (%)	58 (48.7)	46 (38.7)
95% Confidence Interval[a]	39.47, 58.07	29.87, 48.02
Stratified p value[b]	0.1100	
Duration of follow-up (months)		
Median (95% CI)	19.35 (16.66, 22.14)	17.74 (13.93, 22.90)
25th, 75th percentiles	[redacted]	[redacted]

Footnotes: Response as assessed by the IRC based on iwCLL 2018. For subjects with baseline timepoint only and no post baseline timepoints available, BOR is N/A. [a] 2-sided confidence interval is calculated based on the exact binomial method (Clopper-Pearson). [b] 2-sided p-value based on CMH test stratified by the randomisation strata.
Abbreviations: BOR: best overall response; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CR: complete response; IRC: independent review committee; ITT: intention-to-treat; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; NA: not applicable; NE: not evaluable; ORR: overall response rate; PD: progressed disease; PR: partial response; PR-L: partial response with lymphocytosis; SD: stable disease.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 14.2.3.1.[103]

2.6.4 Secondary efficacy endpoint: OS

2.6.4.1 ITT population

The results of OS data analysis, presented in Table 30, are considered to be confounded by crossover treatment of the Investigator's choice of IdelaR or BR arm where eligible patients were allowed to crossover to receive pirtobrutinib at the time of IRC-confirmed PD. Among the 66 patients with PD in IdelaR or BR arm, 50 patients crossed over to pirtobrutinib treatment, resulting in an effective crossover rate of 75.8%. The 50 crossover patients were exposed to pirtobrutinib for a median duration of [redacted] months (range: [redacted] months), and this crossover period allowed patients to derive [redacted] benefit from pirtobrutinib as evidenced by the response rate, PFS, and OS in patients after crossover following PD on IdelaR or BR treatment (efficacy data for the crossover population are presented in Appendix J.2). Several sensitivity analyses for OS were conducted to evaluate the confounding impact of crossover on OS interpretation. Please refer to Section 2.4.2.3 for details on the methodology of the sensitivity analyses and below (Section 2.6.4.1) for the results of these analyses.

The final OS analysis was planned to occur approximately 12 months after the primary analysis of the PFS, or when approximately 70 OS events were observed. Longer follow-up allowed OS data to continue to mature, and the prespecified final analysis occurred with the preplanned 70 OS events. However, the results of OS data analysis remain uncertain with an HR of 1.090, and a wide 95% confidence interval (95% CI: 0.679, 1.749) and overlapping KM curves (Figure 12). Median OS was 29.67 months (95% CI: 27.10, not evaluable [NE]) in the pirtobrutinib arm and was reached when few patients were being followed, producing a less reliable estimate of median OS; in the Investigator's choice of IdelaR or BR arm, median OS was NR (95% CI: 28.88, NE). The 18-month OS rate in the pirtobrutinib arm was 73.4% (95% CI: 63.9, 80.7) and in the Investigator's choice of IdelaR or BR arm was 70.8% (95% CI: 60.9, 78.7) at the final OS analysis.

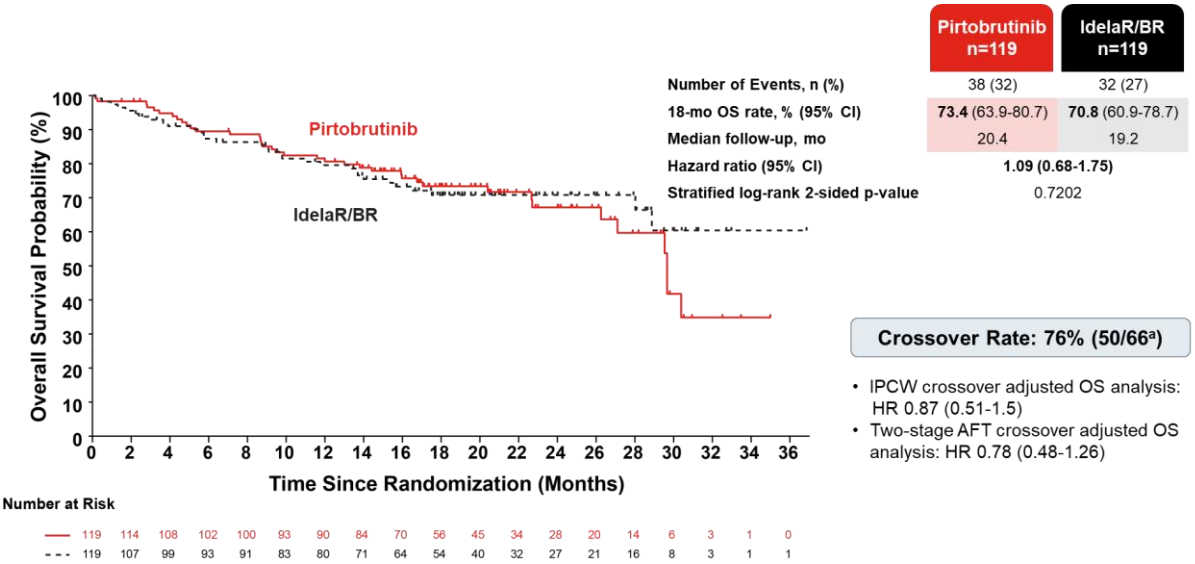
Table 30: OS for patients in BRUIN CLL-321 (ITT population)

Parameter	Pirtobrutinib (N = 119)	IdelaR or BR (N = 119)
Number of Deaths, n (%)	38 (31.9)	32 (26.9)
Number of Patients Censored, n (%)	[redacted]	[redacted]
Alive at data cutoff	[redacted]	[redacted]
Study exit	[redacted]	[redacted]
Unknown survival status	[redacted]	[redacted]
Overall Survival Time (months)[a]		
Median (95% CI)	29.67 (27.10, NE)	NR (28.88, NE)
Min, Max	[redacted]	[redacted]
Stratified Analysis (versus the Investigator's choice of IdelaR or BR arm)[b]		
HR (95% CI)[c]	1.090 (0.679, 1.749)	
p-value[d]	0.7202	
OS Follow-up Time (months)		
Median (95% CI)	20.37 (18.23, 21.88)	19.22 (18.10, 21.06)
Min, Max	[redacted]	[redacted]
Overall Survival Rate, % (95% CI)		
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
15 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]

Footnotes: [a] For min and max, [+] indicates a censored observation. [b] Randomisation stratification factors per IWRS: del(17p) presence and prior venetoclax treatment. [c] Based on the stratified Cox proportional hazards model.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; IdelaR: idelalisib plus rituximab; IRC: Independent Review Committee; ITT: intention-to-treat; IWRS: interactive web-response system; max: maximum; min: minimum; n: number of patients per category; N: number of patients in the population; NA: not applicable.

Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR.[91]

Figure 12: Kaplan-Meier plot of OS (ITT population; including crossover period)



Footnote: [a]Among patients whose event was INV PD and thus had the opportunity to crossover.
Abbreviations: AFT: adjusted for treatment; BR: bendamustine + rituximab; CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib + rituximab; IPCW: inverse-probability-of-censoring weighting; mo: months; NE: not estimable; NR: not reached; OS: overall survival.
Source: Sharman et al. (2025).[104]

Sensitivity analyses of OS

A prespecified sensitivity analysis of OS censored patients at the time of crossover from the Investigator's choice of IdelaR or BR arm, to pirtobrutinib treatment. In this sensitivity analysis, 38 (31.9%) patient deaths occurred in the pirtobrutinib arm, and 22 (18.5%) patient deaths occurred in the Investigator's choice of IdelaR or BR arm.

Two additional post hoc analyses adjusted for crossover were conducted using the IPCW modelling method and the Two-Stage AFT modelling method. Please refer to 2.4.2.3 for further details on these modelling methods.

As presented in Table 31, all three sensitivity analyses meaningfully adjusted the OS hazard ratios below 1, indicating a notable crossover impact on OS and less likelihood of a detrimental effect on OS with pirtobrutinib treatment.

Table 31: Results of sensitivity analyses of OS (29th August 2024 data cut)

	Pirtobrutinib versus IdelaR or BR, HR (95% CI)
Pre-specified sensitivity analysis	
Patients censored at the time of crossover	0.986 (0.570, 1.706)
Post-hoc sensitivity analyses	
IPCW method	0.872 (0.507, 1.500)
Two-stage AFT method	0.776 (0.479, 1.258)

Abbreviations: AFT: accelerated failure time; BR: bendamustine with rituximab; CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib with rituximab; IPCW: inverse probability censoring weighting; OS: overall survival.
Source: Eli Lilly (Data on File). BRUIN CLL-321 Clinical Evidence Module.[105]

2.6.4.2 *Dual-exposed population*

At the follow-up analysis, in those who had received prior treatment with both cBTKi and BCL2i therapy, the results of OS data analysis remained uncertain with an HR of [redacted], and a wide 95% confidence interval ([redacted]; Table 32; Figure 13)

Table 32: PFS based on Investigator assessment (Dual-exposed population)

	Pirtobrutinib (N=60)	IdelaR or BR (N=62)
Number of events, n	[redacted]	[redacted]
Progression-free survival (months)		
Median (95% CI)	[redacted]	[redacted]
Stratified analysis (versus the Investigator's choice of IdelaR or BR arm)		
HR (95% CI)	[redacted]	

Footnotes: Median OS was estimated using the Kaplan-Meier method. Hazard ratio and 95% CI (Wald) were estimated on the unstratified Cox model.
Abbreviations: CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib plus rituximab; N: total number of subjects in the population within the treatment group; NE: not estimable; n: number of patients in each subgroup.
Source: Eli Lilly (Data on File). CSR. Table 14.2.8.2.[91]

Figure 13: Kaplan Meier plot of OS (Dual-exposed population)

Footnotes: [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 vs Arm B.
Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; Arm A: Pirtobrutinib; Arm B: IdelaR or BR; NR: Not Reached.
Source: Eli Lilly (Data on File). CSR.[91]

Subgroup analyses of OS

Generally, subgroup analyses of OS were consistent with the final OS analysis in the ITT population (Section 2.8.2). However, the small number of patients with events in each treatment arm within each subgroup, and the confounding impact of crossover on OS results in general, limit the interpretation of subgroup analyses of OS.

2.6.5 Secondary efficacy endpoint: TTNT

2.6.5.1 ITT population

Follow-up analysis (29th August 2024)

Pirtobrutinib monotherapy resulted in improved TTNT (HR = 0.37, 95% CI: 0.25, 0.52) compared to those receiving IdelaR or BR. Treatment with pirtobrutinib prolonged median TTNT by approximately 13.1 months compared the Investigator's choice of IdelaR or BR arm. As presented in Table 33, the median TTNT was longer for pirtobrutinib (24.0 months, 95% CI: 17.8, 29.7) than for the Investigator's choice of IdelaR or BR arm (10.9 months, 95% CI: 8.7, 12.5).

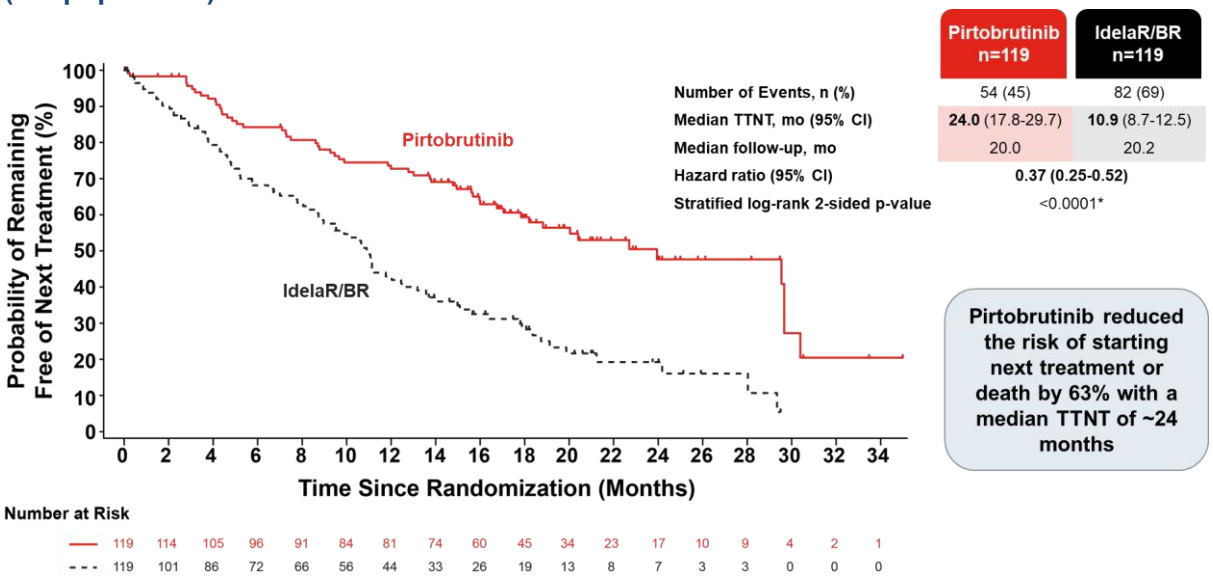
The proportion of patients remaining free of next treatment was numerically higher for the pirtobrutinib arm compared to the Investigator's choice of IdelaR or BR arm beginning at three months (the pirtobrutinib arm: [redacted]; the Investigator's choice of IdelaR or BR arm: [redacted]) and continuing through 24 months (the pirtobrutinib arm: [redacted]; the Investigator's choice of IdelaR or BR arm: [redacted]).

Table 33: Time to next treatment (ITT population)

	Pirtobrutinib (N=119)	IdelaR or BR (N=119)
Number of events, n (%)	54 (45.4)	82 (68.9)
Subsequent anticancer therapy	[redacted]	[redacted]
Death	[redacted]	[redacted]
Crossover from Investigator's choice of IdelaR or BR to pirtobrutinib therapy	[redacted]	[redacted]
TTNT, (months)		
Minimum, maximum	[redacted]	[redacted]
Median (95% CI)	24.0 (17.8, 29.7)	10.9 (8.7, 12.5)
25th, 75th percentiles	[redacted]	[redacted]
TTNT follow-up time (months), n (%)		
Median (95% CI)	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Stratified Analysis (versus the Investigator's choice of IdelaR or BR arm)		
Hazard ratio (95% CI)[c]	0.37 (0.25, 0.52)	
p-value[d]	<0.0001	

Abbreviations: CI: confidence interval; N: total number of participants; n: number of participants in a subgroup; TTNT: time to next treatment.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 14.2.7.[103]

Figure 14: Kaplan Meier plot of time to next treatment based on Investigator Assessment (ITT population)



Footnotes: * Nominal p-value.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; IdelaR: idelalisib plus rituximab; ITT: intention-to-treat; INV: Investigator; mo: months; PFS: progression-free survival; TTNT: time to next treatment.
Source: Sharman et al. (2025).[104]

2.6.5.2 Dual-exposed population

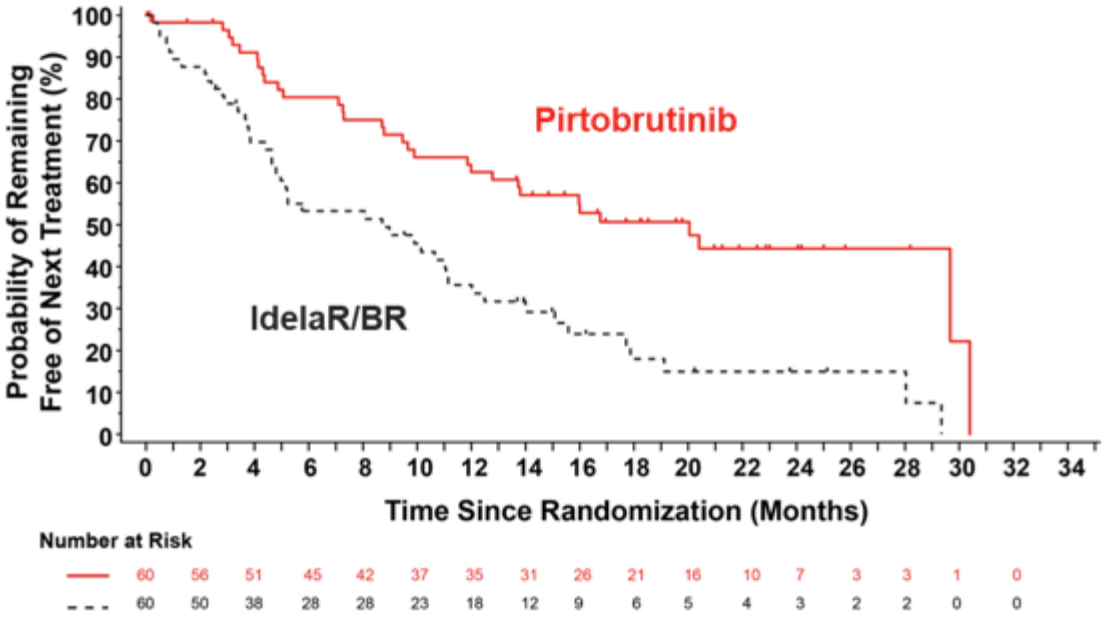
Pirtobrutinib monotherapy resulted in improved TTNT (HR = 0.37, 95% CI: 0.23, 0.60), in those who had received prior treatment with both cBTKi and BCL2i therapy, compared to those receiving IdelaR or BR. Treatment with pirtobrutinib prolonged median TTNT by approximately 11.3 months compared the Investigator's choice of IdelaR or BR arm (Table 34; Figure 15).

Table 34: Time to next treatment (Dual-exposed population)

	Pirtobrutinib (N=60)	IdelaR or BR (N=60)
Progression-free survival (months)		
Median	20.0	8.7
Stratified analysis (versus the Investigator's choice of IdelaR or BR arm)		
HR (95% CI)	0.37 (0.23, 0.60)	
Stratified log-rank 2-sided p-value	<0.0001	

Footnotes: * Nominal p-value. Median TTNT was estimated using the Kaplan-Meier method. Hazard ratio and 95% CI (Wald) were estimated on the unstratified Cox model.
Abbreviations: CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib plus rituximab; N: total number of subjects in the population within the treatment group; NE: not estimable; n: number of patients in each subgroup.
Source: Sharman et al. (2025).[104]

Figure 15: Kaplan Meier plot of time to next treatment (Dual-exposed population)



Footnotes: * Nominal p-value.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; IdelaR: idelalisib plus rituximab; ITT: intention-to-treat; mo: months; PFS: progression-free survival; TTNT: time to next treatment.
Source: Sharman et al. (2025).[104]

2.7 *Subsequent treatments used in the relevant studies*

In BRUIN CLL-321, administration of subsequent anticancer therapies were not allowed until:

- There was evidence of PD any time during treatment as established according to the iwCLL 2018 criteria, or
- A patient withdrew from study treatment

After treatment with the study drug was complete, the following information on subsequent anticancer therapies were collected:

- Receipt of all subsequent anticancer therapies
- iwCLL indication for initiation of subsequent anticancer therapy
- Response to all subsequent anticancer therapies

These data were collected approximately every 12 weeks (Q12W) after the SFU visit for the first two years, and approximately every 24 weeks (Q24W) thereafter until death, withdrawal by patient, loss to follow-up, or study termination, or whichever came first.

Details of the subsequent anticancer data, excluding crossover patients, are presented in Table 35. Further details on subsequent treatments and related costs (post-progression drug acquisition costs), are detailed in Section 3.5.2. The most common subsequent anticancer therapy in both the post-BTKi populations and the dual-exposed population was BCL2 inhibitor therapies. Specifically, in the post-BTKi group, venetoclax was most frequently used, and across both populations, Anti-CD20 antibody therapy was also commonly administered in combination with venetoclax or idelalisib, in line with its expected use in clinical practice.

Table 35: Subsequent anticancer data from BRUIN CLL-321

Treatment class	Post-BTKi population		Dual-exposed population	
	Pirtobrutinib	Inv. choice	Pirtobrutinib	Inv. choice
Patients with ≥1 subsequent anticancer therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Covalent BTK inhibitor, n (%)				
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Non-covalent BTK inhibitor, n (%)				
Pirtobrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
BCL2 inhibitor				
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy				
FCR or Other	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 antibody				
Rituximab, Obinutuzumab or Other	[redacted]	[redacted]	[redacted]	[redacted]
PI3K agent				
Idelalisib or Other	[redacted]	[redacted]	[redacted]	[redacted]
IMID/immunomodulator				
Lenalidomide or Other	[redacted]	[redacted]	[redacted]	[redacted]
CAR-T				
CAR-T	[redacted]	[redacted]	[redacted]	[redacted]
Stem cell transplant				
Allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Other treatments				
Other systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]
Other molecular pathways/small molecule inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Time from first dose to subsequent anticancer therapy				
Mean, months (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The total values presented in this table differ from those in the TTNT analysis as though each therapy is listed individually, some are used in combination (e.g., for VenR). This analysis also accounts for patients who could have received multiple lines of therapy (e.g., VenR followed by CAR-T cell therapy).
Abbreviations: Allo-SCT: allogeneic stem cell transplant; BCL2: B-cell lymphoma 2 inhibitor; BTKi: Bruton tyrosine kinase inhibitor; CAR-T: chimeric antigen receptor T-cell therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide, and rituximab; IMID: immunomodulatory drug; Inv. choice: investigator's choice; PI3K: phosphoinositide 3-kinase; SCT: stem cell transplant.
Source: Eli Lilly (Data on File). CSR. Table 14.1.4.6.[91]

2.8 Subgroup analysis

2.8.1 IRC-assessed PFS

The subgroup analyses of IRC-assessed PFS showed a consistent treatment effect favouring pirtobrutinib in PFS across most subgroups, including, but not limited to, key subgroups defined by lines of prior systemic therapy, prior venetoclax treatment, reason for BTKi discontinuation, choice of comparator (IdelaR or BR), and the presence of high-risk prognostic factors such as unmutated *IGHV*, complex karyotype, and *TP53* mutation and/or deletion 17p The key median IRC-assessed PFS for patients in each the pirtobrutinib arm individual subgroup analyses are shown in Figure 16, with additional subgroup analyses presented in Appendix C.

Subgroup of Intended Comparator

The IRC-assessed PFS was favourable with pirtobrutinib relative to each intended comparator (Figure 16). Compared to IdelaR, pirtobrutinib reduced the risk of PD or death by [redacted] ([redacted]), and compared to BR, pirtobrutinib reduced the risk of PD or death by [redacted] ([redacted]). Median PFS in the pirtobrutinib arm was 13.96 months (95% CI: 11.24, 16.56;

Table 25) as compared to median PFS of [redacted] months ([redacted]) in the subgroup of patients assigned IdelaR treatment, and 8.21 months ([redacted]) in the subgroup of patients assigned BR treatment.

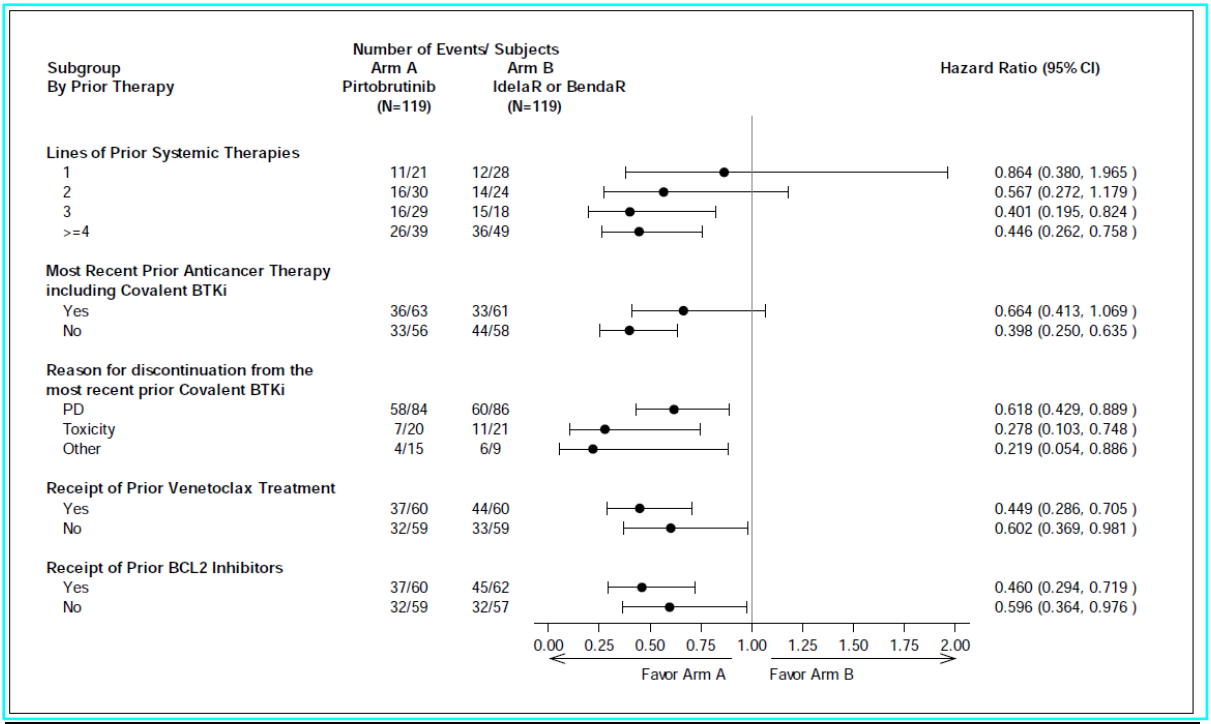
Figure 16: Forest plot of PFS based on IRC assessment for the population in the BRUIN CLL-321 trial

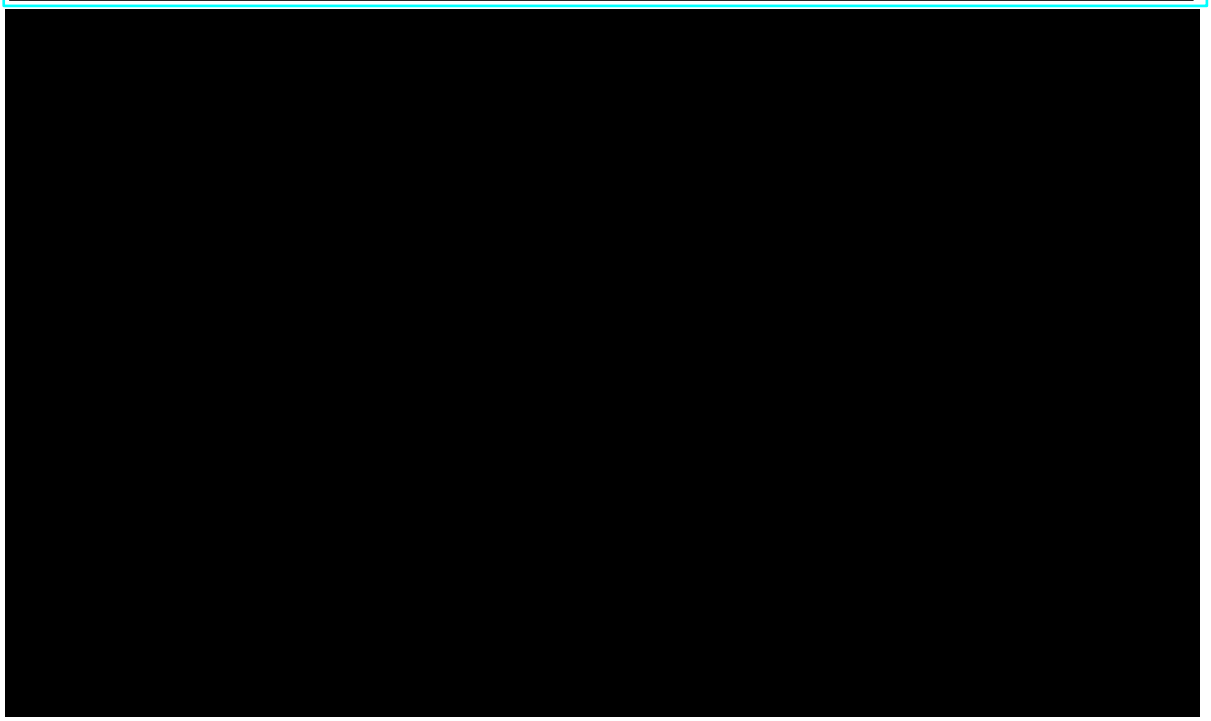
Abbreviations: BCL2: B-cell lymphoma 2; BR: bendamustine plus rituximab; BTKi: Bruton tyrosine kinase inhibitor; CI: confidence interval; CLL: chronic lymphocytic leukaemia; IdelaR: idelalisib plus rituximab; IRC: independent review committee; IWRS: Interactive Web Response System; PD: progressed disease; PFS: progression-free survival.
Source: Eli Lilly (Data on File). CSR Addendum 2. Figure 14.7.1.[103]

2.8.2 *Investigator-assessed PFS*

The Investigator-assessed PFS was favourable with pirtobrutinib relative to each intended comparator (Figure 17). Pirtobrutinib reduced the risk of PD or death compared to IdelaR ([redacted]), and compared to BR ([redacted] Median PFS in the pirtobrutinib arm was 15.3 months (95% CI: 12.8, 19.9) and was [redacted] months ([redacted]) in the IdelaR or BR arm.

Figure 17: Forest plot of PFS based on Investigator assessment for the population in the BRUIN CLL-321 trial





2.8.3 OS

A summary of the subgroup analyses of OS are presented in Table 36 and Figure 18. Generally, subgroup analyses of OS were consistent with the final OS analysis in the ITT population. However, the small number of patients with events in each treatment arm within each subgroup, and the aforementioned confounding impact of crossover on OS results in general, limit the interpretation of subgroup analyses of OS.

Table 36: Summary of OS separated by intended comparator (ITT population; including crossover period)

	Pirtobrutinib (N=119)	IdelaR (N=82)
Number of Deaths, n (%)	38 (31.9)	[redacted]
Number of Patients Censored, n (%)	[redacted]	[redacted]
Alive at data cutoff	[redacted]	[redacted]
Study exit	[redacted]	[redacted]
Unknown survival status	[redacted]	[redacted]

Abbreviations: ITT: intention-to-treat; N: total number of participants; OS: overall survival.
Source: Eli Lilly (Data on File). BRUIN CLL-321 Clinical Evidence Module. Table JZNN.8.13.[105]

Figure 18: Forest plot of OS for the population in the BRUIN CLL-321 trial

Abbreviations: BCL2: B-cell lymphoma 2; BR: bendamustine plus rituximab; BTKi: Bruton tyrosine kinase inhibitor; CI: confidence interval; CLL: chronic lymphocytic leukaemia; IdelaR: idelalisib plus rituximab; IRC: independent review committee; IWRS: Interactive Web Response System; PD: progressed disease; PFS: progression-free survival.
Source: Eli Lilly (Data on File). BRUIN CLL-321 Clinical Evidence Module. Table JZNN.8.2.[105]

2.9 Meta-analysis

A meta-analysis was not conducted as there was no head-to-head comparisons between pirtobrutinib and all comparators within the scope of this submission. Network meta-analyses

(NMA) were also not conducted, based on a robust feasibility assessment of the available literature in R/R CLL. Further details are discussed in Section 2.10.

2.10 Indirect and mixed treatment comparisons

2.10.1 Feasibility assessment

A robust feasibility assessment (FA) was conducted using the available trial data to investigate their suitability to inform ITCs against a range of comparators in the subpopulations of interest in the post-BTKi population. This FA was conducted from a global perspective, but the results are applicable to the UK setting of this submission.

2.10.1.1 Background

Background and objectives

Head-to-head data for pirtobrutinib and the relevant comparator in this submission (IdelaR) are available from the BRUIN CLL-321 trial. However, in the subgroup of patients who have received prior treatment with a BTKi but are naïve to, and suitable for, treatment with venetoclax – i.e., the post-cBTKi, suitable for current SoC subpopulation – it is anticipated that VenR would be a relevant comparator therapy, alongside IdelaR. Additionally, in the subgroup of patients who have received prior treatment with a BTKi but have discontinued treatment due to TEAEs or intolerance, it is anticipated that covalent BTKi would be a relevant comparator. However, there are currently no head-to-head studies comparing pirtobrutinib against these comparators.

An SLR was conducted in September 2023, to identify studies on treatments for R/R CLL. The inclusion criteria for this original SLR search focused on studies involving patients previously treated with any treatment, due to a limited number of studies identified in the target population (patients with CLL/SLL pre-treated with a BTKi) to enable an NMA. A specific interest noted in the FA is understanding the feasibility of comparing a population pre-treated with a BTKi, versus a population pre-treated with other agents as few studies have included a BTKi-pre-treated patient population.

Based on the results of the September 2023 SLR, the FA prioritised assessing the feasibility of performing an NMA using evidence for the pre-treated with BTKi population of interest (consistent with the trial inclusion criteria and the proposed label). The FA also considered the possibility of including evidence from a broader population, R/R CLL/SLL patients pre-treated with any previous treatment, to enable a connected network of evidence.

A key consideration for the similarity assessment of the FA was the evaluation of heterogeneity across studies of the two populations, particularly their pre-treatment regimens. Two networks, therefore, were considered to assess the connection with BRUIN CLL-321:

- R/R CLL/SLL patients pre-treated with BTKi (including dual-exposed patients who have been previously treated with BTKi and BCL2i therapy)
- R/R CLL/SLL patients pre-treated with any prior treatment

Please note that the PICO framework for the feasibility assessment differs slightly from that used in the SLR. While the SLR aimed to capture all evidence across the R/R CLL population, the

feasibility assessment aimed to focus exclusively on PICO analyses relevant from an HTA perspective. Furthermore, despite the February 2025 clinical SLR update, no new studies were identified that would challenge the findings of this analysis conducted based on the September 2023 searches.

Populations, comparators and outcomes of interest

Populations

The following patient populations were considered in the FA:

- Pre-treated with BTKi: R/R patients who have previously been treated with BTKis (ibrutinib, zanubrutinib, acalabrutinib, pirtobrutinib)
- Pre-treated with BTKi and BCL2i (dual-exposed): R/R patients who have previously been treated with both a BTKi (one or more) and BCL2i (venetoclax)
- Pre-treated with any regimen: R/R patients who have previously been treated with therapeutic regimens of any type

Aligning with the population recruited in the BRUIN CLL-321 study, providing comparative efficacy and safety of pirtobrutinib vs comparators for patients pre-treated with BTKi was of primary interest. However, only one RCT (UNITY-CLL) reporting outcome data for this population was identified. Further, this study did not investigate treatments of interest, as it focused on umbralisib, which has been discontinued for use.[106] Notably, the MURANO trial included patients who had previously been treated with BTKi therapy, however, they reported that less than 3% patients had received a BCRi (which encompasses additional therapies with differing mechanisms of action to that of BTKi therapy [BTKi and PI3Ki therapies]), thus making it difficult to interpret meaningful outcomes specifically within the primary population of interest recruited in the BRUIN CLL-321 trial.[107] Thus, ITCs restricted to this population were deemed not to be feasible.

Similarly, for patients pre-treated with BTKi and BCL2i (dual-exposed), only the UNITY-CLL trial allowed recruitment of patients who had previously received both a BTKi and BCL2i, with <1% of the population previously receiving a BCL2i, and no outcome data presented for this subgroup.[108] Thus, ITCs restricted to this population were also deemed not to be feasible.

In the absence of sufficient data for ITCs for the first two populations, a third population comprising patients pre-treated with any regimen was also considered. The similarity assessment (presented in Section 2.10.1.2) explored the appropriateness of combining evidence from the BRUIN CLL-321 population pre-treated with a BTKi (+/- BCL2i) and the studies identified from the SLR recruiting populations pre-treated with any treatment. Where significant heterogeneity between studies was identified, and the assumptions necessary for an NMA were thought to have been violated, alternative analytic methods are recommended (further details on the alternate methods are presented in Section 2.10.1.3). However, these methods cannot compensate for the fundamental differences between trial populations across the included studies.

Comparators

Based on current treatment guidelines (including key regional guidelines i.e., ESMO and NCCN guidelines),[2, 49] NICE technology appraisals and the wider scope of the globally focussed FA —

designed to address the needs of multiple healthcare systems — the treatments outlined in Table 37 were designated as comparators of interest. While this global FA covers a broad range of comparators, not all of these treatments are available within the NHS, and the selection reflects both the global context and the specific considerations relevant to the UK healthcare system.

Table 37: Comparators of interest for the NMA FA

Treatment type	Treatment name
HSCT	• AlloSCT
BCL2i	• Ven-mono • VenR • VenI • VenO
Non-covalent BTKi	• Pirtobrutinib
Covalent BTKi	• Ibrutinib monotherapy • Ibrutinib in combination with rituximab • Zanubrutinib • Acalabrutinib
PI3Ki	• IdelaR • Duvelisib
CIT	• BR • O-Clb

Abbreviations: AlloSCT: allogeneic stem cell transplant; BCL2i: B-cell lymphoma 2 inhibitor; BR: bendamustine in combination with rituximab; BTKi: Bruton's tyrosine kinase inhibitor; CIT: chemoimmunotherapy; FA: feasibility assessment; HSCT: hematopoietic stem cell transplant; IdelaR: idelalisib in combination with rituximab; NMA: network meta-analysis; O-Clb: obinutuzumab in combination with chlorambucil; VenI: venetoclax in combination with ibrutinib; Ven-mono: venetoclax monotherapy; VenO: venetoclax in combination with obinutuzumab; VenR: venetoclax in combination with rituximab.

Outcomes

Efficacy outcomes of interest were OS, PFS, ORR, CR, PR and DOR. Safety outcomes of interest were all-cause discontinuation, overall AEs, Grade ≥3 AEs, SAEs, discontinuation due to AEs and discontinuation due to progressive disease. The EORTC-QLQ C30 questionnaire was deemed as a HRQoL outcome of interest.

Studies excluded from the FA

A total of 25 unique RCTs were included for consideration in the FA, and 18 studies were excluded from the FA and are listed in Table 38 alongside reasons for exclusion. Five studies reported an outcome of interest to the NMA, assessed at least two treatments of interest and thus were included in the FA. Furthermore, two additional studies were added to the FA as they reported an outcome of interest and included a treatment of interest (DUO) or presented a study providing a bridge to the potential network of evidence (RESONATE). Studies included in the FA are summarised in Table 39.

Table 38: Studies excluded from the NMA FA

#	Study	Reason for exclusion	Details
1	152CL201/LUCID	No treatment arms of interest	Treatment arms FCR vs FCR+L are not comparators of interest

#	Study	Reason for exclusion	Details
2	REACH	No treatment arms of interest	Treatment arms FCR vs FC are not comparators of interest
3	HELIOS	Only one treatment arm of interest	Treatment arm ibrutinib + bendamustine + rituximab is not comparator of interest (studied vs bendamustine + rituximab)
4	NCT01569295	Only one treatment arm of interest	Treatment arm idelalisib + bendamustine + rituximab is not comparator of interest (studied vs bendamustine + rituximab)
5	NCT0165902	No treatment arms of interest	Treatment arms idelalisib + ofatumumab vs ofatumumab not comparators of interest
6	NCT02537613	No treatment arms of interest	Treatment arms obinutuzumab vs obinutuzumab + ibrutinib not comparators of interest
7	CHRONOS-3	No treatment arms of interest	Treatment arms rituximab + copanlisib vs rituximab are not comparators of interest
8	NCT01973387	Only one treatment arm of interest	Treatment arm of rituximab is not comparator of interest (studied vs ibrutinib)
9	MABLE	Only one treatment arm of interest	Treatment arm of rituximab + chlorambucil is not comparator of interest (studied vs bendamustine + rituximab)
10	GENUINE	Only one treatment arm of interest	Treatment arm of ublituximab + ibrutinib not comparator of interest (studied vs ibrutinib)
11	NCT01539512	Only one treatment arm of interest	Treatment arm of rituximab is not comparator of interest (studied vs idelalisib + rituximab)
12	UNITY-CLL[24]	Only one treatment arm of interest	Treatment arm umbralisib + ublituximab not comparator of interest (studied vs obinutuzumab + chlorambucil)
13	NCT02337829	Dose comparison study, only one treatment arm of interest	Treatment arm acalabrutinib 200mg QD not of interest (studied vs acalabrutinib 100mg BID)
14	Gritti 2012	Dose comparison study, no treatment arms of interest	Treatment arm of alemtuzumab 3 injections of 10 mg/week not of interest (studied vs 1 infusion of 30 mg/week)
15	NCRI CLL201 (NR)	No treatment arms of interest	Treatment arms of FCR + mitoxantrone vs FC + mitoxantrone are not comparators of interest
16	NCT01313689	No treatment arms of interest	Treatment arms of ofatumumab vs physicians' choice of therapy are not comparators of interest
17	UNITY-NHL	Dose escalation study, no treatment arms of interest	Treatment arms umbralisib vs umbralisib (dose escalation) are not comparators of interest
18	NCT02912754	Only one treatment arm of interest	Treatment arm of ibrutinib + ruxolitinib is not comparator of interest (studied vs ibrutinib)

Abbreviations: BID: twice daily; BR: bendamustine plus rituximab; FA: feasibility assessment; FC: fludarabine in combination with cyclophosphamide; FCR: fludarabine in combination with cyclophosphamide and rituximab; NMA: network meta-analysis; QD: once daily.

2.10.1.2 Similarity assessment

Studies included in the feasibility assessment

A total of eight studies were included in the NMA FA, comprising BRUIN CLL-321 and the seven studies from the SLR; the included studies reported on 10 different treatment regimens. Notably, only one study provided data for a R/R population pre-treated with BTKi therapy (BRUIN 321-CLL). Table 39 provides an overview of the included studies and available patient populations.

For the included studies, the similarity assessment was performed on the following items:

- Population characteristics
    - Treatment effect modifiers
    - Prognostic markers
    - Baseline characteristics
    - Prior treatments
    - Other variables
- Interventions and comparators
    - Dosing and treatment regimens
    - Investigator's choice treatment arm (when relevant)
- Outcomes reported
    - Reported outcomes by study
    - Outcome definitions
- Study design
    - Study dates
    - Multi-center versus single-center studies
    - Study locations
    - Study phase
    - Sample size
    - Length of follow-up
    - Eligibility criteria

Table 39: Studies included in the NMA FA

Study	Intervention and comparator	Study population enrolled	Trial country/region	Study design	Sample size
BRUIN CLL-321[83, 92]	• Pirtobrutinib • Investigator's choice (IdelaR or BR)	R/R CLL or SLL patients, previously treated with BTKi	Multinational (Australia, Austria, Belgium, Canada, China, Croatia, Czechia, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Korea, Republic of, Poland, Russian Federation, Singapore, Spain, Switzerland, Taiwan, Turkey, UK, US)	Multicentre, Phase III RCT	238
ALPINE[99]	• Ibrutinib • Zanubrutinib	R/R CLL or SLL patients ⩾18 years	Multinational (North America, Europe, Asia-Pacific)	Multicentre, Phase III RCT	652
ASCEND[101]	• Acalabrutinib • Investigator's choice (IdelaR or BR)	Previously treated CLL patients ⩾18 years	Multinational (US, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czechia, France, Germany, Hong Kong, Hungary, Israel, Italy, Korea, New Zealand, Poland, Russia, Singapore, Slovakia, Spain, Sweden, Taiwan, Ukraine, UK)	Multicentre, Phase III RCT	310
ELEVATE RR[100]	• Acalabrutinib • Ibrutinib	Previously treated patients with ⩾18 years of age or older; diagnosis of CLL	Multinational (US, Australia, Israel, Turkey, Belgium, Demark, France, Germany, New Zealand, Poland, Italy,	Multicentre, Phase III RCT	533

			Netherlands, Hungary, Spain, UK		
MURANO[107]	• VenR • BR	R/R patients with CLL ⩾ 18 years that required therapy; received one to three previous treatments (including at least one chemotherapy-containing regimen)	Multinational (US, Australia, Austria, Czechia, Korea, Belgium, Canada, Demark, France, Germany, New Zealand, Poland, Italy, Netherlands, Norway, Hungary, Russia, Spain, Sweden, Taiwan, UK)	Multicentre, Phase III RCT	389
NCT02007044[109]	• Ibrutinib + rituximab • Ibrutinib	Previously treated CLL/SLL patients or untreated patients with 17p deletion (del17p) or TP53 mutation were also permitted	US	Single centre, phase II RCT	208; 181 pre-treated
DUO[110]	• Ofatumumab • Duvelisib	R/R CLL or SLL patients who are BTKi naïve	US, Australia, Austria, Belgium, France, Germany, Hungary, Italy, New Zealand, Spain and UK	Multicentre, Phase III RCT	319
RESONATE[111]	• Ibrutinib • Ofatumumab	CLL/SLL patients who received at least one prior therapy	US, Australia, and seven European countries	Multicentre, Phase III RCT	391

Abbreviations: BR: bendamustine in combination with rituximab; BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; FA: feasibility assessment; IdelaR: idelalisib in combination with rituximab; NMA: network meta-analysis; RCT: randomised controlled trial; R/R: relapsed or refractory; SLL: small lymphocytic lymphoma; UK: United Kingdom; US: United States; VenR: venetoclax in combination with rituximab.

Summary of population characteristics

Heterogeneity in baseline characteristics was assessed for the following potential effect-modifiers: Age, sex, race, geographic region, extent of disease (e.g. bulky), cancer type (CLL or SLL), disease stage (Binet or Rai), CLL-IPI, ECOG-PS, mutation status (e.g. del17q, del11q, *TP53*, *IGHV*, C481), prior treatments, type, number of treatments and dual-refractory (BTKi and BCL2i, referred to as dual-exposed elsewhere throughout this submission).

In addition, the following potential effect-modifiers were explored in NICE appraisal for zanubrutinib but were not captured in the extraction for the SLR:[37] β2-macroglobulin, creatinine clearance, cytopenia presence, type of cytopenia, lactate dehydrogenase, time from initial diagnosis, B-symptoms (e.g. weight loss, fatigue, etc.), Cumulative Illness Rating Scale (CIRS), complex karyotype and baseline EORTC-QLQ-C30 score.

Limited data were identified in the SLR for the following population characteristics:

- **Ethnicity/race**: Only two studies (ALPINE, RESONATE)[37, 111] reported, recruiting predominantly white populations (79.8–90.0%), while white population constituted 81.1% of BRUIN
- **Geographic region**: Seven studies were multinational, while one study recruited patients solely from the US
- **Bulky disease**: Five studies (ALPINE, ASCEND, ELEVATE RR, DUO, RESONATE)[99-101, 110, 111] measured bulky disease according to a threshold of ≥5 cm, with the proportion of patients with bulky disease ranging from 44.3–64%. At this threshold, 44.5% of the BRUIN population had bulky disease[91]
- **Cancer type**: Five studies included patients with CLL and SLL (ALPINE, BRUIN, DUO, NCT02007044, RESONATE), while three studies recruited only CLL patients (ASCEND, ELEVATE RR, MURANO)[91, 99, 109-111]
- **CLL-IPI**: Reported by RESONATE only, with majority of patients high- or very high-risk (24–27% and 25–36%, respectively)[111]
- **C481**: Not reported by any of the studies included

If the above population characteristics are potential effect modifiers, the impact of bias on the relative effectiveness in the NMA is unclear as few studies reported these characteristics.

A summary of findings for the similarity assessment are shown in Table 40, and population characteristics for which there were sufficient data from the included studies are shown in the figures and tables presented in the following pages.

Notably, major heterogeneity was identified across the six studies reporting the number of prior treatments received by patients. The BRUIN CLL-321 trial was a more heavily pre-treated population compared to the other studies identified, recruiting a greater number of patients with 3, 4 or more lines of prior treatment (56.3–57.2%, per arm) with a median of 3 prior treatments.[91] Comparatively, the majority (82.1%–86.6%) of recruited patients in the MURANO trial received 1 or 2 prior treatments, with only 2.6% receiving more than 3 lines of prior therapy.[107] In the RESONATE trial, it was only reported in one of the treatment arms that patients had received a median of three prior treatments.[111] Otherwise, of the 6 studies reporting the median number of prior treatments, 2 (ALPINE, NCT02007044)[99, 109] recruited patients with a median of 1 prior

treatment, and 2 (ELEVATE RR, DUO)[100, 110] recruited patients with a median of 2 prior treatments across both treatment arms. These differences in prior treatment exposure likely influence treatment outcomes and make comparison of outcomes across these studies unfeasible.

Major heterogeneity was also identified across the seven studies reporting prior treatment types. Comparisons across studies on the prior use of PI3Ki and BCL2i therapies was limited due to insufficient data reporting. In the BRUIN CLL-321 trial, 100% patients recruited were BTKi pre-treated, with 50% having received prior BCL2i therapy (dual-exposed).[91] Approximately, 10% of patients had received prior PI3Ki therapy, and two thirds had also received prior CIT.[91] Comparatively, across the other six studies identified, patients had almost exclusively received prior CIT only.

Furthermore, considerable heterogeneity was identified across studies in terms of disease stage, and ECOG-PS. Most studies (6 out of 8) included a similar proportion of patients with stage 3 to 4 disease, ranging from 37% to 58%, however, the MURANO study recruited a much lower proportion of patients with stage 3 to 4 disease (12.9–23.1%).[107] Regarding ECOG-PS, heterogeneity was observed in the proportion of patients with ECOG PS 1, which was notably lower in ELEVATE RR, MURANO, BRUIN CLL-321, RESONATE, and ASCEND (41–59%) compared to NCT02007044 (97%).[91, 100, 101, 107, 111] ALPINE only reported the proportion of patients with ECOG PS ≥1 (60.6% and 62.5%), making direct comparisons difficult.[99] Additionally, DUO reported only the proportion of patients with ECOG PS 2 (7–10%), while NCT02007044 predominantly recruited patients with ECOG PS 1.[109, 110]

Out of the eight studies identified reporting del17p mutation, significant heterogeneity was identified. Five out of eight studies included a similar proportion of patients with this mutation, ranging from 13.8% to 29%. However, the ELEVATE RR, BRUIN CLL-321, and RESONATE studies reported substantially higher proportions of patients with del17p mutation, at 45.1–45.3%, 32.8–36.1%, and 32–33%, respectively.[91, 100, 111]

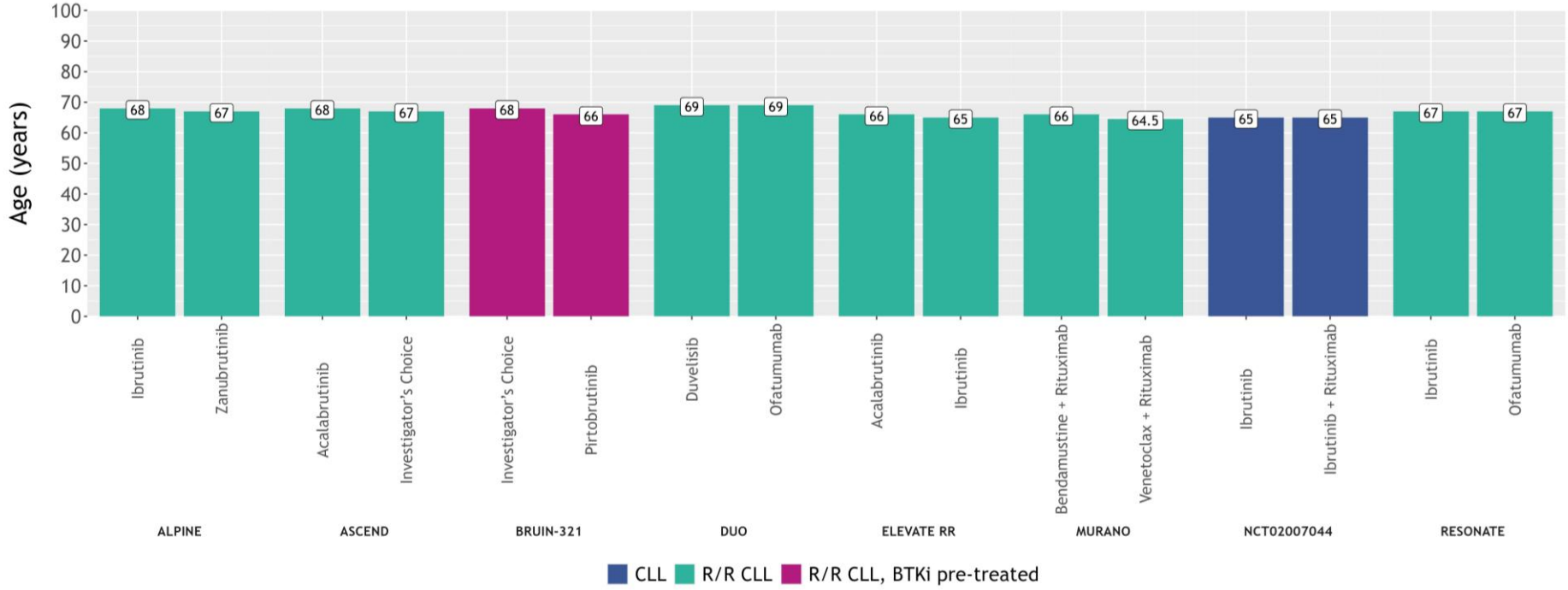
Table 40: Summary of findings of the similarity assessment

Characteristic	Number of studies	Similarity assessment		Outliers?
Age	8	Minor heterogeneity	• Median age was similar across all studies, ranging between 64.5 and 69 years	• None
Sex	8	Minor heterogeneity	• Proportion of males was similar across all studies, ranging between 60% and 77.4%	• None
Disease stage	8	Major heterogeneity	• Most studies (6 out of 8) included a similar proportion of patients with stage 3 to 4 disease, ranging from 37% to 58% • **ALPINE** used Binet staging, while all other studies used Rai. It was assumed that stage groupings are transferable for the purpose of this similarity assessment	• **MURANO** recruited a much lower proportion of patients with stage 3 to 4 disease (12.9–23.1%)
ECOG-PS	8	Major heterogeneity	• Six studies reported proportions with ECOG PS 0, 1, 2 independently. Across these 5 studies, most patients (86–100%) had an ECOG PS 0–1. Within this range, heterogeneity was observed in the distribution with ECOG PS 0 or 1, with the proportion ECOG PS 1 in **ELEVATE RR**, **MURANO, BRUIN CLL-321, RESONATE** and **ASCEND** much lower than **NCT02007044** (41–59% versus 97%, respectively) • **ALPINE** reported only the proportion of patients with ECOG PS ≥1 (60.6% and 62.5%) and is difficult to compare to other study groupings • **DUO** reported only the proportion of patients with ECOG PS 2 (7–10%)	• **NCT02007044** predominantly recruited a population with ECOG PS 1
TP53	8	Major heterogeneity	• Most studies (5 out of 8) included a similar proportion of patients with *TP53* mutation, ranging from 20% to 28%	• **ALPINE** recruited a lower proportion with mutation (7.7–9.2%), whilst **ELEVATE RR** and **RESONATE** recruited a larger proportion with mutations (37.3–51%)
Del11q mutation	6	Major heterogeneity	• Most studies (5 out of 6) included a similar proportion of patients with del11q mutation, ranging from 14% to 32%	• **ELEVATE RR** reported a substantially higher proportion of patients with mutation (62.3–

			• **MURANO** and **DUO** did not report for this characteristic	66.0%)
Del17p mutation	8	Major heterogeneity	• 5 out of 8 studies included a similar proportion of patients with del17p mutation, ranging from 13.8% to 29%	• **ELEVATE RR, BRUIN CLL-321,** and **RESONATE** reported higher proportions of recruited patients with mutation (45.1–45.3%, 32.8–36.1%, and 32–33% respectively)
IGHV unmutated	8	Minor heterogeneity	• All studies included comparable proportions of patients who were *IGHV* unmutated, ranging from 59% to 89.4%	• None
Number of prior treatments	8	Major heterogeneity	• Of the 6 studies reporting the median number of prior treatments, 2 (**ALPINE, NCT02007044**) recruited patients with a median of 1 prior treatment, and 2 (**ELEVATE RR, DUO**) recruited patients with a median of 2 prior treatments across both treatment arms. The median number of prior treatment arms differed between treatment arms in **ASCEND** (1 and 2) and **RESONATE** (3 and 2) • **MURANO** did not report the median number of prior treatments, however, in line with other studies, the majority (82.1–86.6%) of recruited patients received 1 or 2 prior treatments	• **BRUIN CLL-321** recruited a greater number of patients in with 3 and 4 or more lines of prior treatment (56.3–57.2%, per arm) with a median of 3 prior treatments • One of the treatment arms from **RESONATE** had a median of 3 prior treatments
Prior treatment types	7	Major heterogeneity	• Most of the studies (7 out of 8) reported prior antiCD20 treatments, and proportions were similar across the 7 studies (69.7–94%) • 6 out of 8 studies reported prior alkylator use, with proportions of recruited patients with use ranging from 79.4–95.4%. However, reported grouping of alkylators was inconsistent across studies (including/excluding bendamustine), making comparison difficult • Of the 6 studies reporting prior purine analogue use, half (4 out of 8) had similar proportions of recruited patients with use (52–71%) • Comparisons across studies on prior use of several treatments (e.g. PI3Ki and BCL2i) are limited due to insufficient data reporting	• **BRUIN CLL-321** was the only study including patients pre-treated with BTKi. All other studies excluded patients pre-treated with a BTKi • **BRUIN CLL-321** was the only study that reported a high percentage of patients with prior BCL2i treatment (50.4%, 52.1%)

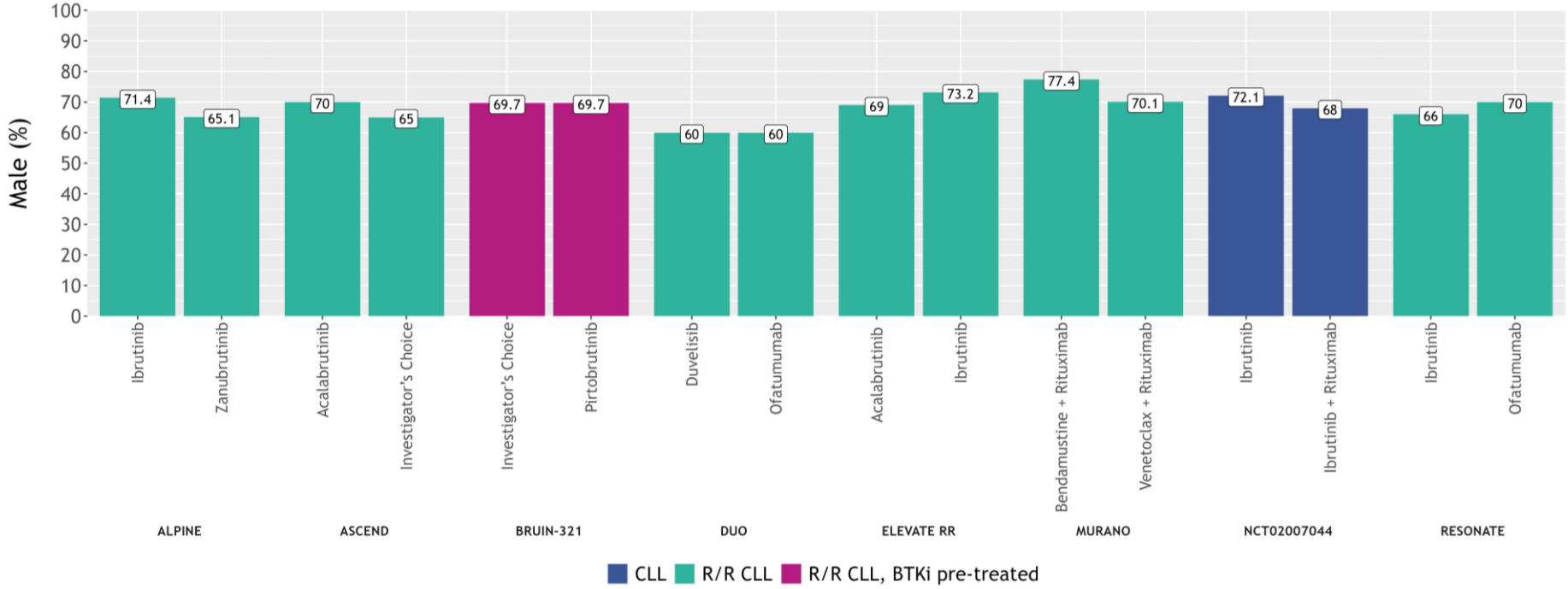
Abbreviations: BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; R/R: relapsed or refractory; SLL: small lymphocytic lymphoma.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 19: Median age (years) of patients across the included studies



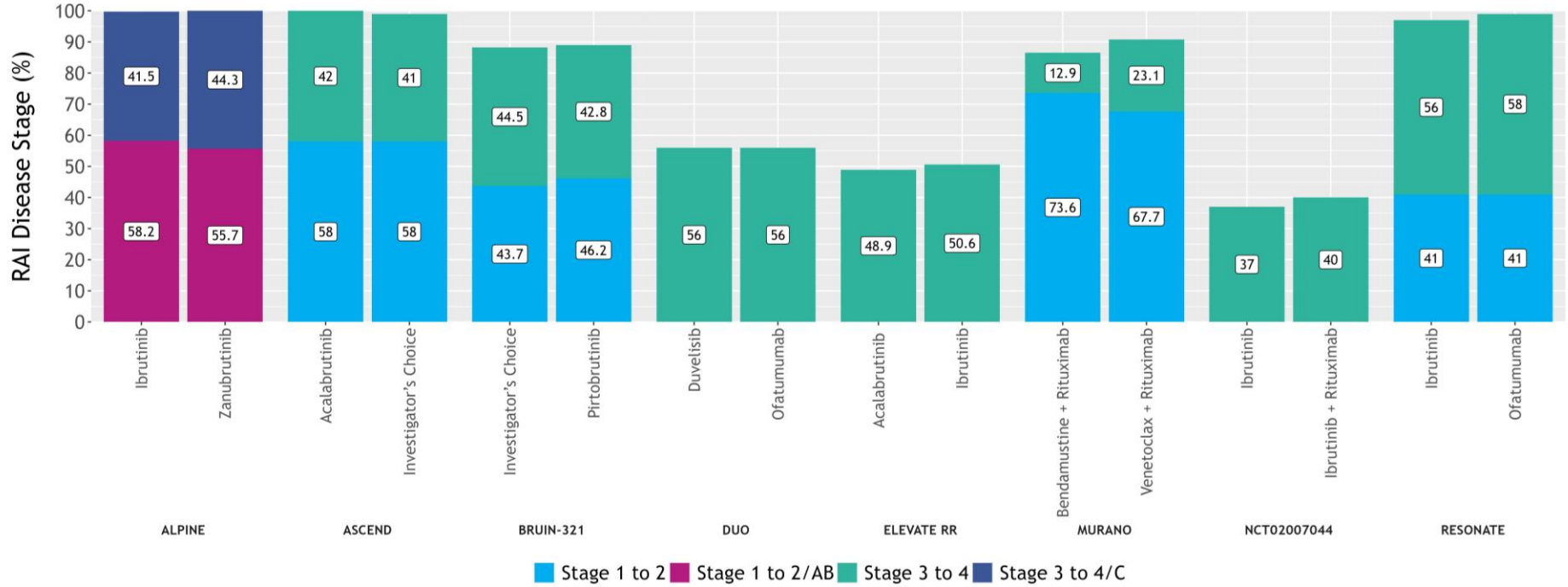
Footnote: Whilst outcome data are available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 20: Percentage of male patients across the included studies



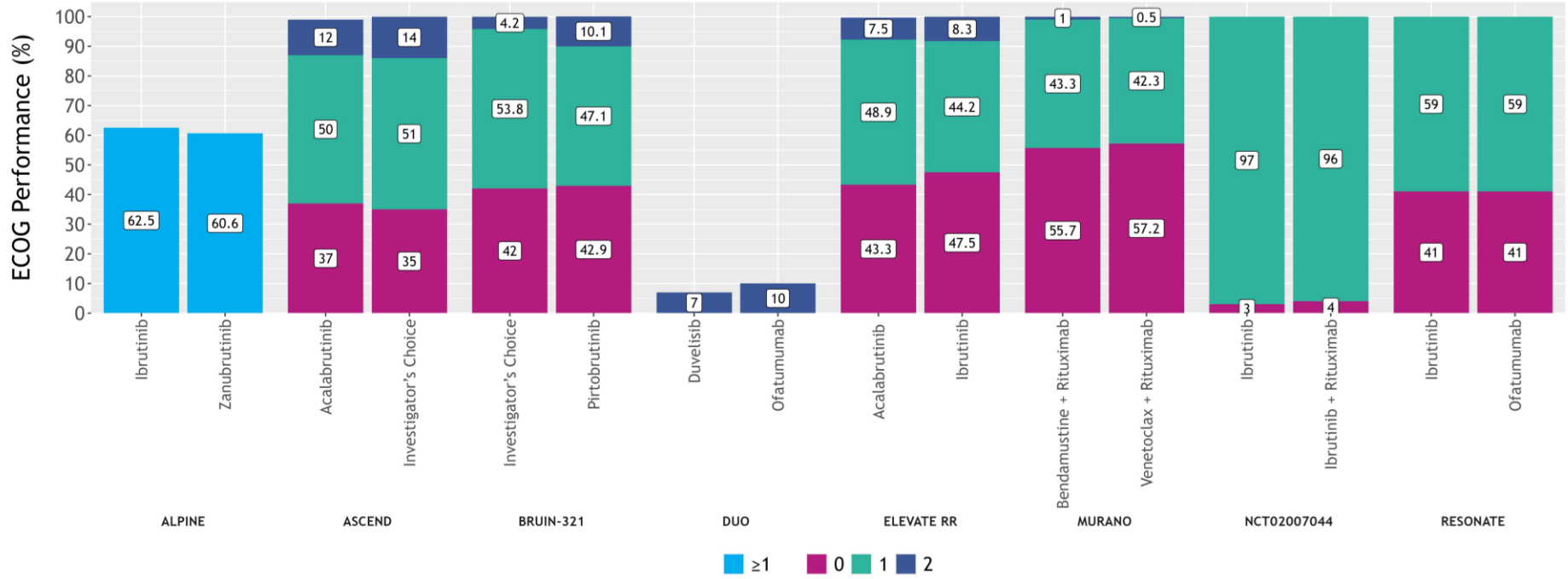
Footnote: Whilst outcome data is available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 21: Percentage disease stage breakdown of patients across the included studies



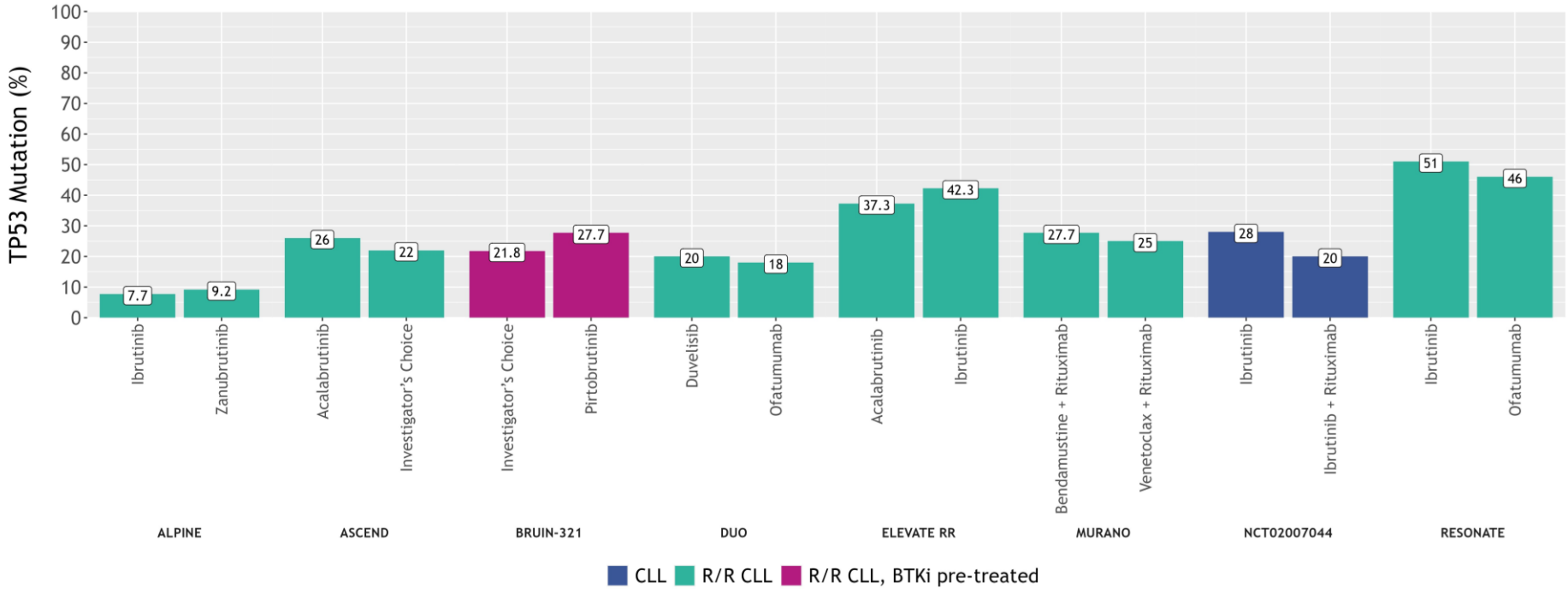
Footnotes: Disease staging given for BRUIN CLL-321 was grouped for similarity assessment with all studies. There was unknown Rai stage at diagnosis for remaining patients in the MURANO study. Whilst outcome data is available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviation: R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 22: Percentage ECOG PS breakdown of patients across the included studies



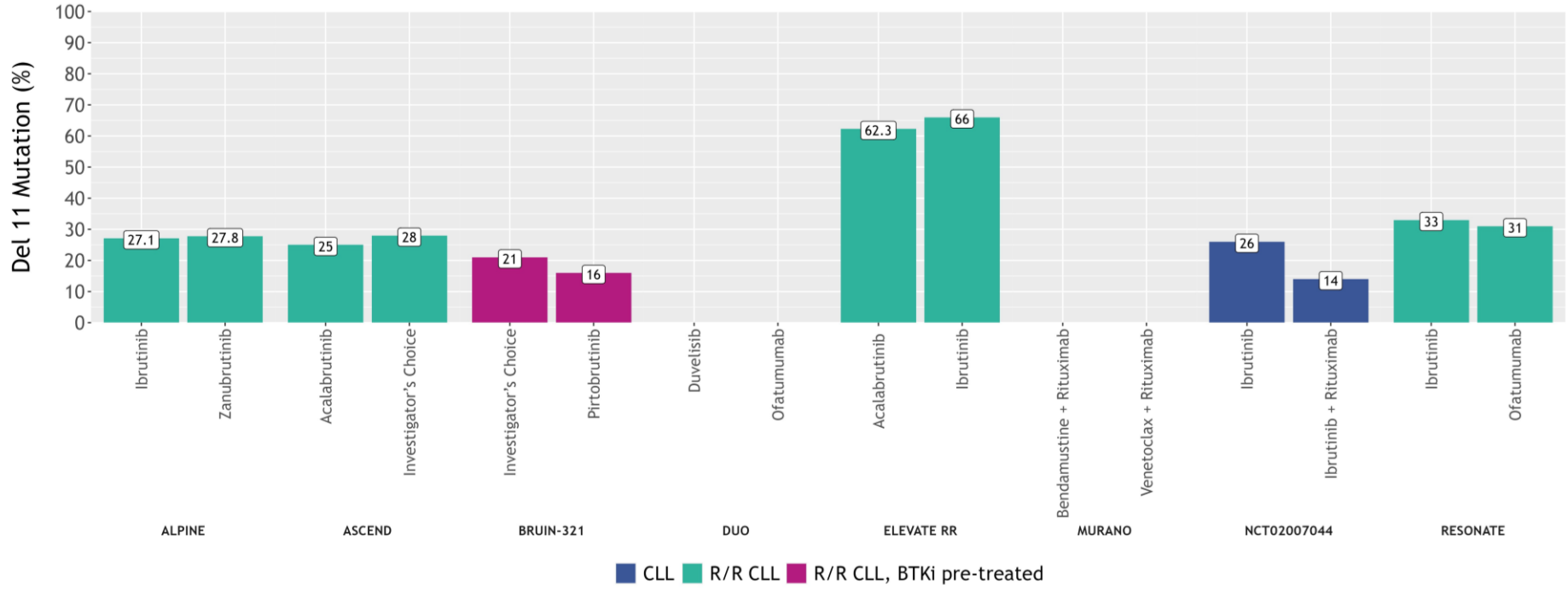
Footnote: Whilst outcome data is available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 23: Percentage of *TP53* mutation patients across the included studies



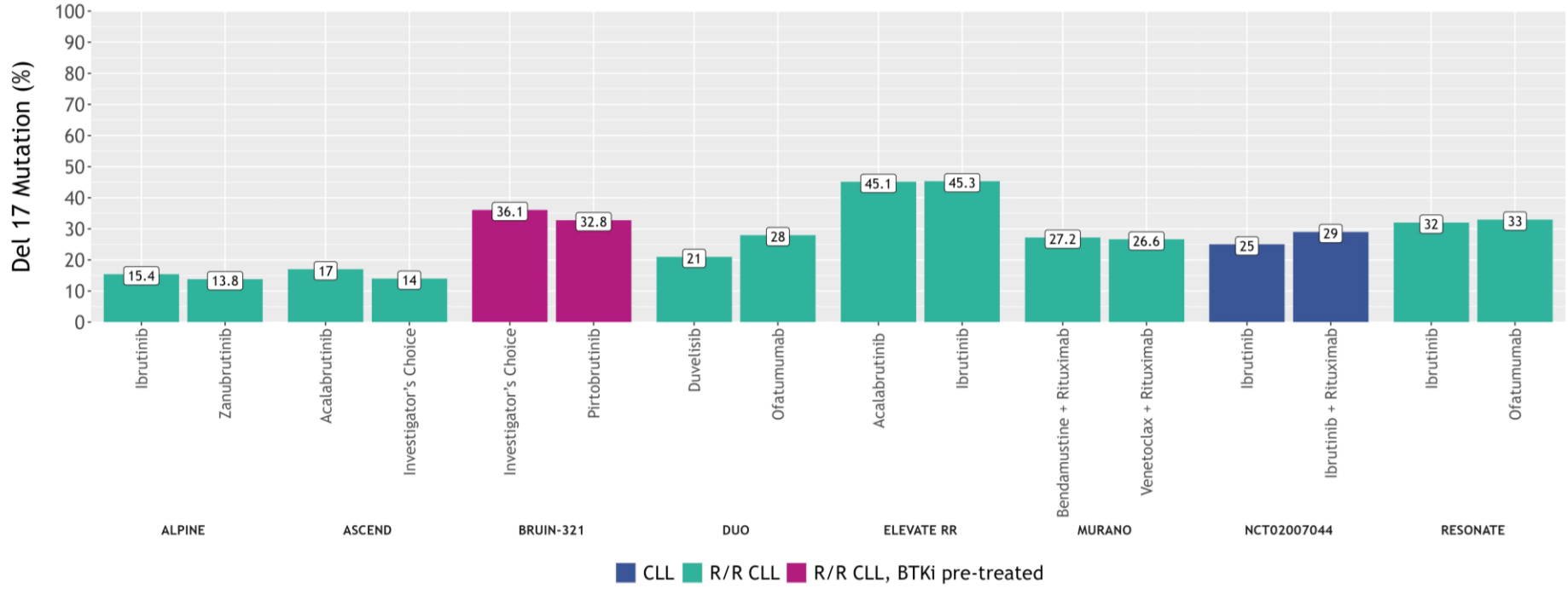
Footnotes: ALPINE reported *TP53* mutation without del17(p) mutation. Whilst outcome data is available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 24: Percentage of del11q mutation patients across the included studies



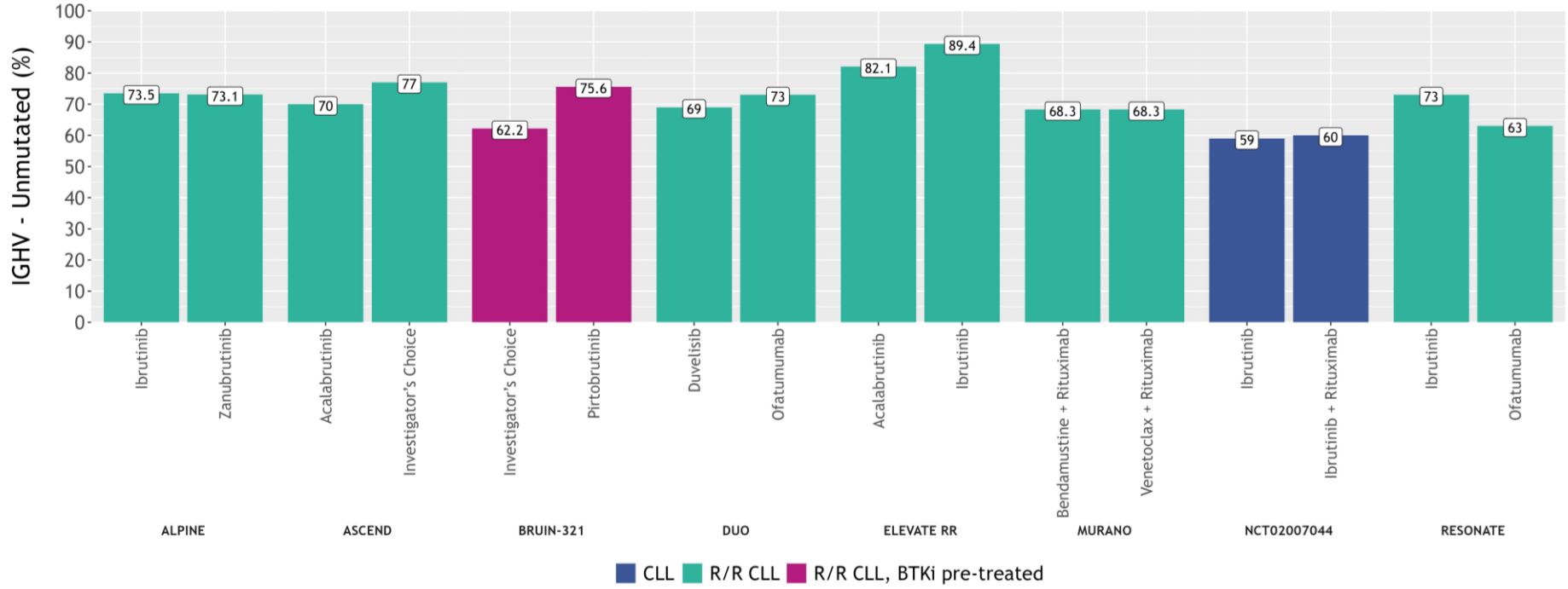
Footnotes: del11q mutation is not reported in DUO and MURANO studies. Whilst outcome data is available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 25: Percentage of del17p mutation patients across the included studies



Footnotes: ALPINE reported del17(p) mutation with or without *TP53* mutation. Whilst outcome data is available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Figure 26: Percentage of *IGHV* (unmutated) patients across the included studies



Footnote: Whilst outcome data is available for NCT02007044, for the R/R subgroup, the trial recruited previously treated and untreated patients (86% previously treated in the ibrutinib arm, 88% previously treated in the ibrutinib + rituximab arm) and baseline characteristics were reported only for the overall population.
Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; R/R: relapsed or refractory.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Table 41: Prior treatments of patients across the included studies

Study ID	Prior treatment inclusion/exclusion criteria	Treatment arm	Number of prior treatment lines (%)				Prior BTKi	Non-BTKi prior treatment types (%)		
			1L	2L	3L	≥4L		Anti-CD20	PI3Ki	BCL2i
BRUIN CLL-321	Previously treated with a covalent BTKi, investigational or approved, and either alone or in combination with other agents. Patients may have received an unlimited number of lines of prior therapy.	PIRTO	17.6	25.2	24.4	32.8	100%	72.3	9.2	50.4
		I+R/BR*	23.5	20.2	15.1	41.2		69.7	9.2	52.1
ALPINE	Patients who had received previous treatment with a BTKi were ineligible.	ZANU	58.7	26.3	7.6	7.3	x	83.8	3.4	2.1
		IBRU	57.2	21.8	11.7	9.2		82.8	5.8	2.5
ASCEND	Must have received ≥ 1 prior systemic therapies for CLL. Patients with a prior exposure to a BCL2i (e.g., venetoclax/ABT-199) or a BCR inhibitor (e.g., BTKi or PI3Ki) were excluded. Prior	ACAL	53	26	11	10	x	84	-	-

	bendamustine is allowed if Investigator's choice for treatment in Arm B is IdelaR. Bendamustine retreatment is allowed if the prior response to bendamustine lasted > 24 months.	I+R/BR*	43	30	15	12		77	-	-
ELEVATE RR	Must have received ≥ 1 prior therapies. Patients with prior exposure to ibrutinib, concomitant warfarin or equivalent vitamin K antagonist treatment, prior BTK or BCL2i treatment, or requiring treatment with proton-pump inhibitors were excluded.	ACAL		87.3			x	84.7	-	-
		IBRU		89.4				86.4	-	-
MURANO	Previously treated patients with at least one but not more than three lines of therapy (a line of therapy is defined as completing at least two cycles of treatment for a given line of therapy), including at least one prior standard chemotherapy containing regimen according to current guidelines. Patients with a history of prior venetoclax treatment were excluded.	VENR	57.2	29.4	11.3	2.1	<3%	78.5	< 3%	-
		BR	60	22.1	17.4	0.5		76.3	< 3%	-
NCT02007044	Included previously treated CLL/SLL. Patients who received previous therapy with agents targeting BTK or other BCR pathway molecules (e.g. idelalisib) were excluded	IBRU	76.4		11.2	12.4	x	NR		
		IBRU+R	82.6		7.6	9.8				

DUO	Patients excluded who received prior BTKi or PI3Ki treatment, refractoriness to prior ofatumumab therapy prior to enrolment in DUO, and a history of Richter transformation, prolymphocytic leukaemia, or allogeneic stem cell transplant.	DUV	-	-	31.3*	x	78.1	-	-
		OFA	-	-	34.6*		83		
RESONATE	Must have received at least one prior therapy for CLL/SLL; Considered not appropriate for treatment or retreatment with purine analogue based therapy; Patients excluded who had prior exposure to ofatumumab or to ibrutinib, autologous transplant within 6 months prior to first dose of study drug, allogeneic stem cell transplant within 6 months or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug	IBRU	18	29	53	x	94	-	-
		OFA	27	27	46		90		

Footnotes: *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).
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
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Table 42: Prior treatments of patients across the included studies, non-BTKi treatments

Study ID	Treatment arm	Chemotherapy/ Chemoimmunotherapy	Alkylators incl. bendamustine	Alkylators excl. bendamustine	Purine analogue
BRUIN CLL-321	PIRTO	68.1	-	-	-
	I+R/BR*	69.7	-	-	-
ALPINE	ZANU	79.5	25.7^	83.8	54.4
	IBRU	76.0	28.9^	79.4	52
ASCEND	ACAL	-	30^	86	70
	I+R/BR*	-	31^	85	67
ELEVATE RR	ACAL	14.6	90.3	-	64.2
	IBRU	14.0	90.6	-	59.6
MURANO	VENR	-	93.3	-	80.5
	BR	-	95.4	-	81.4
NCT02007044	IBRU	-	NR		
	IBRU+R	-			
DUO	DUV	-	36.9^	92.5	60.0
	OFA	-	38.4^	95.0	71.1
RESONATE	IBRU	68.1	43^	93	85
	OFA	69.7	37^	88	77

Footnotes: This table does not present all prior treatments as prior treatment reporting was inconsistent throughout studies. *Indicates the investigator's choice between I+R or BR. ^Only bendamustine percentage was reported
Abbreviations: ACAL: acalabrutinib; DUV: duvelisib; HSCT: hematopoietic stem cell transplantation; I: idelalisib; IBRU; ibrutinib; OFA: ofatumumab; PIRTO: pirtobrutinib; R: rituximab; VEN: venetoclax; ZANU: zanubrutinib
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Summary of intervention and comparator

The dose and regimen of the therapies included in the studies investigated in the similarity assessment are summarised below in Table 43.

Both the ASCEND study and BRUIN CLL-321 included an investigators' choice treatment arm comprising IdelaR and BR. In ASCEND, 77% of patients received IdelaR (23% BR), whereas for BRUIN CLL-321 69% received IdelaR (31% BR).[91, 101] Both combination regimens were recommended treatment options for R/R CLL at the time of study design, however BR is no longer a guideline-recommended treatment for R/R CLL in ESMO and BSH guidelines.[25, 49] IdelaR remains a recommended treatment for post BTKi patients although often reserved for later lines of therapy. Some studies have shown similar median PFS across for the two combination regimens; ASCEND showed differences in safety profiles for IdelaR and BR arms.[101] The MURANO study of VenR included a BR comparator arm (100% BR compared with 23% ASCEND and 31% BRUIN CLL-321).[101, 107]

Investigators' choice arms can present challenges in NMA. Specifically, using a 'lumped' NMA node consistent with the investigators' choice arm requires the assumption of transitivity between the two combination regimens. This assumption has been used for previous NMA/ITCs in R/R CLL: in the NMA submitted as part of NICE TA931 for zanubrutinib, the BR arm of the MURANO trial was also 'lumped' in the NMA node for investigators' choice.[37, 112-114] However, findings from two meta-analysis studies indicate that adding idelalisib to rituximab may be more efficacious than adding bendamustine to rituximab. This potential difference in efficacy complicates the use of IdelaR and BR as a 'lumped comparator', as adding idelalisib to rituximab provides a large benefit over rituximab alone,[115] and as adding bendamustine to rituximab provides little benefit over rituximab alone, while adding idelalisib to BR indicates a larger benefit compared to BR alone. Consequently, the approach taken in Section 3 to model Investigator's choice as IdelaR is more likely to be a conservative approach, as it avoids overestimating combined treatment effects by not assuming equivalence between these regimens.

Table 43: Dose and regimens of the treatment arms across the included studies

Study ID	Treatment arm	Treatment 1	Treatment 1 Regimen	Treatment 2	Treatment 2 Regimen
BRUIN CLL-321	PIRTO	Pirtobrutinib	200 mg QD, oral	N/A	N/A
	IdelaR or BR*	Idelalisib or bendamustine	I: 150 mg BID, oral B: 70 mg/m2 IV on days 1, 2 every 28-day cycle	Rituximab	I+R: IV, 375mg/m2 day 1 cycle 1, 500mg/m2 every 2 weeks for 4 doses, then every 4 weeks for 3 doses for a total of 8 infusions BR: 375mg/m2 day 1 cycle 1, 500mg/m2 on day 1 of cycles 2-6
ALPINE	IBRU	Ibrutinib	420 mg QD, oral	N/A	N/A
	ZANU	Zanubrutinib	160 mg BID, oral	N/A	N/A
ASCEND	ACAL	Acalabrutinib	100 mg BID, oral	N/A	N/A
	IdelaR or BR*	Idelalisib or bendamustine	I: 100 mg BID, oral B: 70 mg/m2 IV on days 1, 2 every 28-day cycle	Rituximab	I+R: IV, 375mg/m2 day 1 cycle 1, 500mg/m2 every 2 weeks for 4 doses, then every 4 weeks for 3 doses for a total of 8 infusions BR: IV, 375mg/m2 day 1 cycle 1, 500mg/m2 on day 1 of cycles 2-6
ELEVATE RR	ACAL	Acalabrutinib	100 mg BID, oral	N/A	N/A
	IBRU	Ibrutinib	420 mg QD, oral	N/A	N/A
MURANO	BR	Bendamustine	IV, 70 mg/m2 on days 1 and 2 every 28-day cycle, for 6 cycles	Rituximab	IV, 375 mg/m2 day 1 cycle 1, 500mg/m2 on day 1 of cycles 2-6
	VENR	Venetoclax	20 mg increased weekly up to a max 400 mg for 6 cycles, oral	Rituximab	IV, 375 mg/m2 day 1 cycle 1, 500mg/m2 on day 1 of cycles 2-6

Footnotes: *Indicates the investigator's choice between I+R or BR.

Abbreviations: ACAL: acalabrutinib; B: bendamustine; BID: twice daily; Idela: idelalisib; IBRU; ibrutinib; IV: intravenous; mg: milligrams; mg/m^2: milligrams per square meter; N/A: not applicable; PIRTO: pirtobrutinib; QD: once daily; R: rituximab; VEN: venetoclax; ZANU: zanubrutinib.
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Outcome definitions

Outcomes of interest in the included studies followed a standardised definition and/or scale, and did not vary across studies. Reported time to event outcome definitions, and response outcomes are presented in Table 44. Where reported, definitions aligned and were consistent, including the use of iwCLL guidelines.

Definitions of safety outcomes were not reported for any of the included trials. Median follow-up of the main publications ranged from 9.4 to 48 months, while the median follow-up for safety outcomes was 22.4 to 63.5 months. Only three studies reported HRQoL data for the EORTC-QLQ-30:

- ALPINE reported mean change from baseline at treatment cycle 7 and cycle 13 for all patients recruited in the study (regardless of treatment arm) broken down by Global Heath Status (GHS), functional, and symptom scales[99]
- ELEVATE RR did not provide quantitative data but noted that the EORTC QLQ-C30 GHS was evaluated at week 12 and stabilised thereafter in both treatment arms with no statistical differences seen between treatments[100]
- RESONATE reported mean change from baseline at week 24 for all patients recruited in the study broken down by GHS, functional, and symptom scales[111]

It was concluded that there was insufficient data for analysis of the HRQoL outcome, and therefore, a network of evidence could not be presented.

Table 44: Time to event and response outcomes across the included studies

Efficacy outcome	Reported definitions	Number of studies
OS	Time from randomisation to any cause of death	3
	NR	4
PFS	Time from randomisation to the first occurrence of progression or relapse using iwCLL guidelines, or death from any cause, whichever occurred first	1
	Time from randomisation until disease progression or death from any cause, using iwCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis	2
	Time from random assignment until disease progression or death from any cause	2
	NR	2
ORR	NR	4
	Defined as CR or PR, per regulatory authority requirement. Disease response was assessed per iwCLL 2008 criteria	2
	Responses were evaluated according to the 2008 iwCLL criteria	1
CR	CR or CR with incomplete bone marrow recovery	2
	Responses were evaluated according to the 2008 iwCLL criteria; CR reported as CR/CRi	2
	NR	3

PR	PR or nodular PR	2
	Responses were evaluated according to the 2008 iwCLL criteria	2
	NR	3
DOR	NR	7

Footnote: This table does not include BRUIN CLL-321 due to data availability.
Abbreviations: CR: complete response; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; NR: not reported; PR: partial response.

Outcome reporting

Outcome reporting was assessed across the eight studies. Certain outcomes such as OS, PFS, ORR, AE, discontinuation due to AEs (DAE), discontinuation due to progressive disease (DPD) were frequently reported, while others (i.e. CR, PR, DOR) were reported infrequently across studies.

An overview of the studies and outcomes that can be assessed in a connected network of evidence is presented in Table 45. However, connecting the networks required using a lumped node for Investigator's choice arms, combining Investigators' choice of IdelaR or BR, and BR treatment arms into one treatment node. As discussed above, this assumption requires the assumption of transitivity between the two combination regimens and the validity of this assumption cannot be guaranteed. While networks are possible to be developed, they disregard similarity considerations and therefore cannot be reliably interpreted.

Table 45: Connected networks per outcome across included studies

Study ID	Treatment	Analysis population	Efficacy outcomes						Safety outcomes					
			OS	PFS	ORR	CR	PR	DOR	All cause discontinuation	AEs	AEs ≥3	SAEs	DAEs	DPD
BRUIN CLL-321	PIRTO IdelaR/BR	R/R CLL, BTKi pre-treated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ALPINE	ZANU IBRU	R/R CLL	✓	✓	✓	-	-	-	-	-	✓	-	✓	✓
ASCEND	ACAL IdelaR/BR	R/R CLL	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ELEVATE RR	ACAL IBRU	R/R CLL	✓	✓	✓	-	-	-	-	-	✓	-	✓	✓
MURANO	VENR BR	R/R CLL	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
NCT02007044	IBRU IBRU+R	R/R CLL	-	-	✓	-	-	-	-	-	-	-	-	-
DUO	DUV OFA	R/R CLL	✓	✓	✓	-	-	-	-	-	✓	-	✓	✓
RESONATE	IBRU OFA	R/R CLL/SLL	✓	✓	✓	-	-	-	-	-	✓	-	✓	✓

Abbreviations: AEs: adverse events; CR: complete response; DAEs: discontinuation due to AEs; DPD: discontinuation due to progressive disease; disc.: discontinuation; DOR: duration of response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; IdelaR: Idelalisib + Rituximab BR: Bendamustine + Rituximab; DUV: Duvelisib; IBRU: Ibrutinib; IBRU+R: Ibrutinib + Rituximab; OFA: Ofatumumab; VENR: Venetoclax + Rituximab
Sources: ALPINE;[99] ASCEND;[101] BRUIN CLL-321;[91] DUO;[110] ELEVATE RR;[100] MURANO;[107] NCT02007044;[109] RESONATE.[111]

Study design

A summary of study characteristics is presented above in Table 39. The included studies were published from 2014 to 2023, and most studies (7) were multicentre studies conducted internationally versus 1 single centre study performed in the US (NCT02007044).[109] Seven studies were Phase 3 RCTs, and one Phase 2 study (NCT02007044)[109] was included. The pre-treated population size ranged from 181 (NCT02007044) to 652 patients (ALPINE).[99, 109] The inclusion criteria in only one study (BRUIN CLL-321) specified patients must have prior BTKi treatment (100%); five studies specified prior BTKi therapy as an exclusion criterion (ALPINE, ASCEND, ELEVATE RR, NCT02007044 and RESONATE).[91, 99-101, 109, 111] Although DUO and MURANO allowed prior BTKi therapy, the proportion of patients with prior BTKi in these two studies was either not reported (DUO) or low (<3% MURANO).[107, 110] Median follow-up time in the main publications ranged from 9.4 (RESONATE) to 48 months (MURANO), however, additional publications with longer follow-ups have been published e.g. for RESONATE with up to 65 months.[107, 111]

Study dates are an important factor, as pre-COVID studies (MURANO, RESONATE, ALPINE, NCT02007044, DUO, and ASCEND)[99-101, 109-111] reflect a patient population with a different standard of care compared to those recruited in the BRUIN CLL-321 trial. Additionally, differences in sample size (ranging from 181 [NCT02007044][109] to 652 patients [ALPINE][99]) limit the ability to identify an adequately matched sample, rendering a MAIC analysis unfeasible.

2.10.1.3 Conclusions

There is a scarcity of RCTs reporting outcomes for patients who have previously received BTKi treatment. The FA sought to assess the relative efficacy and safety of pirtobrutinib in adult patients with CLL/SLL who are R/R despite prior BTKi treatment (in line with BRUIN CLL-321), however, while BTKi and BCL2i treatments have become the mainstay of therapy for patients with CLL, there is a lack of RCTs reporting on R/R CLL patients with prior BTKi treatment and patients with prior BTKi and BCL2i treatment. Accordingly, no relevant RCTs could be identified in the pre-treated with BTKi or pre-treated with BTKi and BCL2i (dual-exposed) population rendering an NMA, or any other form of ITC, in either of these populations unfeasible.

In the absence of comparative evidence in the pre-treated with BTKi patient population, the feasibility of an NMA combining data from BRUIN CLL-321 with studies in R/R CLL patients pre-treated with any treatment was evaluated. However, it was concluded that prior treatment with a BCR kinase inhibitor is an important treatment effect modifier, and attempting to synthesise these data through an NMA, with or without adjustments, would be highly susceptible to bias.[86, 87, 89, 116] Given the substantial heterogeneity observed across multiple key aspects—such as prior treatment number, treatment types, disease stage, ECOG-PS, and del17p mutation prevalence—combining data from the BRUIN CLL-321 trial with other studies in R/R CLL patients pre-treated with various regimens is fundamentally flawed. Notably, the BRUIN CLL-321 population was markedly more heavily pre-treated, with a median of three prior treatments and a higher proportion of patients with ≥3 prior lines, whereas other studies predominantly included less heavily pre-treated populations. As a result, combining studies with heterogeneous prior treatment regimens, and extensive clinical and demographic variability, within any form of an ITC (with or without adjustment for other patient characteristics) would be inappropriate and likely unreliable for informing comparative effectiveness in this patient population.

The similarity assessment (Section 2.10.1.2) indicated substantial heterogeneity in the distribution of known treatment effect modifiers such as prior treatment (lines and types), disease stage, ECOG performance score, and mutation status (TP53, Del 11q, Del 17p, and IGHV) across the studies assessed, potentially violating the similarity assumption and biasing an NMA.

Although a connected network of evidence could theoretically be established to assess the comparative efficacy (PFS and OS) of pirtobrutinib versus acalabrutinib, IdelaR, BR, ibrutinib, VenR, zanubrutinib, and duvelisib including BRUIN CLL-321 and studies of R/R CLL patients pre-treated with any treatment, the results may likely be biased due to the heterogeneity of studies and patient characteristics. An (unadjusted) analysis could be conducted, however, it would overlook the heterogeneity of important known treatment effect modifiers, such as prior treatment regimens, disease stage. Furthermore, this approach assumes the validity of combining the investigators' choice treatment arm, which includes both IdelaR and BR, with the exclusive BR arm from the MURANO study into a single treatment node. In the absence of a combined treatment node, then the MURANO study would not connect to the network, thus requiring an unanchored analysis (with adjustment for treatment effect modifiers and prognostic variables) to enable a comparison versus VenR. However, this approach would introduce additional complexities and uncertainties, potentially undermining the validity of the comparisons and leading to unreliable conclusions.

Given the substantial heterogeneity observed, a population-adjusted ITC would be preferred to account for differences in patient characteristics. Two potential approaches for a population-adjusted ITC (PA-ITC) are:

- Multilevel network meta-regression (ML-NMR) which allows for an adjustment of present heterogeneity in effect modifiers in an NMA framework assessing all comparators in the connected networks of evidence.
- Matching-adjusted indirect comparison (MAIC) which allows for an adjustment of present heterogeneity versus one comparator (per analysis).

However, both ML-NMR and MAIC present challenges in deriving robust results from ITCs when there is considerable heterogeneity in the analysis as both methods rely on re-weighting techniques to adjust for differences in patient characteristics between trials. Re-weighting can lead to an over-reliance on specific subgroups of patients, potentially skewing the results and reducing their generalisability. Furthermore, re-weighting often results in a reduction in the effective sample size (ESS). This is because some patients become more influential in the analysis while others are down-weighted. A smaller ESS can decrease the precision of the estimated treatment effect, making it harder to draw definitive conclusions. It is crucial to note that even with population adjustment, neither method can compensate for fundamental differences between trial populations, such as the difference in prior BTKi treatment.

Consequently, given the results of the feasibility assessment presented above, it was concluded that conducting an ITC against VenR or covalent BTKi was not advised.

2.10.2 Published Phase 2 unanchored MAIC

Lilly acknowledges that an unanchored MAIC has been previously published in the peer-reviewed literature that sought to estimate the treatment effect of pirtobrutinib versus venetoclax monotherapy in patients with R/R CLL previously treated with a cBTKi;[117] however, this analysis was deemed not directly relevant to the decision problem addressed in this submission. The

unanchored MAIC utilised older Phase 2 trial data, but since its publication, the Phase 3 trial data have become available. During the regulatory assessment that lead to the grant of marketing authorisation for CLL, the EMA concluded that the Phase 2 data should not be included in the SmPC. Lilly consider that the findings from this analysis have limited applicability, supporting our overall conclusion that conducting ITCs within the therapies of interest within this submission is infeasible.

2.11 Adverse reactions

2.11.1 Exposure and study intervention compliance

The median durations of treatment were longer for the treatments administered continuously (pirtobrutinib and idelalisib) than for those with fixed administration (rituximab and bendamustine), and among continuous treatments, duration of treatment was longer for pirtobrutinib than for idelalisib (Table 46).

The median durations of treatment were:

- Pirtobrutinib: 15.05 months (compared to [redacted] months at the primary analysis)
- IdelaR: 7.08 months and 5.49 months for idelalisib and rituximab, respectively (compared to [redacted] months and [redacted] months, respectively, at the primary analysis)
- BR: 4.73 months and 4.70 months for bendamustine and rituximab, respectively (compared to [redacted] months and [redacted] months, respectively, at the primary analysis)

Table 46: Drug exposure (safety population)

	Pirtobrutinib (N=116)	Investigator's choice (IdelaR N=77; BR N=32)			
		Idelalisib	Rituximab	Bendamustine	Rituximab
Number of patients who received study drug[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles received per patient: pirtobrutinib or idelalisib[b]					
Patients who received <1 – 3 cycles	[redacted]	[redacted]	–	–	–
Patients who received 4 – 6 cycles	[redacted]	[redacted]	–	–	–
Patients who received 7 – 9 cycles	[redacted]	[redacted]	–	–	–
Patients who received 10 – 12 cycles	[redacted]	[redacted]	–	–	–
Patients who received 13 – 18 cycles	[redacted]	[redacted]	–	–	–

Patients who received 19 – 24 cycles	[redacted]	[redacted]	–	–	–
Patients who received 25 – 30 cycles	[redacted]	[redacted]	–	–	–
Patients who received 31 – 36 cycles	[redacted]	[redacted]	–	–	–
Duration on Therapy (months)[c]					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Q1, Q3)	15.05 [redacted]	7.08 [redacted]	5.49 [redacted]	4.73 [redacted]	4.70 [redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Number of subjects who received at least one dose of study drug (either partial or complete). [b] Patient is considered to have received a treatment cycle after receiving at least one dose of study drug (either partial or complete). [c] Duration of therapy is calculated as (date of last dose - date of first dose + 1)/30, for pirtobrutinib and idelalisib. For bendamustine and rituximab, duration of therapy is calculated as (date of last dose - date of first dose + 28)/30.
Abbreviations: IdelaR: idelalisib plus rituximab; max: maximum; min: minimum; SD: standard deviation.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 14.3.1.1.[103]

2.11.2 Treatment-related adverse events

Fewer AEs were reported in the pirtobrutinib arm (93.1%) compared to those in the Investigator's choice of IdelaR or BR arm (98.2%). The system organ classes with the most reported (in >40% of patients in either arm) AEs are presented in Table 47. As pirtobrutinib is administered orally, there were no cases of infusion-related reactions, whereas infusion-related reaction was reported in 17.4% of patients who were treated with IdelaR or BR ([redacted]).

Table 47: Summary of treatment-emergent AEs (safety population)

	Pirtobrutinib (N=116)	IdelaR or BR (N=119)	IdelaR (N=77)
Subjects with ≥ 1 treatment-emergent AEs (TEAEs), n (%)	108 (93.1)	107 (98.2)	[redacted]
Related to Any Study Treatment[a]	71 (61.2)	90 (82.6)	[redacted]
Related to Pirtobrutinib	[redacted]	[redacted]	[redacted]
Related to Idelalisib	[redacted]	[redacted]	[redacted]
Related to Rituximab	[redacted]	[redacted]	[redacted]
System organ class			
Infections and infestations	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]

Investigations	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]

Footnotes: [a] Includes events that were considered related to study treatment as judged by the Investigator.
Abbreviations: AE: adverse event; IdelaR: idelalisib plus rituximab; N: total number of participants; TEAE: treatment-emergent adverse event.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 30–2.[103]

Exposure adjusted incidence rate

Exposure adjusted incidence rate is based on first occurrence of the event and is calculated as number of events divided by sum of years at risk for a TEAE across all patients times 100. When adjusting for exposure, the incidence rates of TEAEs was lower into the pirtobrutinib arm compared to the Investigator's choice of IdelaR or BR arm (Table 48).

Table 48: Summary of exposure-adjusted incidence rate TEAEs (safety population)

	Pirtobrutinib (N=116)	IdelaR or BR (N=119)	IRR (95% CI)[b]	p-value[c]
Incidence ratio[a]				
Infections[d]	94.5	125.5	0.75 (0.53-1,07)	0.11
Pneumonia[e]	20.4	19.5	1.04 (0.54-2.03)	0.90
Anaemia	11.1	33.4	0.33 (0.17-0.65)	0.001
Neutropenia[f]	18.5	30.3	0.61 (0.33-1.12)	0.11
Cough	26.4	66.5	0.40 (0.25-0.64)	<0.001
Diarrhea	14.3	30.8	0.47 (0.25-0.88)	0.02
Pyrexia	15.3	63.7	0.24 (0.14-0.42)	<0.001
Fatigue	11.1	52.4	0.21 (0.11-0.40)	<0.001
Nausea	9.5	34.2	0.28 (0.14-0.55)	<0.001
Vomiting	9.8	38.3	0.26 (0.13-0.51)	<0.001
ALT increased	5.8	29.6	0.19 (0.08-0.44)	<0.001
Weight decreased	2.8	33.6	0.08 (0.03-0.25)	<0.001

Footnotes: [a]IR is based on first occurrence of the event and is calculated as number of event (n) divided by sum of years at risk for a TEAE across all patients (PYE, patient years at risk) times 100. [b]IRR is based on pirtobrutinib IR relative to IdelaR/BR IR. [c]The nominal two-sided p-value and 95% CIs for IRR are based on Poisson regression. [d]Aggregate of all preferred terms indicating infection and including COVID-19. Grade ≥3 infection IR was 26.8 with pirtobrutinib and 43.5 with IdelaR/BR; the IRR was 0.62 (95% CI, 0.37-1.02), nominal p value = 0.062. [e]Grade ≥3 pneumonia IR was 15.2 with pirtobrutinib and 18.0 with IdelaR/BR; the IRR was 0.85 (95% CI, 0.41-1.73), nominal p value = 0.646. [f]Aggregate of neutropenia, neutrophil count decreased, febrile neutropenia and neutropenic sepsis.
Abbreviations: ALT: alanine transaminase; BR: bendamustine plus rituximab; CI: confidence interval; IdelaR: idelalisib plus rituximab; IR: incidence rate per 100 patient years; IRR: incidence rate ratio.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 25–6.[103]

2.11.3 Serious adverse events

SAEs occurred in similar frequencies in both arms, with pneumonia being the most common SAE reported. Of those in the pirtobrutinib arm, 15.5% of patients reported pneumonia compared to 11.0% in patients receiving Investigator's choice of IdelaR or BR. Occurrence of treatment-related SAEs were fewer in patients in the pirtobrutinib arm ([redacted] than in patients receiving Investigator's choice of IdelaR or BR ([redacted] A summary of the SAEs is presented in Table 49.

Table 49: Treatment-emergent SAEs (safety population)

	Pirtobrutinib (N=116)	IdelaR or BR (N=119)	IdelaR (N=77)
Subjects with ≥ 1 SAEs, n (%)	55 (47.4)	51 (46.8)	[redacted]
Related to Any Study Treatment[b]	16 (13.8)	23 (21.1)	[redacted]
Related to Pirtobrutinib	16 (13.8)	[redacted]	[redacted]
Related to Idelalisib	[redacted]	[redacted]	[redacted]
Related to Rituximab	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)			
Pneumonia	18 (15.5)	12 (11.0)	[redacted]
Anaemia	3 (2.6)	2 (1.8)	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Diarrhoea	0	4 (3.7)	[redacted]
Infusion related reaction	0	3 (2.8)	[redacted]
Subjects with ≥ 1 TESAEs, n (%)	16 (13.8)	23 (21.1)	[redacted]

Abbreviations: IdelaR: idelalisib plus rituximab; N: total number of participants; SAE: serious adverse event; TESAE: treatment-emergent serious adverse event.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 25–6.[103]

2.11.4 Adverse events of special interest

Adverse events of special interest (AESIs) were identified based on the known safety profile of BTKi therapies, non-clinical toxicology, and emerging safety data during the conduct of the study. Key AESIs are infections, bleeding, cytopenias, and atrial fibrillation and atrial flutter, and are presented in Table 50.

Infections

Infection AESIs were experienced by 74 patients (63.8%) in the pirtobrutinib arm, and 54 patients (49.5%) in the Investigator's choice of IdelaR or BR arm, with infections occurring in more patients treated with IdelaR ([redacted]). The most common infection AESIs were pneumonia (26 patients [22.4%] in the pirtobrutinib arm, and 13 patients [11.9%] in the Investigator's choice of IdelaR or BR arm) and COVID-19 (15 patients [12.9%] in the pirtobrutinib arm, and 20 patients [18.3%]) in the Investigator's choice of IdelaR or BR arm.

Bleeding

Bleeding AESIs included categories of bruising and haemorrhage. Bleeding AESIs were experienced by 25 patients (21.6%) in the pirtobrutinib arm, and 11 patients (10.1%) in the Investigator's choice of IdelaR or BR arm. A Grade 5 bleeding AESI occurred in one patient receiving IdelaR, where the patient experienced a Grade 5 haemorrhage due to hematoma that was considered not related to study treatment. There were no treatment-related Grade 5 bleeding AESIs reported in either treatment arm.

Cytopenias

The predominant cytopenia AESI was neutropenia, followed by anaemia. Neutropenia TEAEs of any grade were experienced by 31 patients (26.7%) in the pirtobrutinib arm, and 37 patients (33.9%) receiving IdelaR or BR. Treatment-related neutropoenias were experienced by [redacted] patients ([redacted]) in the pirtobrutinib arm, and [redacted] patients ([redacted]) receiving Investigator's choice of IdelaR or BR. Neutropenia SAEs were experienced by two patients (1.7%) in the pirtobrutinib arm, and four patients (3.7%) treated with IdelaR or BR.

Atrial fibrillation and flutter

The frequency of patients who experienced atrial fibrillation and atrial flutter TEAEs were low, three patients (2.6%) in the pirtobrutinib arm and one patient (0.9%) in the Investigator's choice of IdelaR or BR arm, with one patient (0.9%) in the pirtobrutinib arm having a treatment-related event. There were no Grade 4 or 5 events, nor SAEs of atrial fibrillation and atrial flutter.

Table 50: Summary of AESIs (safety population)

	Pirtobrutinib (N=116)	IdelaR or BR (N=119)	IdelaR (N=77)
Infections, n (%)			
Patients with any infection TEAEs	74 (63.8)	54 (49.5)	[redacted]
Any grade (excluding COVID-19)	67 (57.8)	47 (43.1)	[redacted]
Related to study treatment (all infections)	18 (15.5)	17 (15.6)	[redacted]
SAE (all infections)	34 (29.3)	26 (23.9)	[redacted]
SAE related to study treatment (all infections)	8 (6.9)	7 (6.4)	[redacted]
SAE (excluding COVID-19)	[redacted]	[redacted]	[redacted]
Bleeding, n (%)			
Patients with any AESI	25 (21.6)	11 (10.1)	[redacted]
Related to study treatment	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
SAE related to study treatment	[redacted]	[redacted]	[redacted]
Cytopenia, n (%)			
Patients with anaemia	24 (20.7)	[redacted]	[redacted]
Related to study treatment	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
SAE related to study treatment	[redacted]	[redacted]	[redacted]
Patients with neutropenia	[redacted]	[redacted]	[redacted]

Related to study treatment	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
SAE related to study treatment	[redacted]	[redacted]	[redacted]
Atrial Fibrillation and Atrial Flutter, (%)			
Patients with any AESI	3 (2.6)	1 (0.9)	[redacted]
Related to study treatment	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
SAE related to study treatment	[redacted]	[redacted]	[redacted]

Abbreviations: AESI: adverse event of special interest; COVID-19: coronavirus disease 2019; IdelaR: idelalisib plus rituximab; N: total number of participants; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 41–44.[103]

2.11.5 Deaths

There were no patient deaths due to AEs while on treatment in either treatment arm. Patient deaths due to any AEs within 30 days of the last dose were reported in nine (7.8%) patients in the pirtobrutinib arm and seven patients treated with Investigator's choice IdelaR or BR (6.4%). No deaths due to treatment-related AEs occurred in either arm while on treatment or within 30 days after the last dose. Patients with fatal treatment-emergent AEs occurred at a similar frequency in the pirtobrutinib arm and in those receiving Investigator's choice of IdelaR or BR (10.3% versus 9.2%), with infections and infestations being the main causes of death in both the arms.

Table 51: Summary of all deaths (safety population; not including the crossover period)

	Pirtobrutinib (N=116)	IdelaR or BR (N=119)	IdelaR (N=77)
All deaths, n (%)	37 (31.9)	32 (26.9)	[redacted]
Deaths on therapy, n (%)	[redacted]	[redacted]	[redacted]
Patients with fatal TEAE, n (%)	12 (10.3)	10 (9.2)	[redacted]
Deaths within 30 days of last dose of study drug, n (%)			
Adverse events	[redacted]	[redacted]	[redacted]
Adverse events related to study treatment	[redacted]	[redacted]	[redacted]
Disease Progression	[redacted]	[redacted]	[redacted]
Deaths after 30 days of last dose of study drug, n (%)			
Adverse events	[redacted]	[redacted]	[redacted]
Adverse events related to study treatment	[redacted]	[redacted]	[redacted]
Disease Progression	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Abbreviations: N: total number of participants; TEAE: treatment-emergent adverse event.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 33–4.[103]

2.11.6 Discontinuation due to adverse events

AEs that led to permanent discontinuation of study drug were reported in fewer patients in the pirtobrutinib arm than in the Investigator's choice of IdelaR or BR arm, and those in the Investigator's choice of IdelaR or BR arm were more frequently reported in patients treated with IdelaR (Table 52). Infection AEs were the most common cause of discontinuation in both arms.

Table 52: Summary discontinuations due to AEs (safety population)

	Pirtobrutinib (N=116)	IdelaR or BR (N=119)	IdelaR (N=77)
Subjects who discontinued study treatment due to AE, n (%)	20 (17.2)	38 (34.9)	[redacted]
Related to Any Study Treatment, n (%)[a]	6 (5.2)	23 (21.1)	[redacted]
Related to Pirtobrutinib, n (%)	6 (5.2)	–	[redacted]
Related to Idelalisib, n (%)	[redacted]	[redacted]	[redacted]
Related to Rituximab, n (%)	[redacted]	[redacted]	[redacted]
Adverse events, n (%)			
Infections and infestations	11 (9.5)	10 (9.2)	[redacted]
Gastrointestinal disorders	1 (0.9)	9 (8.3)	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	1 (0.9)	5 (4.6)	[redacted]
Arterial thrombosis	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	0	4 (3.7)	[redacted]
Subjects who discontinued study treatment due to SAE	[redacted]	[redacted]	[redacted]
Related to Any Study Treatment[a]	[redacted]	[redacted]	[redacted]
Related to Pirtobrutinib	[redacted]	[redacted]	[redacted]
Related to Idelalisib	[redacted]	[redacted]	[redacted]
Related to Rituximab	[redacted]	[redacted]	[redacted]

Footnotes: [a] Includes events that were considered related to study treatment as judged by the Investigator.
Abbreviations: AE: adverse event; N: total number of participants; SAE: serious adverse event.
Source: Eli Lilly (Data on File). CSR Addendum 2. Table 37–40. Table 4.[103]

2.12 Ongoing studies

The BRUIN CLL-321 trial (NCT04666038) is currently in the long-term follow-up (LTFU) stage of the trial, and is expected to be completed in 2027. Upon treatment discontinuation, the LTFU occurs Q12W (± 4 weeks) for up to two years and Q24W thereafter, until the patient withdraws consent for further participation, is lost to follow-up, dies, or the study closes. Upon PD, all patients will then be placed on LTFU, every three months until death, lost to follow-up, or consent withdrawal.

There is an ongoing Phase 2 trial (NCT03740529) of oral pirtobrutinib in patients with CLL/SLL and Non-Hodgkin Lymphoma (NHL) who have failed or are intolerant to standard of care. Study completion is expected in 2028, with primary completion estimated in 2027.

2.13 Interpretation of clinical effectiveness and safety evidence

While there are several treatment options for patients with CLL, they frequently have significant limitations that increase patient burden. Moreover, the burden arising from resistance or intolerance to current therapies highlights the urgent need for new, effective treatments with improved safety profiles. This is particularly vital for patients who have been previously treated with at least one BTKi or BCL2i or cannot tolerate existing treatments. Non-covalent BTKis like pirtobrutinib are key to overcoming resistance from BTK mutations, providing additional options for these patients.[80]

The efficacy and safety of pirtobrutinib for treating CLL after one or more BTKi has been assessed through a comprehensive Phase 3 RCT, the BRUIN CLL-321 trial. The clinical efficacy results demonstrate that pirtobrutinib facilitates a statistically significant and clinically meaningful improvement in IRC-assessed PFS of 13.96 months (95% CI: 11.24, 16.56) in the pirtobrutinib arm compared to 8.74 months (95% CI: 8.08, 10.38) in the Investigator's choice of IdelaR or BR arm.

Longer follow-up (the follow-up analysis) allowed the PFS data to further mature and pirtobrutinib continued to show a clinically meaningful benefit in IRC assessed PFS compared to IdelaR or BR with an HR of 0.536 (95% CI: 0.385, 0.746). The IRC-assessed PFS benefit was also observed across prespecified subgroups, ranging from prior systemic therapy, including prior venetoclax treatment, high-risk prognostic factors, reason for BTKi discontinuation and, choice of comparator.

The meaningful PFS benefit is further supported by the favourable secondary endpoint results. Real-world evidence shows that in venetoclax-naïve patients, the median TTNT discontinuation after a cBTKi-based treatment was 9.5 months (95% CI, 8.8 to 10.4), and 5.6 months (95% CI, 4.3 to 6) after discontinuation from both cBTKi and venetoclax.[83] As the number of CLL patients in the post-cBTKi setting rises, the need for therapies with proven efficacy becomes critical. In the BRUIN CLL-321 study, pirtobrutinib demonstrated a clinically meaningful improvement in TTNT compared to the Investigator's choice of IdelaR or BR, with a median TTNT of approximately two years for patients treated with pirtobrutinib. In contrast, patients in the Investigator's choice of IdelaR or BR arm required new treatment at a median of only 10.91 months after starting the study treatment. Pirtobrutinib monotherapy resulted in improved Investigator-assessed TTNT (HR = 0.365; 95% CI: 0.254, 0.524). Clinicians emphasised that the trial's TTNT data illustrate the value of using pirtobrutinib beyond disease progression.[35]

The EFS endpoint also incorporates tolerability, and the result also strongly favours pirtobrutinib, aligning with the observed safety profile. Pirtobrutinib monotherapy resulted in improved Investigator-assessed EFS (HR = 0.387; 95% CI: 0.280, 0.534) compared to the Investigator's choice of IdelaR or BR arm.

The results of BRUIN CLL-321 demonstrate that pirtobrutinib monotherapy has a favourable safety profile compared to IdelaR. Pirtobrutinib was generally better tolerated than IdelaR, with a pattern of less frequent and lower grade AEs observed in the pirtobrutinib arm compared to the Investigator's choice of IdelaR or BR arm, with the exception of similar frequency SAEs reported in both the pirtobrutinib and the Investigator's choice of IdelaR or BR arms (47.4% and 46.8% respectively). Dose interruptions, discontinuations, and reductions were experienced less frequently by patients in the pirtobrutinib arm compared to patients in the Investigator's choice of IdelaR or BR arm. Aggregate analyses of AESIs did not reveal any new or unexpected safety findings, and no patients died on pirtobrutinib treatment as a result of treatment-related AEs.

The efficacy and tolerability profile observed demonstrates the potential of pirtobrutinib to extend benefit of BTKi treatment for those who could not tolerate or progressed on prior covalent BTKi treatment.

Strengths of the clinical evidence base

The BRUIN CLL-321 trial was the first global, prospective, randomised controlled study conducted entirely in a post-BTKi population, providing the most robust and relevant data to demonstrate an effective treatment option in patients with previously treated CLL. Since all patients had prior BTKi therapy, and approximately 50% had also received prior BCL2i therapy – both current SoC for patients within R/R CLL – this study offers the strongest evidence base available in the dual-exposed setting. The trial accounted for all available cancer therapies in the post BTKi setting, by enrolling all patients with BTKi-pretreated CLL regardless of prior line of therapy, including venetoclax. Inclusion of prior venetoclax as a randomisation stratification factor ensured the number of patients with or without prior venetoclax exposure was balanced between treatment arms. Clinical experts highlighted that there is scarce evidence from clinical trials for patients who have progressed after both BTKi and BCL2i therapies, making pirtobrutinib especially valuable in these settings; approximately half of the patients randomised in the BRUIN CLL-321 trial were BCL2i-exposed.[35] The BRUIN CLL-321 trial provides evidence for patients who have progressed on a BTKi, demonstrating the efficacy of pirtobrutinib regardless of prior venetoclax exposure. This positions pirtobrutinib as a valuable option in the 2L+ space, offering clinicians flexibility in treatment sequencing and expanding therapeutic choices for managing complex cases in R/R CLL.

The trial was conducted as an open-label study, but the primary endpoint was agreed upon with the EMA and was determined to be an appropriate efficacy determinant within this trial, also, the independent disease evaluation and management throughout the trial aligned with established iwCLL 2018 guidelines.[16] As the sponsor was blinded to aggregate comparative data, any potential bias in assessing the primary endpoint was mitigated by IRC evaluation, who remained blinded until they confirmed PD. PD was evaluated by two assessors which also aids in mitigating any potential bias. The IRC-assessed PFS benefit is considered a reliable and unbiased response assessment given that it aligns with the iwCLL guidelines, which incorporates disease-related constitutional symptoms, physical examination, and clinical and radiographical assessments.[16]

The overall trial patient demographics were broadly reflective of those expected for people with CLL in the UK, as validated by external clinical experts for this submission.[35] The proportions of trial participants who were male (69.7%), White (81.1%), and aged 65 years or older (63.0%), with patients enrolled predominantly from Europe (58.4%), are broadly aligned with the population expected in UK clinical practice. [14, 26]

An additional strength of the BRUIN CLL-321 trial is its LTFU phase, with assessments every 12 weeks for up to two years, and every 24 weeks thereafter. This ongoing monitoring allows exploration of sustained efficacy and will hopefully support the expectation that the real-world effectiveness of pirtobrutinib will reflect the outcomes observed during the trial.

Limitations of the clinical evidence base

A limitation of the BRUIN CLL-321 trial is the crossover treatment, for patients crossing over from the Investigator's choice of IdelaR or BR arm to the pirtobrutinib arm. While allowing crossover offers ethical benefits by enabling patients who completed or discontinued treatment due to toxicity to receive pirtobrutinib promising benefit/risk profile, it confounds the OS data analysis. Consequently, there is a lack of improvement in the key secondary endpoint, OS, when unadjusted for crossover. Although 70 OS events were observed at the final OS analysis, OS remained uncertain with a wide 95% CI on the HR (HR: 1.090; 95% CI: 0.679, 1.749), as it was highly confounded by crossover. The favourable pirtobrutinib response rate, PFS, and OS in patients after crossover is notable. Three sensitivity analyses meaningfully adjusted the OS hazard ratios and also indicate a significant crossover impact on OS, however, there is no evidence of an OS detriment.

The enrolled population comprised of patients with advanced stage disease and poor molecular characteristics, which may represent a more aggressive form of CLL compared to that of the general population of patients in the post-BTKi population. Despite this, the trial demonstrated meaningful efficacy data—particularly in terms of progression-free survival – in this heavily pre-treated post-BTKi population. However, it should be noted that in general, baseline disease characteristics were similar across the study arms, with the exception of the pirtobrutinib arm having higher rates of Rai Stage IV (39.5% versus 29.4%), ECOG PS 2 (10.1% versus 4.2%), unmutated *IGHV* (75.6% versus 62.2%), and complex karyotype (44.5% versus 37.0%). The trial was conducted in a very high-risk population of patients, yet efficacy was still able to be achieved in this population.

Given the complexity of this heavily pre-treated population, marked by advanced disease and adverse molecular features, it is important to acknowledge that, while the trial demonstrates meaningful efficacy of pirtobrutinib, generating direct comparative data in this rapidly evolving treatment landscape is inherently challenging. The ongoing diversification of treatment sequencing, the lack of well-established treatment algorithms, and the heterogeneity of R/R disease - compounded by the limited availability of efficacious and tolerable therapies - make the design and interpretation of head-to-head trials exceedingly difficult. Variability in patient characteristics, such as molecular risk profiles, comorbidities and prior lines of therapy (note that the range of prior therapies received by patients in the BRUIN CLL-321 trial spanned from one to 13), further complicates comparability, as real-world practice is often influenced by clinician preference and local resource availability, rather than uniform treatment pathways.[35] Moreover, trial populations frequently do not fully reflect the heterogeneity seen in routine practice, especially in terms of molecular and clinical diversity.[35]

Therefore, the emphasis should be on the demonstrated benefits of pirtobrutinib within this difficult-to-treat cohort, recognising the persistent unmet need for more effective and tolerable treatment options in this population. This approach ensures that the focus remains on addressing the critical gaps in current management, especially for patients with limited options due to resistance or intolerance to existing therapies, rather than relying solely on direct comparisons that are difficult to establish in such a dynamic and complex environment.

The BRUIN CLL-321 trial was an open-label study; however, it was randomised to minimise bias in patient assignment, ensure an even distribution of known and unknown patient attributes, and enhance the validity of statistical comparisons across treatment groups.

Conclusion

Pirtobrutinib is a first-in-class, non-covalent BTKi that has shown statistically significant and clinically meaningful improvements in IRC-assessed progression-free survival (HR = 0.536; 95% CI: 0.385, 0.746; nominal p = 0.0002) compared to the Investigator's choice of IdelaR or BR arm. Its innovative mechanism of action marks a major advancement for BTKi pre-treated populations, addressing the unmet needs caused by resistance or intolerance to existing therapies.

Non-covalent BTKis like pirtobrutinib are essential for overcoming resistance mediated by BTK mutations at C481S, providing an important treatment option for these patients. For those with R/R disease after covalent BTKi therapy pirtobrutinib offers a favourable safety profile and promising treatment outlook. The pivotal BRUIN CLL-321 trial demonstrated that pirtobrutinib significantly enhances progression-free survival and delays the need for subsequent therapy. Implementing pirtobrutinib in the UK would provide additional options for the post-BTKi and dual-exposed populations, reducing anxiety and stress by addressing uncertainties about future treatment availability and tolerability.

3 Cost Effectiveness

Summary of the cost-effectiveness analysis

De novo cost-effectiveness model

- A *de novo* economic model was developed to assess the cost effectiveness of pirtobrutinib for the treatment of adults with R/R CLL, who had been previously treated with a BTKi.
- The model used a partitioned survival structure to best model OS and PFS based on study-observed events, facilitating the replication of within-trial data, and allow the clinical benefit of pirtobrutinib versus IdelaR, to be captured by reflecting the increased proportion of patients expected to be alive/progression-free over time.
- The model structure comprised of three mutually exclusive health states: progression-free, progressive disease, and death.
- Patients move between states based on PFS and overall survival OS curves; PF state occupancy is determined by the proportion alive and without progression.
- The PD state is populated by those alive but with documented disease progression, and the death state is an absorbing state with associated palliative care costs.
- The analysis assumes a lifetime horizon with a 28-day cycle length, using NHS and PSS costs, and adheres to NICE guidelines with a discount rate of 3.5% for costs and effects.
- Costs and health-related utilities are allocated to each health state and are used to calculate weighted costs and QALYs per cycle.
- Health state unit costs and resource use were sourced from NHS Reference Costs (2023/4), the electronic market information tool (eMIT) and the Monthly Index of Medical Specialties (MIMS).[118-120]

Base case cost-effectiveness results

- The base case probabilistic ICER for pirtobrutinib versus IdelaR, in the post-cBTKi and dual-exposed sub-populations, were [redacted] and [redacted] per QALY gained.
- Overall, the results demonstrate that pirtobrutinib would introduce substantial QALY benefits compared to IdelaR in UK clinical practice and provide patients who otherwise face a poor prognosis with an effective alternative treatment option.

Sensitivity and scenario analysis

- The deterministic sensitivity analyses (DSA) results showed that the ICER was most sensitive to the HR used to adjust the OS Investigator's choice curve, post-progression drug acquisition costs, pirtobrutinib acquisition cost, and the progression-free utility weight.
- Based on findings from the PSA, – at the list price for pirtobrutinib – [redacted] and [redacted] of iterations fell below the WTP threshold of £30,000, for the post-cBTKi and dual-exposed populations respectively.

Conclusion

- The cost-effectiveness analyses demonstrates pirtobrutinib to introduce significant QALY benefits compared to IdelaR in UK clinical practice, providing patients who otherwise face a poor prognosis with an effective alternative treatment option. Pirtobrutinib, the first-of-its-kind, non-covalent BTKi therapy, represents a significant advancement in addressing the unmet need for more efficacious and tolerable treatments in patients with R/R CLL.

3.1 Published cost-effectiveness studies

A *de novo* SLR was conducted to identify economic studies in any patients with R/R CLL, regardless of prior treatment, including studies in which patients were previously treated with a

BTKi. The original SLR searches were performed in February 2022 and updated in April 2022 (SLR update 1), October 2023 (SLR update 2), September 2024 (SLR update 3).

In the original SLR and SLR update 1, a total of 1,547 records were retrieved; 1,108 from electronic databases, 93 from internet searches and, 346 from hand searches. Of these, 419 were duplicates, resulting in 1,128 novel records that were screened at the initial title/abstract review stage. Upon an initial title/abstract screen, 367 records were progressed to further full-text articles. Following a secondary full text screen, 75 articles were selected for data extraction and included in the systematic review.

In the SLR update 2, a total of 557 records were retrieved; 343 from electronic databases, 83 from internet searches and, 131 from hand searches. Of these, 240 were duplicates, resulting in 317 novel records being screened at the initial title/abstract review stage. Of these, 88 were selected following a secondary full text review and 37 were included in the systematic review.

In the SLR update 3, a total of 455 records were retrieved; 403 from electronic databases, 29 from internet searches and, 23 from hand searches. Of these, 67 were duplicates, resulting in 363 novel records being screened at the initial title/abstract review stage. Of these, 52 were selected following a secondary full text review and 23 were included in the systematic review.

Further details of the economic SLR, including the methodology and search strategy, are presented in Appendix E.

A total of 41 articles reporting economic evaluation evidence, 36 reporting cost and healthcare resource utilisation, seven reporting utility data and 22 reporting HRQoL or PRO data, were identified for the broader R/R CLL population. However, none of these studies were specifically conducted in the post-cBTKi populations of relevance to this submission. As no economic analyses pertaining to the post-cBTKi populations were identified, the details of the studies identified in this SLR, have not been presented within the submission, but can be located in Appendix E.

3.2 Economic analysis

The objective of this economic analysis was to assess the cost-effectiveness of pirtobrutinib as a treatment for patients with R/R CLL who have previously been treated with a BTKi.

A cost-effectiveness analysis of pirtobrutinib versus IdelaR, as per the decision problem for this submission presented in Section 1.1, was performed. It should be noted that clinical efficacy data in the model is informed by the Investigator's choice of IdelaR or BR arm, from the BRUIN CLL-321 trial. It was considered appropriate to use a basket comparator to inform the efficacy inputs as this allowed for trial randomisation to be maintained and to maintain a large enough sample size to allow sufficient power for testing PFS in an error-controlled fashion; a majority of patients (70.6%) in the comparator arm of BRUIN CLL-321 were treated with IdelaR. Clinical experts approached for this submission agreed on the generalisability of the data for the basket comparator to patients treated with IdelaR in UK clinical practice.

The analysis was conducted from the perspective of the National Health Service (NHS) and the Personal Social Services (PSS) of the UK, over a lifetime time horizon of the patient cohort from the initiation of treatment.

Studies identified in the SLR, presented in Appendix E, did not yield relevant economic analyses nor cost-effectiveness models for pirtobrutinib in adults with R/R CLL. However, the economic analyses highlighted the common structures, inputs, and assumptions across the different models developed for its comparators and thus provided a useful insight for the development of the *de novo* economic model and cost-effectiveness analyses that was therefore conducted.

3.2.1 Patient population

The economic analyses considered a subgroup of adult patients with R/R CLL who had previously been treated with a covalent BTKi and a BCL2i (sequentially or in combination), i.e., the dual-exposed population. The dual-exposed population aligns with a subgroup population investigated in BRUIN CLL-321 (please refer to Section 2.8). Additionally, the economic analyses also considered a population of adult patients with R/R CLL who had been previously treated with a cBTKi, who are unsuitable for current SoC, i.e., the post-cBTKi, unsuitable for current SoC population. The post-cBTKi population aligns with the primary trial population investigated in the BRUIN CLL-321 clinical trial. These populations reflect the anticipated positioning of pirtobrutinib if approved for routine commissioning in UK clinical practice.

Due to the insurmountable challenges in generating robust estimates of comparative treatment efficacy between pirtobrutinib and VenR, based on the NMA feasibility assessment discussed in Section 2.10, economic analyses for the post-cBTKi, suitable for current SoC population (detailed in Section 1.1 and Section 1.3.3) could not be conducted. As such, the economic analysis of pirtobrutinib versus IdelaR for the post-cBTKi, unsuitable for current SoC population is considered the only suitable proxy for this positioning.

3.2.2 Model structure

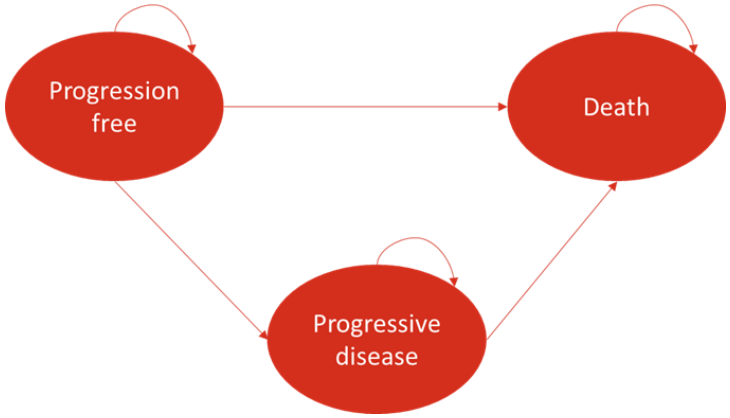
Partitioned Survival Model

An economic model was developed in Microsoft Excel® to evaluate the cost-effectiveness of pirtobrutinib versus IdelaR, the relevant comparator in UK clinical practice in the populations of interest to this submission. A PSM was developed, consisting of three mutually exclusive health states:

- Progression free (PF): The disease has not progressed; all patients start the model in this health state
- Progressed disease (PD): The disease has progressed; all patients discontinue their current treatment and switch to best supportive care (BSC)
- Death: Death has occurred due to CLL or another cause

The partitioned survival approach was selected as it allows for modelling of OS and PFS based on study-observed events, which facilitate the replication of within-trial data and allows the clinical benefit of pirtobrutinib versus IdelaR, to be captured by reflecting the increased proportion of patients expected to be alive/progression-free over time.

Figure 27: Partitioned survival model structure

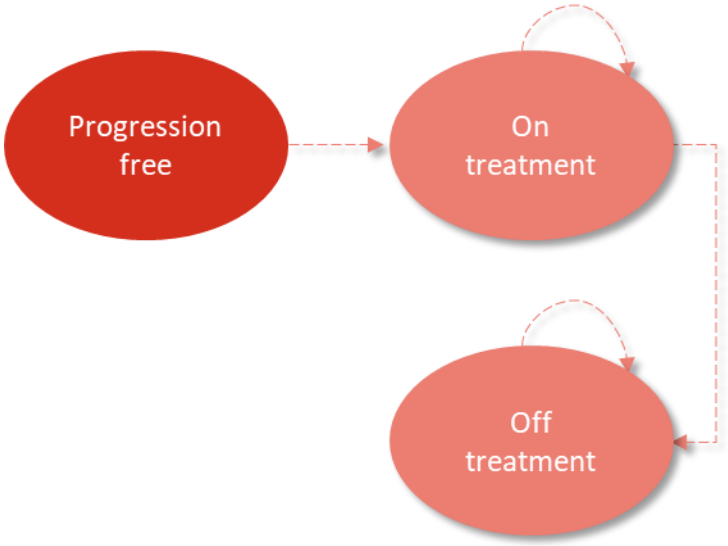


As discussed above, the PSM comprises the three mutually exclusive health states PF, PD and death. A cohort of people with R/R CLL who have received one or more lines of BTKi were modelled to enter into the PF health state and to receive pirtobrutinib or IdelaR. The proportion of patients in each health state at each 28-day model cycle was then determined for each therapy directly from cumulative survival probabilities from PFS and OS curves as follows:

- The proportion of patients occupying the PF state was calculated as the proportion alive and progression-free (based on the PFS curve). All patients enter and occupy the PF state and are in stable disease, as defined by the PFS measure assessed in BRUIN CLL-321, and are not actively progressing. Within the progression-free health state, substates exist to capture time on and off pirtobrutinib therapy (Figure 28) where time on pirtobrutinib therapy is modelled using time to treatment discontinuation (TTD). For treatments that have a maximum duration, such as rituximab, (e.g., maximum of six or eight cycles), the model followed the TTD curve up until the maximum has been reached. Following that point, no further drug administrations occurred, and no drug costs were incurred in the progression-free health state.
- The proportion of patients occupying the PD health state was calculated as the proportion alive (based on OS curve) minus the proportion of patients alive and progression-free (based on PFS curve). Patients occupying the PD state have documented progressive disease, as defined and assessed in BRUIN CLL-321.
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on the OS curve). This is an absorbing state, and a cost associated with palliative care is applied as a one-off cost upon death (further details are presented in Section 3.5.4).

Patients were redistributed among the three health states at each model cycle. The model structure does not allow for patients to improve their health state, which reflects the progressive nature of the condition, and the death health state is an absorbing health state.

Figure 28: Progression-free health state



Features of the analysis

As per the economic SLR conducted to identify economic studies in patients with R/R CLL, no prior evaluations of pirtobrutinib were found. Additionally, there are no economic evaluations available for other therapies within the post-BTKi CLL population. Therefore, the economic evaluation in this submission was compared to previous NICE models for R/R CLL, despite these models not being entirely aligned with the specific decision problem addressed in this submission and, in some cases, using alternative approaches to economic modelling e.g., cost-minimisation analyses over cost-utility analyses. The economic analyses of comparator therapies used in the broader R/R CLL indication are therefore presented below in Table 53. The economic analyses for the following NICE technology appraisals in R/R CLL were considered:

- Zanubrutinib for treating chronic lymphocytic leukaemia (TA931)
- Acalabrutinib for treating chronic lymphocytic leukaemia (TA689)
- Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (TA561)

Key features of the economic analyses in the TAs noted above have been summarised, alongside justification on the approach taken for the analysis within this submission, in Table 53.[27, 37, 69] The approach taken in the model developed for use in this submission broadly aligned with these previous appraisals.

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. Cost components that were considered in the model included: drug acquisition costs for pirtobrutinib and comparators and associated drug administration costs, drug posology, healthcare resource utilisations costs (by health state), AE costs, and the cost of end-of-life palliative care. Effectiveness measures included life years (LYs) and QALYs. The ICER of pirtobrutinib versus IdelaR was evaluated in terms of the incremental cost per QALY gained.

The analysis was conducted from the perspective of the NHS, including direct medical costs and PSS costs, over a lifetime horizon aligned with the patient cohorts treatment initiation, considering a mean age of 67.0 years (based on data from BRUIN CLL-321, see Table 44) at model entry. A lifetime horizon was used in the base case, a 28-day cycle length was considered

in the base case, and both costs and effects were discounted by 3.5%, in line with NICE reference case.[121]

The economic analysis was conducted using the most recent estimates of healthcare resource use costs, and costs relating to the treatment-related AEs, available from NHS Cost Collection (2023/24),[118] whilst treatment costs were sourced from the electronic market information tool (eMIT) and the Monthly Index of Medical Specialties (MIMS), with eMIT being the preferred source and MIMS used when eMIT cost data were not available for selected drugs.[119, 120] End-of-life costs were sourced from Round *et al.* (2015) and inflated to 2022/23 using the NHS cost inflation index.[122, 123]

Table 53: Features of the economic analysis

Factor	Previous evaluation			Current evaluation	
	TA931	TA689	TA561	Chosen values	Justification
Model structure	Partition survival model	Partition survival model; cost-minimisation	Partition survival model	Partitioned survival model	Accurately reflect disease progression and the observed survival profile of patients treated with pirtobrutinib and comparator therapies and in line with previous appraisals and available data
Time horizon	Lifetime horizon (30 years)	Lifetime horizon (30 years)	Lifetime horizon (30 years)	Lifetime horizon	NICE reference case[121]
Cycle length	28 days	28 days	28 days	28 days	The model cycle length was chosen as 28 days to be consistent with the pirtobrutinib dosing described in the BRUIN CLL-321 clinical trial protocol
Discount rate	3.5%	Not applied in the base case; 3.5% explored in scenario analysis	3.5%	3.5%	NICE reference case[121]
Source of utilities	Base-case: N/A Scenario: NICE TA561[69] and Holzner 2004[124] • PFS: 0.7830 • PD: 0.6000	N/A	Base-case: Study 116 and Dretzke 2010[125] • PFS: 0.748 • PPS: 0.600 **Disutilities** • ALT/AST elevation: 0.050	Base-case: BRUIN CLL-321[126] and TA931[37] • PFS: [redacted] • PD: 0.600 • Disutilities: NICE TA931[37]	In line with the NICE reference case, EQ-5D data form the BRUIN CLL-321 trial informed the base case economic analysis.

	Disutilities • Anaemia: 0.0900 • Thrombocytopenia: 0.1100 • Pneumonia: 0.1950 • Neutropenia: 0.1630 • Hyponatremia: 0.0200 • Hypertension: 0.0200 • Febrile Neutropenia: 0.1630 • Cataract: 0.0900 • Atrial fibrillation: 0.2200		• Anaemia: 0.090 • Autoimmune haemolytic anaemia: 0.090 • Hypophosphatemia: 0.000 • Infusion related reaction: 0.200 • Neutropenia: 0.163 • Pneumonia: 0.195 • Thrombocytopenia: 0.108		The post-progression utility value of 0.600 published by Holzner et al. (2004) was used in the base case and was accepted by the NICE appraisal committee in several HTA submissions: TA931, TA487, TA561, TA429, TA359.[37, 66-69, 124]
Source of costs	NHS Reference Costs PSSRU BNF[127]	NHS Reference Costs PSSRU BNF[127]	NHS Reference Costs PSSRU BNF[127]	NHS Reference Costs[118] eMIT[119] MIMS[120] Round et al. (2015), inflated to 2022/23 using the NHS cost inflation index[122, 123]	Established sources of costs within the NHS. In line with the NICE reference case.[121]
Resource use	Resource use was derived from prior appraisals[27] and validated by expert opinion	Resource use was derived from prior appraisals[69]	Resource use was derived from prior appraisals[67]	Resource use was derived from prior appraisals[37] and validated by expert opinion	Prior NICE technology appraisals were considered a relevant source for resource use data.

Health effects measures	QALYs	QALYs	QALYs	QALYs	NICE reference case[121]

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BNF: British National Formulary; EQ-5D: EuroQol five dimensions questionnaire; eMIT: electronic market information tool; HTA: health technology assessment; MIMS: Monthly Index of Medical Specialties; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; PD: progressed disease; PFS: progression-free survival; PPS: post-progression survival; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years.

3.2.3 Intervention technology and comparators

Intervention

The intervention of interest is pirtobrutinib administered QD in 28-day continuous cycles until progressive disease or unacceptable toxicity, or other reasons for treatment discontinuation. The pirtobrutinib dose included in the economic model is 200 mg orally QD in line with the dose for adult patients receiving pirtobrutinib in the BRUIN CLL-321 trial, and the SmPC for pirtobrutinib.[4] [4, 91]

Comparator: IdelaR

Aligned with rationale presented in Section 1.1 and Section 1.3.3, IdelaR is included in the model as the relevant comparator to pirtobrutinib comparator across all anticipated sub-populations in UK clinical practice that are addressed in this submission. UK clinical experts confirmed that IdelaR is the sole relevant comparator to pirtobrutinib in UK clinical practice, within the dual-exposed and post-cBTKi, unsuitable for current SoC sub-populations, and therefore in alignment with the BRUIN CLL-321 trial data, IdelaR has been parameterised for both these populations in the model. It was assumed that the results for IdelaR, as presented for the post-cBTKi, unsuitable for current SoC sub-population, would also be applicable to the post-cBTKi, suitable for current SoC sub-population in this submission.

VenR treatment and cBTKi therapies (as comparators in the post-cBTKi, suitable for current SoC sub-population) have not been included within the model due to a number of limitations identified in the conducted FA that preclude the use of the identified data in generating comparative effectiveness estimates between pirtobrutinib and these comparators (further details on the FA are presented in Section 2.10). These challenges in generating robust comparative efficacy estimates between pirtobrutinib and VenR and cBTKis were acknowledged by UK clinical experts. Therefore it was concluded that, any economic analyses conducted in the absence of head-to-head comparisons between pirtobrutinib and these comparators, within the scope of this submission, would either overlook the heterogeneity of important known treatment effect modifiers, or would produce biased results that could not be reliably interpreted. In the absence of suitable comparator efficacy estimates for VenR and cBTKi, the economic analyses conducted versus IdelaR in the post-cBTKi, unsuitable for current SoC sub-population is considered the only suitable proxy for these treatments in this positioning.

3.3 Clinical parameters and variables

Clinical trial data informing the cost-effectiveness model were primarily sourced from the BRUIN CLL-321 trial. Clinical data for the dual-exposed population were derived from subgroup data within BRUIN CLL-321, while the primary trial population – investigated in BRUIN CLL-321 – served as the basis for the post-cBTKi populations considered in this submission

3.3.1 Baseline characteristics

Patient baseline characteristics used in the model are presented below in Table 54. Data for the post-cBTKi cohort are based on data for the ITT population in BRUIN CLL-321, with data on the dual-exposed population derived from the subgroup of patients who received prior treatments, including cBTKi and BCL2i therapy.

The starting age in the model was set at 67.0 years for the post-cBTKi cohort, and 66.8 years for the dual-exposed cohort, based on the mean age of patients for the respective populations in the BRUIN CLL-321 trial. The percentage of female patients was modelled at 30.3% and 40.0% in the post-cBTKi and dual-exposed populations, respectively. Baseline patient body surface area (BSA) was also similar across the two sub-populations (1.92 and 1.93 m^2 in the post-cBTKi and dual-exposed populations, respectively).

Table 54: Baseline characteristics of modelled cohort

Parameter	Post-cBTKi population	Dual-exposed population	Source
Mean age, years	67.0	66.8	BRUIN CLL-321[91]
Percentage female, %	30.3%	40.0%	
Mean patient BSA, m^2 (SD)	1.92 (0.24)	1.93 (0.26)	

Abbreviations: BSA: body surface area; CLL: chronic lymphocytic leukaemia; SD: standard deviation.

3.3.2 Time-to-event analysis

The main objective of the survival analyses was to determine survival curves for pirtobrutinib and Investigator's choice of IdelaR or BR, for the OS, TTD, Investigator-assessed PFS, and IRC-assessed PFS endpoints. Survival analyses for pirtobrutinib and Investigator's choice of IdelaR or BR were conducted using the 29th August 2024 DCO from the BRUIN CLL-321 trial. As noted in Section 3.2, clinical validation informed the use of the basket comparator of Investigator's choice of IdelaR or BR to inform the efficacy inputs as this allowed for trial randomisation to be maintained and to maintain a large enough sample size to allow sufficient power for testing PFS in an error-controlled fashion.

Survival analyses followed the guidance of NICE Decision Support Unit (DSU) technical support documents (TSD): TSD14 for standard parametric models and TSD21 for flexible spline models.[95] The analysis consisted of Cox models and parametric survival analyses. The parametric survival analysis attempted to fit a series of parametric survival functions to observed survival data from the BRUIN CLL-321 trial to identify information regarding the survival differences between the trial arms. The following models were used to fit the data: exponential, Weibull, Gompertz, log-normal, log logistic, gamma, generalised gamma, and flexible-spline–based Weibull with one, two, or three knots.

Models were fit with and without treatment (e.g., stratified models) as a covariate. Stratified models allow curve parameters (e.g., shape, scale, gamma) to vary by treatment effectively mimicking curves fit to each treatment individual. However, the fit statistics (e.g., Akaike's information criteria [AIC] and Bayesian information criteria [BIC]) were on a scale that was comparable to models fit with a treatment covariate. Thus, they allowed for an easier comparison of goodness-of-fit to treatment covariate models while curves fit individually are not as easily compared.

Statistical tests and diagnostic hazard plots (e.g., log-log plots, Schoenfeld residuals; included in the reference pack to this submission) were inconsistent in assessing proportional hazards with plots tending to show nonproportionality and statistical tests unable to reject the null hypothesis

of proportionality due to nonsignificant results. Given the inconsistency and the inclusion of an option to apply HRs directly to the unbiased pirtobrutinib curve (effectively allowing both nonproportional and proportional hazard analysis to be modelled), stratified models were carried forward into the model, and models with treatment as a covariate were discarded as well as exponential models that assume constant hazards.

Base-case model selection followed best practices from TSD14 and TSD21 examining both plausibility of fit and statistical goodness-of-fit. Base case model selection followed a stepwise process with the first step being based on which models produced long-term plausible extrapolations. Charts showing long-term predicted survival probabilities were used to check the plausibility of the OS extrapolations, i.e., that they were close to those from studies with long-term follow-up and a similar patient population and that they do not exceed survival predictions from an age-matched general population.[128-132] Models that did not meet this criterion were excluded from base-case consideration. Summaries of survival curve projections at approximately 1, 3, 5, 10, and 15 years are presented in the relevant sections below.

The remaining models were assessed for goodness-of-fit using AIC, the BIC, and visual fit of the models overlaid with empirical KM estimates. As AIC and BIC are statistical measures of goodness-of-fit to the observed data only (i.e., they do not indicate clinically plausible survival in the projected or tail portions of the survival estimates), distributions producing the lowest goodness-of-fit statistics were not always considered as the best. Instead, AIC and BIC criteria were used as a guide alongside the visual overlays and clinical plausibility (assessed via studies cited above and expert clinical opinion elicited for this submission) to determine the base-case distribution.

To compare survival functions based on different distributions, a graphical evaluation of model fit was conducted. A visual comparison was made of the parametric curve overlaid with the Kaplan-Meier curve of the observed data. This comparison ensured that the parametric model selected was the model that best described the most critical sections of the observed survival curve.

3.3.2.1 PFS

PFS assessed by the Investigator was selected for the base case for both the post-cBTKi and dual-exposed populations because it was considered more reflective of clinical practice – supported by clinical expert opinion obtained for this submission – and is consistent with previous NICE submissions in CLL.[37, 69, 133] A scenario analysis using PFS by IRC was explored; this is reported in Section 3.11.

Post-cBTKi population

The goodness-of-fit statistics for each distribution using Investigator PFS for the post-cBTKi population are summarised in Table 55. A summary of the survival extrapolations for the modelled PFS distributions for the post-cBTKi population are presented in Figure 29.

Table 55: Pirtobrutinib versus Investigator's choice PFS goodness-of-fit statistics for the post-cBTKi population

Distribution	AIC	BIC	AIC rank	BIC rank	Clinically plausible?[a]	Reason for exclusion[b]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--

Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	No	1
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	No	1, 2
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 1	[redacted]	[redacted]	[redacted]	[redacted]	No	1
Spline k = 2	[redacted]	[redacted]	[redacted]	[redacted]	No	1, 2
Spline k = 3	[redacted]	[redacted]	[redacted]	[redacted]	No	1, 2

Footnotes: [a]Clinical plausibility assesses whether each distribution's survival curve aligns with expected disease progression in the target population. Distributions marked "Yes" show realistic trends, while those marked "No" display implausible behaviour. [b]Reasons for exclusion from best-fit consideration: 1 = survival curves cross; 2 = unrealistic long-term projections of survival in one or both arms.
Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 29: PFS by Investigator KM plots and summary distribution overlays (post-cBTKi population)

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; Inv. Choice: investigator's choice; k: knots; KM: Kaplan-Meier; PFS: progression free survival.

With the exception of the gamma and the Weibull distributions, seven of the nine modelled distributions were excluded from consideration. This was based on either the survival curves for pirtobrutinib intersecting with the comparator arm – and remaining lower than the comparator for the remainder of the model time horizon – or due to the presence of unrealistic long-term projections of survival in one or both arms, or a combination of both these criteria. Reasons for exclusion for each distribution are presented in Table 55, above.

It was determined that the gamma distribution was the best fit. Gamma was the most clinically and scientifically plausible among the distributions with low AIC and BIC values (see Figure 30 and Figure 31) as the Weibull distribution overestimated Investigator's choice PFS toward the end of the Kaplan-Meier plot, with curves converging at around 75 months. With the gamma distribution, the PFS benefit in favour of pirtobrutinib was maintained over the long term,

converging with the comparator at around 90 months, which was considered more realistic given the trend in the data from BRUIN CLL-321. The gamma distribution is used in the base-case analysis and Weibull is explored in a scenario analysis.

A summary of landmark estimates for PFS (by Investigator) at 1, 3, 5, 10 and 15 years for the post-cBTKi population are presented in Table 56.

Figure 30: PFS by Investigator Kaplan-Meier plot and detailed distribution overlay for the post-cBTKi population: Gamma

Abbreviations: Inv.: investigator; PFS: progression-free survival.

Figure 31: PFS by Investigator Kaplan-Meier plots and summary distribution overlays for the post-cBTKi population: Weibull

Abbreviations: Inv.: investigator; PFS: progression-free survival.

Table 56: PFS (by Investigator) landmark estimates for modelled distributions (post-cBTKi population)

	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull	Spline k = 1	Spline k = 2	Spline k = 3
Pirtobrutinib									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigators choice									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; k: number of knots; PFS: progression-free survival.

Dual-exposed population

The goodness-of-fit statistics for each distribution using investigator PFS assessment source for the dual-exposed population are summarised in Table 57. A summary of the survival extrapolations for the modelled PFS distributions for the dual-exposed population are presented in Figure 32.

Table 57: Pirtobrutinib versus Investigator's choice PFS goodness-of-fit statistics for the dual-exposed population

Distribution	AIC	BIC	AIC rank	BIC rank	Clinically plausible?[a]	Reason for exclusion[b]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 1	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 2	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 3	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--

Footnotes: [a]Clinical plausibility assesses whether each distribution's survival curve aligns with expected disease progression in the target population. Distributions marked "Yes" show realistic trends, while those marked "No" display implausible behaviour. [b]Reasons for exclusion from best-fit consideration: 1 = survival curves cross; 2 = unrealistic long-term projections of survival in one or both arms.
Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 32: PFS by Investigator KM plots and summary distribution overlays (dual-exposed population)

Abbreviations: Inv. Choice: investigator's choice; k: knots; KM: Kaplan-Meier; PFS: progression free survival.

Only two of the nine distributions (Log-logistic and Log-normal) were excluded from consideration due to concerns with clinical plausibility as discussed for the post-cBTKi population above.

Ultimately, the gamma distribution was chosen for the dual-exposed population in the base case. Gamma was the most clinically and scientifically plausible among the distributions with low AIC and BIC values, supported by clinical expert opinion elicited for this submission (see **Error! Reference source not found.**).[35] Weibull is explored as a scenario analysis.

A summary of landmark estimates for PFS (by Investigator) at 1, 3, 5, 10 and 15 years for the dual-exposed population are presented in Table 58.

Figure 33: PFS by Investigator Kaplan-Meier plots and summary distribution overlays for the dual-exposed population: Gamma

Abbreviations: Inv.: investigator; PFS: progression-free survival.

Figure 34: PFS by Investigator Kaplan-Meier plots and summary distribution overlays for the dual-exposed population: Weibull

Abbreviations: Inv.: investigator; PFS: progression-free survival.

Table 58: PFS (by Investigator) landmark estimates for modelled distributions (dual-exposed population)

	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull	Spline k = 1	Spline k = 2	Spline k = 3
Pirtobrutinib									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigators choice									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: k: number of knots; PFS: progression-free survival.

3.3.2.2 OS

As discussed in Section 2.3.1, upon PD in the comparator arm of BRUIN CLL-321, patients could switch to pirtobrutinib therapy. A total of 50 of 66 patients eligible for crossover (75.86%) in the Investigator's choice arm crossed over to receive at least one dose of pirtobrutinib, with a median duration of exposure of 7.85 months. To explore potential confounding in OS and to adjust for the bias introduced by crossover, sensitivity analyses of OS for patients who crossed over from the pirtobrutinib arm were conducted. Details of these analyses are discussed in Sections 2.4.2.3 and 2.6.3.

As discussed earlier, simple adjustment methods include censoring crossover patients at the point of treatment switching or excluding crossover patients. However, these approaches are highly prone to selection bias, as crossover is likely to be associated with prognosis. The NICE DSU 16 guidelines, updated in TSD24, do not recommend these simple methods and instead refer to several other adjustment methods to consider when adjusting for treatment switching.[95] These methods include:

- Rank Preserving Structural Failure Time Models (RPSFTMs) (nonparametric, semiparametric, and parametric method) represent randomisation-based methods for estimating counterfactual survival times (i.e., survival times that would have been observed in the absence of switching). A method referred to as g-estimation is used to estimate a time acceleration factor that can be applied to survival times in the control to create the counterfactual data
- Two-stage method: when switching is permitted only after disease progression, this timepoint can be used as a secondary "baseline." An AFT model (such as a Weibull model) that includes covariates measured at the time of progression and a covariate indicating treatment switch can be fitted to the post-progression control group data to produce an estimate of the treatment effect received by patients who switched compared with control group patients who did not switch. The resulting acceleration factor can then be used to "shrink" the survival times of switching patients to derive a counterfactual data set unaffected by switching
- The IPCW method represents an observational-based approach, whereby data for switchers are censored at the point of switch and remaining observations in the control arm that did not switch are weighted with the aim of removing any censoring-related selection bias

However, the TSDs 16 and 24 state that these methods all make important limiting assumptions. The RPSFTM relies on the "common treatment effect" assumption—that is, the treatment effect received by crossover patients is the same as that in the patients that received pirtobrutinib at randomisation. Observational-based adjustment methods (such as IPCW and the two-stage method) are reliant on the "no unmeasured confounders" assumption—i.e., data must be available on baseline and time-dependent variables that predict both treatment switching and prognosis. RPSFTM and iterative parameter estimation have been reported to produce larger CIs than those produced by IPCW and the two-stage method.[134]

RPSFTM analyses are considered to perform relatively poorly by Latimer *et al.* (2024).[134] Although treatment effect estimates generally fell within the 95% CIs of the expected truths, the point estimates were closer to 1 than expected, and CIs were extremely wide, indicating a lack of precision.[134] These results were explained by arguing that if there is very little difference in observed outcomes between randomised groups, the RPSFTM will attribute only a very small treatment effect to any additional exposure to treatment that is present in either randomised group.[134, 135] Fundamentally, the RPSFTM will successfully identify treatment effects only if there

are appreciable differences in exposure to the experimental treatment in the two randomised groups and if this results in an appreciable difference in outcomes in an ITT analysis. The TSDs argue that given the limitations associated with the adjustment methods, the ITT analysis should always be presented.

RPSFTM and the two-stage method estimate a single value for the time acceleration factor, and IPCW provides a single set of weights for the patients who crossover. This means that no uncertainty for the time acceleration factor or weights is incorporated into the predictions. These limitations can be overcome by using bootstrapping. However, bootstrapping small samples can cause convergence issues due to having too few events in a bootstrap sample and/or some covariate values poorly represented in some samples.

Furthermore, these methods complicate the process of extrapolation. If bootstrapping is performed, the main output is an array of parameters from parametric models. This means that external data such as those described by Guyot *et al.* (2017) and Vickers (2019) were not appropriate.[136, 137] This leaves extrapolating the survival curves without external data (i.e., following the NICE TSD14 guidelines using hazard rates from a separate model fitted to the external data (Vickers, 2019), or using hazard rates from a model fitted to the randomised controlled trial that includes physician beliefs in expected survival (e.g., Jackson [2023]).[95, 137, 138]

In summary, there was no single treatment switching that was considered to be the most robust method. Therefore, all three treatment-switching models were performed for parametric analyses with results of the most appropriate adjustment method (two-stage AFT) chosen for the base case and a secondary adjustment method (IPCW) presented as sensitivity analyses (shown in Section 3.11.3).

Two-stage AFT was selected as the base-case method as TSD24 notes that “when switching proportions are high IPCW results can be prone to substantial bias, especially when sample sizes are small,” both occurring in BRUIN CLL-321. The IPCW method relies on predicting treatment switching using the covariates available at time of progression in the control arm. To do this, a large sample may have been needed. If treatment-switching rates are high, then the effective sample size may be small.

While conducted for completeness, the RPSFTM method was not included in the model. Deng *et al.* (2023) stated that the switching probability and the switching time are key determinants for power decreasing and thus the sample size required to maintain the desired power in the analysis.[139] In BRUIN CLL-321, a high proportion of eligible patients switched treatment (75.86%) and the time to progression/switch treatment was relatively short compared with the observed time to deaths. This meant that the exposure time to the control arm was relatively small compared with pirtobrutinib. In this scenario, the two treatment arms were effectively pirtobrutinib, and little difference in OS between treatment arms were expected. Gorrod *et al.* (2024) argued that if there is very little difference in observed outcomes between randomised groups, the RPSFTM would attribute only a very small treatment effect to any additional exposure to treatment that is present in either randomised group. As explained above, the RPSFTM will successfully identify treatment effects only if there are appreciable differences in exposure to the experimental treatment in the two randomised groups and if this results in an appreciable difference in outcomes in an ITT analysis. Therefore, it was expected that the RPSFTM would make negligible difference to survival estimates in the BRUIN CLL-321 trial.

The two-stage method estimates survival outcomes in patients that have progressed in the control arm for those that switched to pirtobrutinib versus those that did not switch. The data for this part of the model are essentially observational data, and there may be issues with unknown

confounders and correlated data. Like IPCW, this method is also underpowered if there is a high proportion of eligible patients that switch treatment. Therefore, this method is likely conservative and potentially underestimates the OS treatment effect of pirtobrutinib. Table 59 summarises HRs resulting from Cox models for the unadjusted, IPCW, and two-stage OS analyses for the ITT population. Given the small sample size of the dual-exposed population, these models were not considered robust enough to be included in the model and ITT values were carried forward for that population.

Table 59: Results of sensitivity analyses of OS (29th August 2024 data cut)

Method	Pirtobrutinib versus IdelaR or BR, HR	95% CI
Unadjusted	1.090	0.679-1.749
IPCW	0.872	0.507-1.500
Two-stage	0.776	0.479-1.258

Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; HR: hazard ratio; IdelaR: idelalisib with rituximab; IPCW: inverse probability of censoring weighting; OS: overall survival.
Source: Sharman et al. (2025).[104]

It is important to note that BRUIN CLL-321 was not powered to detect differences in OS, and OS projections in the Investigator's choice arm were further hampered by the majority of patients eligible for crossover receiving pirtobrutinib (75.86%, as discussed above) following disease progression, thus confounding OS trial results as an ORR of partial response or better of 60% was observed among crossover patients. Attempts were made to adjust for the crossover impact using the methods discussed earlier, but due to the small number of patients who did not cross over, these adjustments led to unlikely parametric OS predictions given the observed PFS benefit. This included pirtobrutinib OS hazards increasing faster than Investigator's choice values and the treatment arms crossing shortly after the Kaplan-Meier follow-up period ended.

Simon *et al.* (2025) examined the association between PFS and OS in CLL in a frontline CLL trial and found high correlation between improved PFS and OS with a joint-frailty copula model estimating a 0.91 correlation for targeted therapies (nonchemotherapy/CIT) among patients in German CLL Study Group trials and 0.75 PFS/OS correlation in a meta-analysis of nine trials including both chemotherapy/CIT and targeted therapies.[140] In R/R CLL, Maheshwari *et al.* (2024) conducted a systematic review of CLL trials up to March 2023 that reported both PFS and OS.[141] Overall, 25 studies were included in the analysis that examined the relationship between six-month PFS and OS at 12, 24, and 36 months. Results of the analyses for cBTKi are presented in Table 35 with eight, seven, and six cBTKi studies report PFS and OS data at 12, 24, and 36 months, respectively. Additional analyses of all targeted therapies (cBTKi, BCL2i, and PI3Ki) increased the number of studies analysed (13, 11, and 9 for the 12-, 24-, and 36-month timepoints) and with correlations increasing as the number of studies included increased.

Table 60: Correlation between PFS and OS in R/R CLL

Correlation between 6-month PFS and OS	Weighted ($1/SE_{OS}$) Spearman	Weighted (N) Spearman
cBTKi		
12-month OS	0.72 (0.26, 0.99)	0.87 (0.30, 0.99)
24-month OS	0.87 (0.43, 1.00)	0.86 (0.42, 1.00)
36-month OS	0.80 (0.14, 1.00)	0.88 (0.33, 1.00)

cBTKi, BCL2i, PI3Ki		
12-month OS	0.81 (0.58, 0.96)	0.91 (0.60, 0.96)
24-month OS	0.91 (0.63, 0.99)	0.92 (0.62, 0.99)
36-month OS	0.90 (0.53, 1.00)	0.93 (0.51, 1.00)

Abbreviations: B-cell lymphoma 2 inhibitor; cBTKi: covalent Bruton's tyrosine kinase inhibitor; OS: overall survival; PI3Ki: phosphoinositide 3-kinase inhibitor; PFS: progression-free survival; SE: standard error.
Source: Maheshwari *et al.* (2024)

High correlations between PFS and OS supported the modelling of a continued OS benefit over time rather than the converging and subsequent crossing of arms as observed in the BRUIN CLL-321 parametric analyses. Thus, in the base-case, Investigator's choice OS is modelled by applying the HR from the two-stage crossover Cox model to the unbiased pirtobrutinib OS curve in each analysis, allowing for continued treatment benefit.

OS adjusted by the two-stage crossover method was selected for the base case for both the post-cBTKi and dual-exposed populations as IPCW was considered prone to substantial bias when crossover rates are high, and sample sizes are small (please refer to Section 2.4.2.3, and above, for more details).

Post-cBTKi population

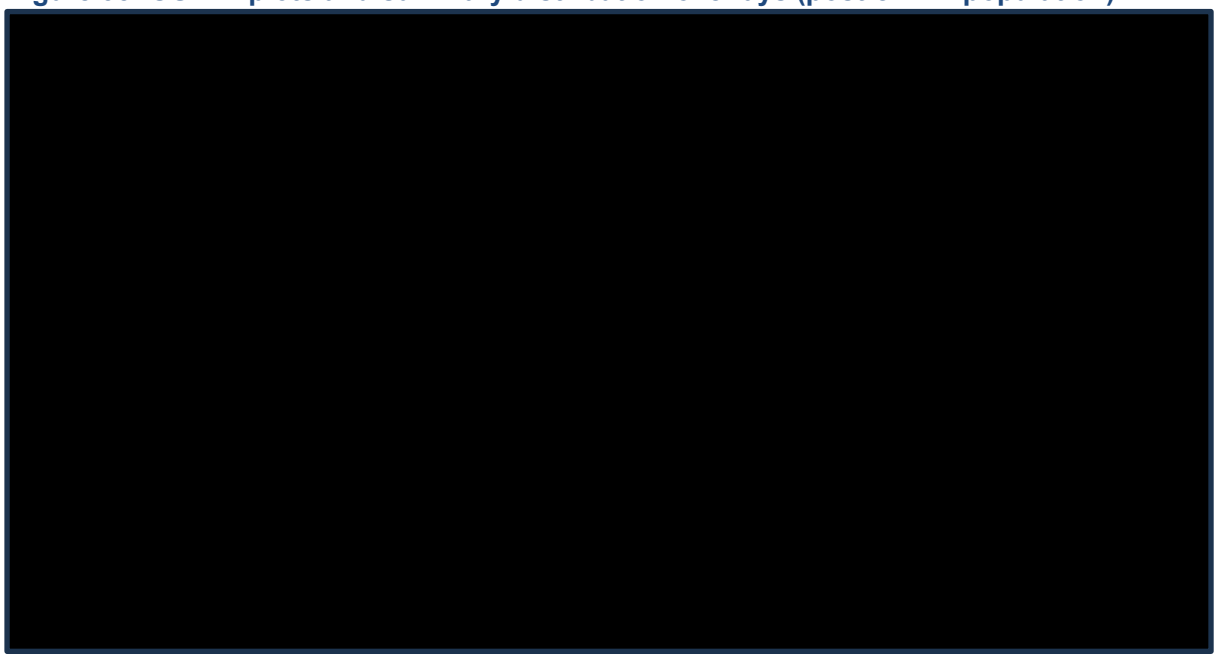
The goodness-of-fit statistics for each regression on OS – adjusted for crossover using two-stage AFT method – for the post-cBTKi population are summarised in Table 61. A summary of the survival extrapolations for the modelled OS distributions (two stage AFT-adjusted) for the post-cBTKi population distributions are presented in Figure 35.

Table 61: Pirtobrutinib versus Investigator's choice OS goodness-of-fit statistics for the post-cBTKi population

Distribution	AIC	BIC	AIC rank	BIC rank	Clinically plausible?[a]	Reason for exclusion[b]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	No	1,2
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	No	1,2
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 1	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Spline k = 2	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Spline k = 3	[redacted]	[redacted]	[redacted]	[redacted]	No	1,2

Footnotes: [a]Clinical plausibility assesses whether each distribution's survival curve aligns with expected disease progression in the target population. Distributions marked "Yes" show realistic trends, while those marked "No" display implausible behaviour. [b]Reasons for exclusion from best-fit consideration: 1 = survival curves cross; 2 = unrealistic long-term projections of survival in one or both arms.
Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 35: OS KM plots and summary distribution overlays (post-cBTKi population)



Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; Inv. Choice: investigator's choice; k: knots; KM: Kaplan-Meier; OS: overall survival.

As for PFS in the post-cBTKi population, seven of the nine modelled distributions were excluded from consideration. This was based on either the survival curves for pirtobrutinib intersecting with the comparator arm – and remaining lower than the comparator for the remainder of the model time horizon – or due to the presence of unrealistic long-term projections of survival in one or both arms, or a combination of both these criteria.

It was determined that the Gamma distribution is the best fit; Weibull is explored in a scenario analysis; this was supported by clinical expert opinion.[35] Gamma was the most clinically and scientifically plausible among the distributions with low AIC and BIC values (see Figure 36 and Figure 37) because the Weibull overestimated the comparator long-term OS and slightly underestimated pirtobrutinib OS. Gamma was deemed as more appropriate than Weibull for the model base case given that the use of the two-stage AFT model could be perceived as a conservative estimation of the OS effect.

A summary of landmark estimates for OS (two-stage AFT-adjusted) at 1, 3, 5, 10 and 15 years for the post-cBTKi population are presented in Table 62.

Figure 36: Pirtobrutinib versus Investigator's choice: OS Kaplan-Meier plot and detailed distribution overlay for the post-cBTKi population: Gamma

Abbreviations: HR: hazard ratio; Inv.: investigator; OS: overall survival.

Figure 37: Pirtobrutinib versus Investigator's choice: OS Kaplan-Meier plot and detailed distribution overlay for the post-cBTKi population: Weibull

Abbreviations: HR: hazard ratio; Inv.: investigator; OS: overall survival.

Table 62: OS landmark estimates for modelled distributions (post-cBTKi population, two-stage AFT adjusted)

	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull	Spline k = 1	Spline k = 2	Spline k = 3
Pirtobrutinib									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigators choice via HR									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFT: accelerated failure time; cBTKi: covalent Bruton's tyrosine kinase inhibitor; HR: hazard ratio; k: number of knots; OS: overall survival.

Dual-exposed population

The goodness-of-fit statistics for each regression on OS for the dual-exposed population are summarised in Table 63. A summary of the survival extrapolations for the modelled OS distributions (two stage AFT-adjusted) for the dual-exposed population distributions are presented in Figure 39.

Table 63: Pirtobrutinib versus Investigator's choice OS goodness-of-fit statistics for the dual-exposed population

Distribution	AIC	BIC	AIC rank	BIC rank	Clinically plausible?[a]	Reason for exclusion[b]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 1	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Spline k = 2	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Spline k = 3	[redacted]	[redacted]	[redacted]	[redacted]	No	2

Footnotes: [a]Clinical plausibility assesses whether each distribution's survival curve aligns with expected disease progression in the target population. Distributions marked "Yes" show realistic trends, while those marked "No" display implausible behaviour. [b]Reasons for exclusion from best-fit consideration: 1 = survival curves cross; 2 = unrealistic long-term projections of survival in one or both arms.
Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 38: OS KM plots and summary distribution overlays (dual-exposed population)

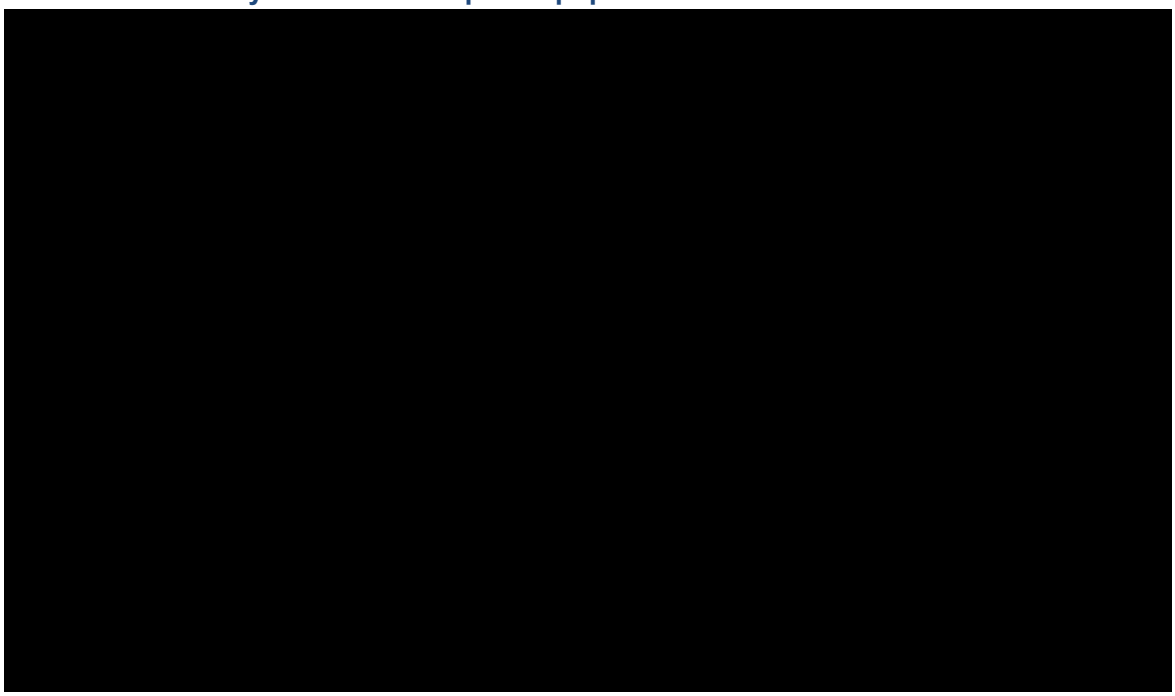
Abbreviations: Inv. Choice: investigator's choice; k: knots; KM: Kaplan-Meier; OS: overall survival.

Seven of the nine modelled distributions were excluded from consideration due to unrealistic long-term survival projections or the crossing of pirtobrutinib and comparator survival curves.

It was determined that the gamma distribution was the best fit; Weibull is explored in a scenario analysis. Gamma was the most clinically and scientifically plausible among the distributions with low AIC and BIC values (supported by clinical expert opinion[35] and statistical analyses, see Figure 39 and Figure 40) because the Weibull overestimated the comparator long-term OS.

A summary of landmark estimates for OS (two-stage AFT-adjusted) at 1, 3, 5, 10 and 15 years for the dual-exposed population are presented in Table 64.

Figure 39: Pirtobrutinib versus Investigator's choice: OS Kaplan-Meier plot and detailed distribution overlay for the dual-exposed population: Gamma



Abbreviations: HR: hazard ratio; Inv.: investigator; OS: overall survival.

Figure 40: Pirtobrutinib versus Investigator's choice: OS Kaplan-Meier plot and detailed distribution overlay for the dual-exposed population: Weibull

Abbreviations: HR: hazard ratio; Inv.: investigator; OS: overall survival.

Table 64: OS landmark estimates for modelled distributions (dual-exposed population, two-stage AFT adjusted)

	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull	Spline k = 1	Spline k = 2	Spline k = 3
Pirtobrutinib									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigators choice via HR									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFT: accelerated failure time; HR: hazard ratio; k: number of knots; OS: overall survival.

3.3.2.3 *Time-to-treatment discontinuation*

TTD was a post-hoc endpoint used in the model to estimate drug costs. TTD was defined as the time from the date of first exposure to treatment to the treatment discontinuation date. For patients who crossed over, the treatment discontinuation date is the earlier of the treatment discontinuation date before crossover or the time of first exposure in the crossover period. Patients with ongoing treatment were censored at the date of last exposure to treatment.

Time on treatment can be modelled from either TTD or PFS curves. In the base-case analysis, TTD curves are applied to align with data from the BRUIN CLL-321 trial and clinical practice where treatment beyond progression is common. Per protocol in the BRUIN CLL-321 clinical trial, trial participants could continue receiving pirtobrutinib following disease progression if the Investigator believed the treatment was still benefiting the participant. The model allowed for TTD to exceed PFS, consistent with the trial protocol, or to constrain TTD to be less than or equal to PFS.

In the base case, TTD was permitted to extend beyond PFS to reflect the trial design. When time on treatment is modelled using PFS curves, it is assumed to be equivalent to PFS except for treatments that have a maximum number of cycles (e.g., BR).

Post-cBTKi population

The goodness-of-fit statistics for each regression on TTD for the post-cBTKi population is presented in Table 65. A summary of the survival extrapolations for the modelled TTD distributions for the post-cBTKi population are presented in Figure 41.

Table 65: Pirtobrutinib versus Investigator's choice: TTD goodness-of-fit statistics for the post-cBTKi population

Distribution	AIC	BIC	AIC rank	BIC rank	Clinically plausible?[a]	Reason for exclusion[b]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 1	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 2	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 3	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--

Footnotes: [a]Clinical plausibility assesses whether each distribution's survival curve aligns with expected disease progression in the target population. Distributions marked "Yes" show realistic trends, while those marked "No" display implausible behaviour. [b]Reasons for exclusion from best-fit consideration: 1 = survival curves cross; 2 = unrealistic long-term projections of survival in one or both arms.
Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

Figure 41: TTD KM plots and summary distribution overlays (post-cBTKi population)

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; Inv. Choice: investigator's choice; k: knots; KM: Kaplan-Meier; TTD: time to treatment discontinuation.

Among the modelled distributions, only the Log-logistic and Log-normal distributions were excluded from consideration due to concerns with clinical plausibility (see footnotes of Table 65 for further details).

It was determined that the Gompertz distribution is the best fit; Weibull is explored in a scenario analysis. Gompertz has the lowest AIC and BIC values and was deemed the most plausible (see Figure 42 and Figure 43) where the Weibull appears to overestimate TTD for pirtobrutinib. On visual inspection the Gompertz distribution also demonstrated closer alignment with the trial KM data at the tail end of the curve. Gompertz is used as the base-case distribution with Weibull in the scenario analysis.

A summary of landmark estimates for TTD at 1, 3, 5, 10 and 15 years for the post-cBTKi population are presented in Table 66.

Figure 42: Pirtobrutinib versus Investigator's choice: TTD Kaplan-Meier plot and detailed distribution overlay for the post-cBTKi population: Gompertz

Abbreviations: Inv.: Investigator; TTD: time to treatment discontinuation.

Figure 43: Pirtobrutinib versus Investigator's choice: TTD Kaplan-Meier plot and detailed distribution overlay for the post-cBTKi population: Weibull

Abbreviations: Inv.: Investigator; TTD: time to treatment discontinuation.

Table 66: TTD landmark estimates for modelled distributions (post-cBTKi population)

	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull	Spline k = 1	Spline k = 2	Spline k = 3
Pirtobrutinib									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigators choice									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; k: number of knots; TTD: time to treatment discontinuation.

Dual-exposed population

The goodness-of-fit statistics for each regression on TTD for the dual-exposed population is presented in Table 67. A summary of the survival extrapolations for the modelled TTD distributions for the dual-exposed population are presented in Figure 44.

Table 67: Pirtobrutinib versus Investigator's choice: time-to-treatment discontinuation goodness-of-fit statistics for the dual-exposed population

Distribution	AIC	BIC	AIC rank	BIC rank	Clinically plausible?[a]	Reason for exclusion[b]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	No	2
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 1	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 2	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--
Spline k = 3	[redacted]	[redacted]	[redacted]	[redacted]	Yes	--

Footnotes: [a]Clinical plausibility assesses whether each distribution's survival curve aligns with expected disease progression in the target population. Distributions marked "Yes" show realistic trends, while those marked "No" display implausible behaviour. [b]Reasons for exclusion from best-fit consideration: 1 = survival curves cross; 2 = unrealistic long-term projections of survival in one or both arms.
Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

Figure 44: TTD KM plots and summary distribution overlays (dual-exposed population)

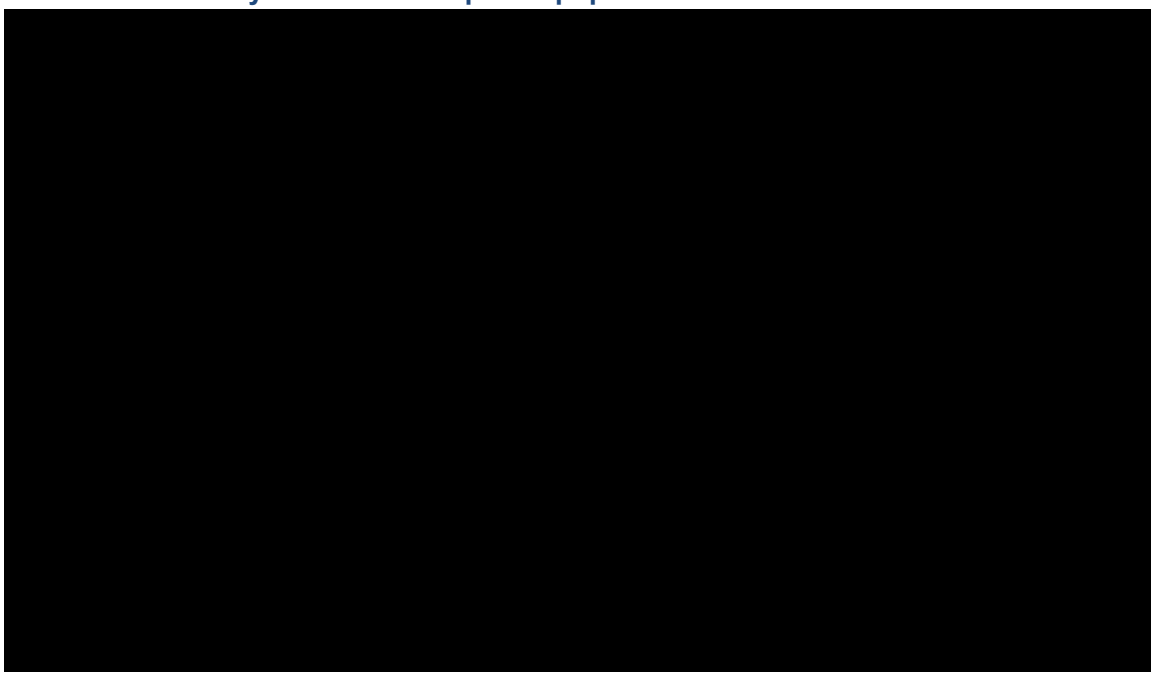
Abbreviations: Inv. Choice: investigator's choice; k: knots; KM: Kaplan-Meier; TTD: time to treatment discontinuation.

Among the modelled distributions, only the Log-logistic and Log-normal distributions were excluded from consideration due to concerns with clinical plausibility (see footnotes of Table 67 for further details).

It was determined that the Gompertz distribution is the best fit; Weibull is used in the scenario analysis. Gompertz has the lowest AIC and BIC values and is clinically plausible (see Figure 45 and Figure 46) where the Weibull appears to overestimate TTD for pirtobrutinib. Gompertz is used as the base-case distribution with Weibull in the scenario analysis.

A summary of landmark estimates for TTD at 1, 3, 5, 10 and 15 years for the dual-exposed population are presented in Table 68.

Figure 45: Pirtobrutinib versus Investigator's choice: TTD Kaplan-Meier plot and detailed distribution overlay for the dual-exposed population: Gamma



Abbreviations: Inv.: Investigator; TTD: time to treatment discontinuation.

Figure 46: Pirtobrutinib versus Investigator's choice: TTD Kaplan-Meier plot and detailed distribution overlay for the dual-exposed population: Weibull

Abbreviations: Inv.: Investigator; TTD: time to treatment discontinuation.

Table 68: TTD landmark estimates for modelled distributions (dual-exposed population)

	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull	Spline k = 1	Spline k = 2	Spline k = 3
Pirtobrutinib									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigators choice									
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: k: number of knots; TTD: time to treatment discontinuation.

3.3.2.4 Summary of survival approaches

An overview of the approaches adopted to model OS, PFS and TTD for each treatment arm in the base case cost-effectiveness analyses are presented in Table 69 and Table 70 for the post-cBTKi and dual-exposed populations, respectively.

Table 69: Summary of selected base case survival approaches – post-cBTKi population

Endpoint	Pirtobrutinib	IdelaR
PFS	Gamma	
OS	Gamma	
TTD	Gompertz	

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; IdelaR: idelalisib with rituximab; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 70: Summary of selected base case survival approaches – dual-exposed population

Endpoint	Pirtobrutinib	IdelaR
PFS	Gamma	
OS	Gamma	
TTD	Gompertz	

Abbreviations: IdelaR: idelalisib with rituximab; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

3.3.3 Adverse events

Adverse event costs were assumed to occur once throughout the model because AEs are commonly experienced early in the treatment course.[91] Adverse event incidence (presented in Section 2.11) was sourced from the August 2024 DCO of the BRUIN CLL-321 trial.[103] Grade 3 or 4 AEs were included if their reported incidence was 2% or higher in the trial, please refer to Section 2.11 for further details.

For each included grade 3 or 4 AE, the incidence rate was multiplied by the corresponding treatment cost to estimate the total cost impact of the AE. The costs associated with the management of AEs are presented in Section 3.5.3. The disutilities associated with AEs are presented in Section 3.4.4.

Table 71: Grade 3 or 4 Adverse event incidence

Adverse event	Pirtobrutinib incidence	Investigator choice of IdelaR or BR incidence	IdelaR only incidence
Alanine aminotransferase increased	0.9%	[redacted]	[redacted]
Anaemia	11.2%	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]
COVID-19	0.0%	[redacted]	[redacted]
Diarrhoea	0.0%	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]

Hypertension	2.6%	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]
Lymphocyte count increased	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Neutropenia	14.7%	[redacted]	[redacted]
Neutrophil count decreased	5.2%	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
Pneumonia	15.5%	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
WBC decreased	[redacted]	[redacted]	[redacted]

Abbreviations: BR: bendamustine with rituximab; COVID-19: coronavirus disease 2019; IdelaR: idelalisib with rituximab; WBC: white blood cell count.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

HRQoL data were collected in BRUIN CLL-321 as described in Section 2.3.1 and 2.4.2.1. EQ-5D-5L data collected in the trial were mapped to EQ-5D-3L indices as noted in Section 3.4.2 below.

3.4.2 Mapping

In line with the NICE reference case, the EQ-5D-5L indices were mapped to EQ-3D-3L indices using the Hernandez-Alava (2022) crosswalk algorithm.[142, 143] Once mapped, the EQ-5D-3L utility scores at all visits were analysed using a mixed-effects linear regression with a random intercept for each patient to account for repeated measures (see Section 2.4.2.1 for further details).

3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify studies reporting on the HRQoL of patients with R/R CLL. Full details of the SLR search strategy and study selection can be found in Appendix F. A summary of the studies extracted (n=6) is provided in Appendix F.2.1, and utility values used in the model are described in Section 3.4.5.

3.4.4 Adverse reactions

Adverse event disutilities are incorporated in the base-case analysis. Patients incur a one-time disutility for the occurrence of each grade 3/4 AE listed in Table 72. These disutilities are multiplied by the duration of each AE (see Table 88) to calculate the total disutility incurred by each event. Quality-adjusted life-years lost due to disutility are assumed to occur in the first model cycle. No impact on mortality was considered for AEs because it was assumed to be accounted for in OS.

Table 72: Adverse event disutilities

Pirtobrutinib and Investigator choice AE disutilities	Mean	SE	Source
Alanine aminotransferase increased	−0.050	0.010	NICE TA561[69] based on NICE TA347.
Anaemia	−0.090	0.018	NICE TA561[69] based on NICE TA359, assumed the same as thrombocytopenia.
Cardiac failure	−0.020	0.004	Assumed equal to hypertension.
COVID-19	−0.220	0.044	Assumed equal to infections and infestations from NICE TA689.
Diarrhoea	−0.200	0.040	NICE TA689[27] based on NICE TA359.
Febrile neutropenia	−0.200	0.040	NICE TA689[27] based on NICE TA359.
Hyperkalaemia	−0.020	0.004	Assumed equal to hypertension.
Hypertension	−0.020	0.004	NICE TA931[37] based on Wehler et al. (2018).
Infusion-related reaction	−0.200	0.040	NICE TA561[69] based on NICE TA344.
Lymphocyte count increased	−0.108	0.022	Assumed equal to thrombocytopenia.
Lymphopenia	−0.108	0.022	Assumed equal to thrombocytopenia.
Neutropenia	−0.163	0.033	NICE TA561[69] based on Tolley et al. (2013).
Neutrophil count decreased	−0.163	0.033	Assumed equal to neutropenia.
Platelet count decreased	−0.108	0.022	Assumed equal to thrombocytopenia.
Pneumonia	−0.195	0.039	NICE TA561[69] based on Tolley et al. (2013).
Thrombocytopenia	−0.108	0.022	NICE TA561[69] based on NICE TA359.
WBC decreased	−0.108	0.022	Assumed equal to thrombocytopenia.
Total pirtobrutinib disutility	**−0.0045**	-	-
Total IdelaR disutility	**−0.0048**	-	-

Abbreviations: COVID-19: coronavirus disease 2019; NICE: National Institute for Health and Care Excellence; SE: standard error; WBC: white blood cell count.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Progression-free utility weight was estimated from the BRUIN CLL-321 trial. A linear mixed model of utility weights was calculated from EQ-5D-5L responses prior to disease progression from the trial.

Limited post-progression utility data were available from BRUIN CLL-321, and therefore any utilities generated from the data were assumed to lack face validity. As such, the post-progression utility value of 0.60 published by Holzner *et al.* (2004) is used in the model base case.[124] This post-progression utility source has been used in multiple other HTA submissions to NICE (TA931[37]; TA487;[144] TA561;[69] TA429;[67] TA359[66]).

Progression-free and PD utilities are presented in Table 73. A single progression-free utility value was applied across both the mono and dual failure health states for consistency given that the same utility value is applied post progression.

Table 73: Utility weights used in the model

	Mean	SE
Progression free		
BRUIN CLL-321[103]	0.814[a]	0.018
Progressive disease		
NICE TA931[37]	0.600	0.060

Footnotes: [a]Intercept of the linear mixed model 4a (ITT population) where utility weights are the response variable and the covariates are the centred EQ-5D-5L utility weight baseline scores (mean population baseline utility − subject baseline utility) and centred age (mean population age − subject age) and the time period of observed utility weight is PF.
Abbreviations: EQ-5D-5L: EuroQol five dimensions questionnaire, 5-level version; ITT: intention-to-treat; NICE: National Institute for Health and Care Excellence; PF: progression-free; SE: standard error.

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify any relevant cost and healthcare resource use data associated with the treatment of adults with R/R CLL. Details of the SLR search strategy and study selection can be found in Appendix G.

The cost categories in the model are derived from several key sources. Among others, drug acquisition and administration costs are based on pricing from the electronic market information tool (eMIT) and the Monthly Index of Medical Specialties (MIMS) (see Section 3.5.1 for further details).[119, 120] Dosing schedules and costs consider drug wastage, population averages, and assumptions from literature and SmPCs. Healthcare resource utilisation costs are informed by HCRU studies and expert opinion, covering both drug and non-drug administration for patients with and without disease progression. Adverse event management costs focus on Grade 3 and 4 events, sourced from literature, SmPCs, and trial data. The end-of-life care costs use estimates from Round *et al.* (2015), adjusted for inflation. Utility weights for progression-free and post-progression states are taken from specific trials and publications, with options for AE disutilities.

Cost categories included in the model

The cost perspective adopted was that of the NHS and PSS. As such, the base-case economic analysis included only costs that would be incurred by the NHS and PSS. Appropriate sources of unit costs, such as NHS Reference Costs, the electronic market information tool (eMIT) and the Monthly Index of Medical Specialties (MIMS), were used for cost inputs in the model.[119, 120]

Specifically, the following cost components were considered in the model:

- Dug acquisition costs for interventions and comparators
- Associated drug administration costs
- Drug posology
- Healthcare resource use costs
- Costs associated AEs, and AE management
- Cost of end-of-life palliative care

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs (presented in Table 74) were sourced from the electronic market information tool (eMIT) and the Monthly Index of Medical Specialties (MIMS), with eMIT being the preferred source and MIMS used when eMIT cost data were not available for selected drugs.[119, 120] For pirtobrutinib, the list price in the UK is included in the model, and presented in Table 74 below. A PAS price is to be included within the model once finalised, and is anticipated to be submitted to NICE following finalisation. The posology (i.e., recommended dose amounts and dosing schedules) for each drug were identified from the published literature and/or the SmPC.[4, 57, 58, 61] The drug dosing schedules and distributions of use are described in Table 75.

Drug acquisition costs are calculated at the individual drug level using drug dosage assumptions from the respective SmPCs. Costs per cycle were calculated based on the following methods and assumptions for IV drugs:

- Based on available vial sizes, the number of vials needed to dose up to the maximum BSA (assumed to be 5 m^2) is calculated for each vial size
- The possible permutations of all vial sizes and number of vials up to the maximum number are constructed
- The doses that can be administered within each vial size permutation are calculated
- The cost of each vial size permutation for each dose is calculated, and the minimum cost is selected if multiple permutations have the same resulting dose
- If a vial size permutation for a higher BSA results in lower costs than the minimum cost selected for that group, then the lower cost is used
- Using the population means and standard deviations, the percentages of patients that would receive each dose are calculated assuming BSA follows normal distributions
- The cost per BSA grouping is multiplied by the percentage of patients in each vial permutation and costs summed to create a population weighted average cost that includes drug wastage

The model base case includes drug costs per cycle accounting for vial wastage.

Table 74: Drug acquisition costs

Drug	Form	Dose per unit	Pack size	List price	Sources/assumptions
Pirtobrutinib	Oral	50 mg	28 tablets	[redacted]	Lilly
	Oral	100 mg	56 tablets	[redacted]	Lilly
Idelalisib	Oral	100 mg	60 tablets	£3,114.75	MIMS 2025[120]
	Oral	150 mg	60 tablets	£3,114.75	MIMS 2025[120]
Rituximab	IV	100 mg/10 mL	2 vials	£314.33	MIMS 2025[120]
	SC	500 mg/50 mL	1 vial	£785.84	MIMS 2025[120]

Abbreviations: IV: intravenous; MIMS: Monthly Index of Medical Specialities; SC: subcutaneous.

Table 75: Modelled treatments and posology

Drug	Dosing schedule	Distribution of Use	Sources
Pirtobrutinib	200 mg orally once daily	N/A	Pirtobrutinib SmPC[4]
IdelaR	Idelalisib 150 mg orally twice daily Rituximab 375 mg/m^2 intravenously on day 1 of cycle 1, 500 mg/m^2 on day 15 of cycle 1, day 1 and 15 of cycle 2, and day 1 of every 28-day cycle from cycles 3-6, for a maximum of 6 cycles	100%	Idelalisib SmPC[57]

Abbreviations: CLL: Chronic Lymphocytic Leukaemia; IV: intravenous; IdelaR: idelalisib plus rituximab; MIMS: Monthly Index of Medical Specialties; N/A: not applicable; SC: subcutaneous; SmPC: Summary of Product Characteristics.

Drug administration costs

Drug administration resource use was identified according to dosing routes and schedules specified in the published literature and/or the SmPC for each product (Table 74 and Table 75). These inputs were validated by checking other NICE submissions for consistency (TA931[37]; TA487[144]; TA561[69]; TA429[67]; TA359[66]).

Administration costs were not considered for pirtobrutinib or idelalisib as they are self-administered orally by patients. Unit costs for IV administration are only applicable for rituximab, as a part of IdelaR, and were based on the 2023/24 NHS reference cost codes SB12Z, SB14Z, and SB15Z codes.[145] These approaches aligned with assumptions made in previous NICE TAs for BTKi in the R/R CLL indication and were accepted by the respective committees.[27, 37]

Table 76: Drug administration costs

Resource	Unit cost	Use per cycle			Source
		Pirtobrutinib	IdelaR		
			Cycles 1-2	Cycles 3-6	
Deliver simple parenteral chemotherapy at first attendance	£203.98	0	1	1	2023/24 NHS Schedule of Reference Costs[145]
Deliver subsequent elements of a chemotherapy cycle	£295.13	0	1	0	
Deliver complex chemo, including prolonged treatment at 1st attendance	£501.32	0	0	0	
Per cycle administration cost, mean (SE)		£0 (0)	£499.10 (99.82)	£203.98 (40.80)	

Abbreviations: IdelaR: idelalisib plus rituximab; NHS: National Health Service; SE: standard error.

Patients accrued drug acquisition and drug administration costs for the duration of time on treatment, which was based on either PFS or TTD. A maximum treatment duration of six drug cycles were assumed in the model for rituximab. Furthermore, treatment costs were calculated for IdelaR based on the indicated cycle length in the SmPC. Doses per cycle were calculated for each model cycle (28 days in length) to attain the treatment costs per model cycle.

Post-progression costs

Given the number of participants in the pirtobrutinib arm who have progressed during data follow-up and the high amount of crossover in the comparator arm of the BRUIN CLL-321 trial, post-

progression drug acquisition and administration costs that would be generalisable in real-world clinical practice were difficult to project.

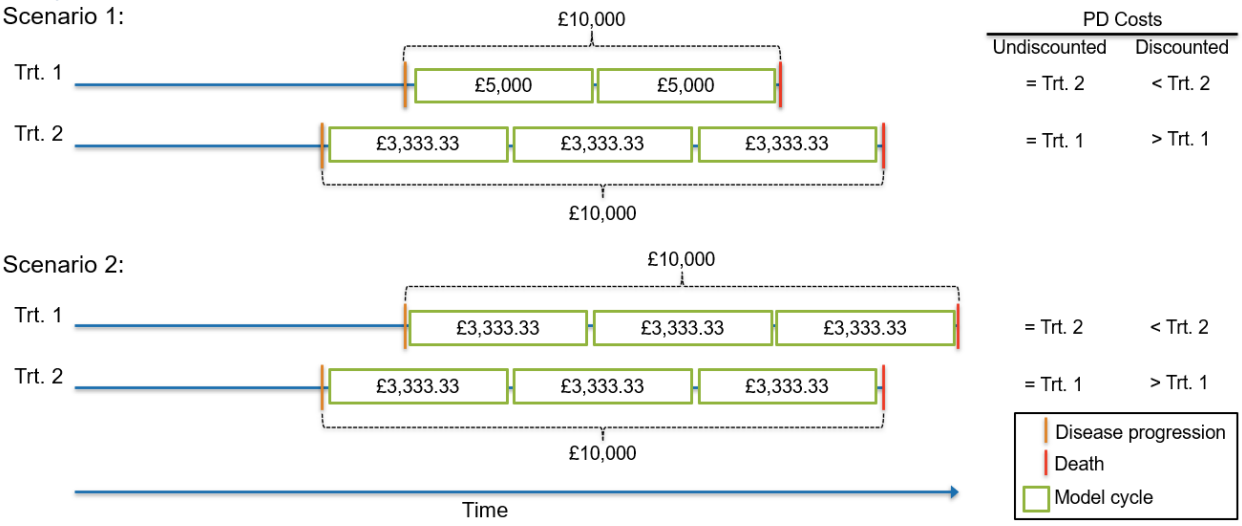
In the base case, post-progression costs were assumed to be "different in both regards," meaning that costs for patients on pirtobrutinib and IdelaR were assumed to differ following progression. That is, costs incurred by patients treated with pirtobrutinib and those receiving IdelaR are not assumed to be equivalent, either in total cost or in cost per cycle following progression (i.e., both cost per cycle and length of time in the PD health state impact costs). This reflects differences in the treatment mix for each comparator following disease progression.

Two different subsequent therapy costing approaches were included as scenario analyses:

- **"Equivalent in total":** The total post-progression costs were assumed to be equal across modelled regimens. In this scenario, treatments associated with longer PFS delayed the onset of post-progression cost accrual, resulting in lower total discounted post progression costs for those treatments.
- **"Equivalent per cycle":** Post-progression costs were assumed to be the same on a per cycle basis across modelled regimens. Consequently, treatments with a longer duration in the progressed health state were associated with higher overall post progression costs

Figure 47 and Figure 48 graphically depict the "equivalent in total" and "equivalent per cycle" scenarios, respectively. In Figure 47, post-progression costs for two hypothetical treatments are presented in two hypothetical survival scenarios. Because the setting is for post-progression costs to be equivalent in total, both treatments and both scenarios have total post-progression costs of £10,000. In the first scenario, treatment 1 has two cycles post progression and treatment 2 has three cycles post progression, where the total costs are partitioned equally per model cycle. Treatment 1 also has delayed progression compared with treatment 2. In this situation, undiscounted costs are equivalent between treatments, but because treatment 1 has delayed accrual of these costs, discounted costs are less for treatment 1 compared with treatment 2. Scenario 2 reflects a paradigm where the number of post-progression cycles is also equal between treatments. Total undiscounted post-progression costs are equal, and treatment 1 has less discounted post-progression costs because of delayed progression.

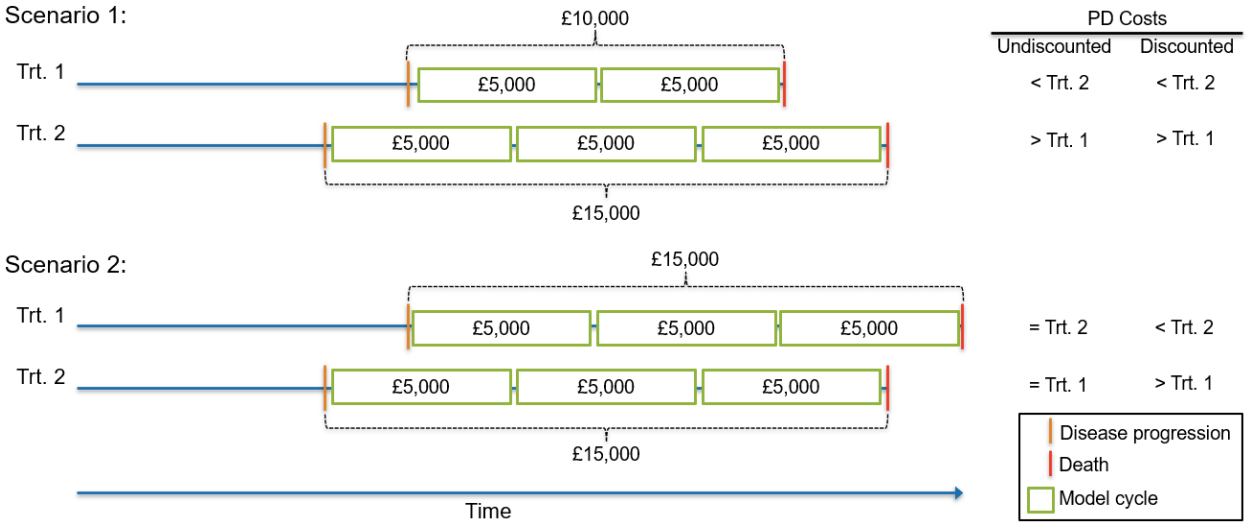
Figure 47: Example of post-progression costs of the "equivalent in total" scenario analysis



PD = progressive disease; Trt. = treatment.

Figure 48 presents the same two survival scenarios under the scenario analysis of post-progression costs being "equivalent per cycle", in this case a hypothetical £5,000. In scenario 1, treatment 1 has fewer model cycle post progression and delays the onset of progression. Thus, its total undiscounted and discounted post-progression costs are less than treatment 2. In scenario 2, both treatments have the same number of cycles and, thus, the same total undiscounted post-progression costs, but treatment 1 delays progression and discounted post-progression costs are lower.

Figure 48: Example of post-progression cost setting of the "equivalent per cycle" scenario analysis



PD = progressive disease; Trt. = treatment.

The drug acquisition costs for active treatment following disease progression are shown in Table 77. The costs for idelalisib and rituximab are presented in Table 74. Allogeneic stem cell transplant (AlloSCT) and chimeric antigen receptor T-cell (CAR-T) cost derivations are provided in Table 78 to Table 81. Subsequent anticancer therapy is based on data from the BRUIN CLL-321 trial (presented in Section 2.7).[91] Anticancer therapy distribution and treatment duration are shown in Table 82. Some simplifying assumptions regarding representative drugs for a class of drugs have been made; FCR is assumed for chemotherapy class, rituximab is assumed for anti-CD20 class, idelalisib is assumed for PI3K class, and lenalidomide is assumed for immunomodulatory drug (IMID) class.

Active treatment costs only impacted model results if less than 100% of patients receive BSC. These inputs impacted modelled costs but did not influence projected survival or QALYs. It is important to note that Lilly understand there to be PAS discounts in place for a number of active subsequent treatments considered in Table 77 below (e.g., zanubrutinib, acalabrutinib or venetoclax). As these discounts are confidential and unknown to Lilly, only the list prices for these therapies, as published within the eMIT or MIMS are considered in the economic analysis.

Table 77: Active treatment following progressive disease drug acquisition costs

Drug	Supplied strength (route)	Units per package	Price per package (£)	Sources/assumptions
Acalabrutinib	100 mg (oral)	60	5,059.00	MIMS 2025[120]
Cyclophosphamide	500 mg (IV)	1	11.18	eMIT 2024[119]
	1,000 mg (IV)	1	13.11	eMIT 2024[119]
	2,000 mg (IV)	1	27.50	eMIT 2024[119]
	2,000 mg (IV)	1	27.50	eMIT 2024[119]
Fludarabine	50 mg/2 mL (SC)	1	105.93	eMIT 2024[119]
Lenalidomide	25 mg (oral)	21	28.27	eMIT 2024[119]
Venetoclax	10 mg (oral)	14	59.87	MIMS 2025[120]
	50 mg (oral)	7	149.67	MIMS 2025[120]
	100 mg (oral)	7	299.34	MIMS 2025[120]
	100 mg (oral)	112	4,789.47	MIMS 2025[120]
	100 mg (oral)	112	4,789.47	MIMS 2025[120]
Zanubrutinib	80 mg (oral)	120	4,928.65	MIMS 2025[120]

Abbreviations: eMIT: electronic market information tool; IV: intravenous; MIMS: Monthly Index of Medical Specialties; SC: subcutaneous.

Table 78: Weighted cost for stem cell harvesting

Code	Description	Currency Code	Currency Description	No. of finished consultant episodes	Cost (£)	National average unit cost	No. of submissions	Sector	Weighted Cost (£)
DC	Day case	SA18Z	Bone Marrow Harvest	13	35,800	2,754	7	Acute	267.75
NEL	Non-Elective Inpatient - Long Stay	SA18Z	Bone Marrow Harvest	*	18,529	*	3	Acute	
NES	Non-Elective Inpatient - Short Stay	SA18Z	Bone Marrow Harvest	*	13	*	1	Acute	

RP	Regular Day or Night Admissions	SA18Z	Bone Marrow Harvest	*	9,269	*	2	Acute	
DC	Day case	SA34Z	Peripheral Blood Stem Cell Harvest	2,666	3,265,097	1,225	31	Acute	527.43
NEL	Non-Elective Inpatient - Long Stay	SA34Z	Peripheral Blood Stem Cell Harvest	52	859,881	16,536	22	Acute	5,052.67
NES	Non-Elective Inpatient - Short Stay	SA34Z	Peripheral Blood Stem Cell Harvest	53	49,642	937	9	Acute	117.13
RP	Regular Day or Night Admissions	SA34Z	Peripheral Blood Stem Cell Harvest	57	36,963	648	3	Acute	27.00
								Weighted average	**5,991.97**

Source: NHS Schedule of Reference Costs 2023/24.[118]

Table 79: Weighted cost for AlloSCT procedure

Code	Description	Currency Code	Currency Description	No. of finished consultant episodes	Cost (£)	National average unit cost	No. of submissions	Sector	Weighted Cost (£)
DC	Day case	SA20A	Bone Marrow Transplant, Allogeneic Graft (Sibling), 19 years and over	*	£4,746	*	1	Acute	
NEL	Non-Elective Inpatient - Long Stay	SA20A	Bone Marrow Transplant, Allogeneic Graft (Sibling), 19 years and over	*	£59,159	*	3	Acute	

NES	Non-Elective Inpatient - Short Stay	SA21A	Bone Marrow Transplant, Allogeneic Graft (Volunteer Unrelated Donor), 19 years and over	*	£896	*	1	Acute	
DC	Day case	SA27A	Peripheral Blood Stem Cell Transplant, Syngeneic, 19 years and over	*	£9,271	*	1	Acute	
DC	Day case	SA38A	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 19 years and over	*	£32,561	*	5	Acute	
NEL	Non-Elective Inpatient - Long Stay	SA38A	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 19 years and over	13	£797,259	61,328	5	Acute	61,328.00
								Weighted average	**61,328.00**

Abbreviations: AlloSCT: allogeneic stem cell transplant.
Source: NHS Schedule of Reference Costs 2023/24.[118]

Table 80: AlloSCT follow-up costs

Cost	Cost (£)	Cost Year	Source
Reported cost	43,745.53	2021/2022	NICE TA975 based on data originally from the UK Stem Cell Strategy Oversight Committee.[146]
Inflated cost	46,820.84	2022/2023	Jones *et al.* (2024)[123]

Abbreviations: AlloSCT: allogeneic stem cell transplant; UK: United Kingdom.

Table 81: CAR-T administration cost

Component	Cost (£)
Administration	
NHS CAR-T tariff	41,101.00
Bridging chemotherapy	1,394.57
Lymphodepleting chemotherapy	404.52
Hospitalisation	33,788.47
ICU	5,402.29
Total	***82,090.85***
Acquisition	
Bridging chemotherapy	36.50
Lymphodepleting chemotherapy	92.37
CAR-T	282,000.00
PAS discount (50%)	-141,000.00
Total	***141,128.87***

CAR-T costs are based on NICE TA975.[146] The CAR-T in this TA has a patient access scheme with an unknown discount for the drug acquisition costs. A 50% discount is assumed.
Abbreviations: CAR-T: chimeric antigen receptor T-cell; ICU: intensive care unit; NHS: National Health Service; PAS: patient access scheme; TA: technology assessment.

Table 82: Anticancer therapy distribution and treatment duration

Treatment	Post-cBTKi population			Dual-exposed population		
	Post-progression use		Mean 28-day cycles	Post-progression use		Mean 28-day cycles
	Pirtobrutinib	Inv. choice		Pirtobrutinib	Inv. choice	
Covalent BTK inhibitor						
Acalabrutinib	0.0%	13.3%	25.36	0.0%	16.7%	21.05
Zanubrutinib	4.0%	0.0%	22.44	8.3%	0.0%	18.63
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
Noncovalent BTK inhibitor						
Pirtobrutinib	0.0%	33.3%	17.29	0.0%	41.7%	14.35
Other	0.0%	6.7%	17.29	0.0%	8.3%	14.35
BCL2i						
Venetoclax						
Week 1	48.0%	6.7%	1	0.0%	0.0%	1
Week 2	48.0%	6.7%	1	0.0%	0.0%	1
Week 3	48.0%	6.7%	1	0.0%	0.0%	1
Week 4	48.0%	6.7%	1	0.0%	0.0%	1

Weeks 5+	48.0%	6.7%	14.75	0.0%	0.0%	12.07
Other	4.0%	6.7%	15.75	0.0%	0.0%	13.07
Chemotherapy						
FCR						
Fludarabine	20.0%	33.3%	3.33	33.3%	33.3%	2.76
Cyclophosphamide	20.0%	33.3%	3.33	33.3%	33.3%	2.76
Rituximab	20.0%	33.3%		33.3%	33.3%	-
Cycle 1	20.0%	33.3%	1	33.3%	33.3%	1
Cycles 2-6	20.0%	33.3%	2.33	33.3%	33.3%	-
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
Anti-CD20 antibody						
Rituximab						
Cycle 1	60.0%	26.7%	1	58.3%	16.7%	1
Cycles 2-6	60.0%	26.7%	3.98	58.3%	16.7%	3.13
Obinutuzumab						
Cycle 1	0.0%	0.0%	1	0.0%	0.0%	1
Cycles 2+	0.0%	0.0%	10.58	0.0%	0.0%	8.61
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
PI3K agent						
Idelalisib	28.0%	0.0%	8.71	50.0%	0.0%	7.23
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
IMID/immunomodulator						
Lenalidomide	0.0%	6.7%	3.33	0.0%	8.3%	2.76
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
CAR-T	4.3%	3.8%	1	8.3%	4.8%	
Stem cell transplant						
AlloSCT	0.0%	0.0%	1	0.0%	0.0%	1
Other	0.0%	3.8%	1	0.0%	4.8%	1
Other systemic therapy						
Other systemic therapy	0.0%	7.7%	3.33	0.0%	9.5%	2.76
Other molecular pathways/small molecule inhibitors						
Other molecular pathways/small molecule inhibitors	8.5%	3.8%	25.36	16.7%	4.8%	21.05

Abbreviations: AlloSCT: allogeneic stem cell transplant; BCL2i: B-cell lymphoma 2 inhibitor; BTK: Bruton tyrosine kinase; CAR-T: chimeric antigen receptor T-cell therapy; FCR: fludarabine, cyclophosphamide, and rituximab; IMID: immunomodulatory drug; Inv. choice: investigator's choice; PI3K: phosphoinositide 3-kinase.
Source: Eli Lilly (Data on File). BRUIN CLL-321 CSR.[91]

3.5.2 Health-state unit costs and resource use

Other medical costs and utilisation inputs are shown in Table 83, Table 84, and Table 85. Healthcare resource utilisation costs (presented in Table 85) are calculated for progression-free

patients and patients with progressed disease based on two expected patterns of use: 1) For patients that are currently on an anticancer therapy, or have completed their course of anticancer therapy and have not yet progressed (i.e., those in the progression-free health state or those in the PD health state that are receiving subsequent anticancer therapy); and 2) For patients that have progressed and are receiving BSC. NICE TA561 (2019) provides healthcare resource utilisation estimates for progression-free and post-progression health states.[69] In that analysis, no subsequent anticancer therapy is considered after disease progression. Thus, it was assumed that resource use for patients on treatment in any model health state was the same for the progression-free health state, and PD health state costs are calculated as a weighted average of time for patients on subsequent treatment and those on no treatment (BSC) in the model (Table 84).

Table 83: Healthcare resource costs

Resource	Mean	Source	Code/description
Full blood count	£3.10	NHS 2023/2024[118]	Haematology; PATH05; directly accessed pathology services.
Lactate dehydrogenase	£1.53	NHS 2023/2024[118]	Clinical biochemistry; PATH04; directly accessed pathology services.
X-ray	£101.10	NHS 2023/2024[118]	Directly accessed plain film; PF – Plain Film; community diagnostic centres.
Bone marrow exam	£452.43	NHS 2023/2024[118]	Diagnostic bone marrow extraction; SA33Z (Service code 303); outpatient procedures; clinical haematology.
Haematologist visit	£192.53	NHS 2023/2024[118]	Non-admitted face-to-face attendance, follow-up; WF01A (Service code 303); outpatient care; clinical haematology.
Inpatient visit (medical)	£561.69	NHS 2023/2024[118]	Weighted average cost of CLL, SA32A-D; admitted patient care; day case, plus cost of medical consultant hour, including qualifications (£143).
Blood transfusion	£386.96	NHS 2023/2024[118]	Single plasma exchange or other intravenous blood transfusion, 19 years and over; SA44A (Service code 303); outpatient procedures, clinical haematology.

Abbreviations: CLL: chronic lymphocytic leukaemia; NHS: National Health Service.

Table 84: Healthcare resource utilisation

Resource	Annual resource utilisation	
	PF or PD on treatment	PD off treatment
Full blood count	4	8
Lactate dehydrogenase	2	0
X-ray	0	2
Bone marrow exam	0	1
Haematologist visit	2	6
Inpatient visit (medical)	0	4
Blood transfusion	0	11

Abbreviations: PD: progressive disease; PF: progression free.

Table 85: Annual health state cost for healthcare resource utilisation

Health state cost	Annual cost	
	Mean	SE
On treatment	£400.49	80.10
Off treatment	£8,337.84	1,667.57

Abbreviations: SE: standard error.

3.5.3 *Adverse reaction unit costs and resource use*

The costs to treat treatment-related AEs (Table 86) were sourced from the NHS Schedule of Reference Costs 2023/24;[118] these costs were multiplied by incidence values (Table 71) to get the total cost of AEs per treatment (Table 87). Adverse event duration (Table 88) were aligned with data informing past NICE appraisals in R/R CLL (TA561, TA689, and TA931).[27, 37, 69]

Table 86: Adverse event cost

Adverse event	Cost to treat grade 3/4 adverse events	
	Cost	Code(s)
Alanine aminotransferase increased	£767.65	GC01F
Anaemia	£766.57	SA01G, SA01H, SA01J, SA01K
Cardiac failure	£718.05	EB03A, EB03B, EB03C, EB03D, EB03E
COVID-19	£701.51	DX01A, DX11A, DX21A
Diarrhoea	£564.22	FD10J, FD10K, FD10L, FD10M
Febrile neutropenia	£567.22	WJ07A, WJ07B, WJ07C, WJ07D
Hyperkalaemia	£584.31	KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N
Hypertension	£404.67	EB04Z
Infusion-related reaction	£549.10	WH07A, WH07B, WH07C, WH07D, WH07E, WH07F, WH07G
Lymphocyte count increased	£752.52	SA12G, SA12H, SA12J, SA12K
Lymphopenia	£752.52	SA12G, SA12H, SA12J, SA12K
Neutropenia	£752.52	SA12G, SA12H, SA12J, SA12K
Neutrophil count decreased	£752.52	SA12G, SA12H, SA12J, SA12K
Platelet count decreased	£752.52	SA12G, SA12H, SA12J, SA12K
Pneumonia	£679.80	DZ11K, DZ11L, DZ11M, DZ11N, DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V
Thrombocytopenia	£752.52	SA12G, SA12H, SA12J, SA12K
WBC decreased	£752.52	SA12G, SA12H, SA12J, SA12K

Abbreviations: COVID-19: coronavirus disease 2019; WBC: white blood cell count.

Table 87: Total adverse event costs

Treatment	Mean	SE
Pirtobrutinib	£492.97	98.59
IdelaR	£589.00	117.80

Abbreviations: IdelaR: idelalisib plus rituximab; SE: standard error.

Table 88: Adverse event duration

Adverse event	Duration (days)		Source/Notes
	Mean	SE	
Alanine aminotransferase increased	21	4.2	NICE TA561[69] based on NICE TA347.
Anaemia	23	4.6	NICE TA561[69] based on NICE TA359, assumed the same as thrombocytopenia.
Cardiac failure	21	4.2	Assumed the same as hypertension.
COVID-19	14	2.8	Assumption based on NICE TA689.
Diarrhoea	3	0.6	NICE NICE [133]TA689[27] based on NICE TA403.
Febrile neutropenia	4	0.8	NICE TA689[27] based on NICE TA403.
Hyperkalaemia	20	4.0	Assumed the same as hypertension.
Hypertension	21	4.2	NICE TA931.[37]
Infusion-related reaction	4	0.7	NICE TA561[69] based on NICE TA344.
Lymphocyte count increased	23	4.6	Assumed the same as thrombocytopenia.
Lymphopenia	23	4.6	Assumed the same as thrombocytopenia.
Neutropenia	15	3.0	NICE TA561[69] based on NICE TA306.
Neutrophil count decreased	15	3.0	Assumed the same as neutropenia.
Platelet count decreased	23	4.6	Assumed the same as thrombocytopenia.
Pneumonia	18	3.6	NICE TA561[69] based on NICE TA359, Study 116.
Thrombocytopenia	23	4.6	NICE TA561[69] based on NICE TA306.
WBC decreased	23	4.6	Assumed the same as thrombocytopenia.

Abbreviations: COVID-19: coronavirus disease 2019; NICE: National Institute for Health and Care Excellence; SE: standard error; TA: technology appraisal; WBC: white blood cell.

3.5.4 Miscellaneous unit costs and resource use

Terminal care costs were applied in the model as a one-time cost upon the transition to the death health state. The cost used in the model was sourced from Round *et al.* (2015) and inflated to 2022/2023 using the NHS cost inflation index.[122, 123]

Table 89: End-of-Life Care Costs

Parameter	Mean annual cost	SE	Source
End-of-life care costs	£12,187.14	2,437.43	Round *et al.* (2015)[147]

Abbreviations: SE: standard error.

3.6 Severity

Quality-adjusted life-year weighting for severity were completed to adjust the QALYs based on the severity of illness. In the model, both absolute QALY shortfall and proportional QALY shortfall were calculated, using the severity modifier tool developed by the Sheffield Centre for Health and Related Research (SCHARR).[148] In line with the NICE reference case, the Hernandez-Alava 2017 study, which mapped the EQ-5D-5L to the EQ-5D-3L, was used.[142, 143] A summary of the features of the QALY shortfall analysis are presented in Table 90 with results from the analysis for the post-cBTKi and dual-exposed population presented in Table 91. The results indicate that the dual-exposed population is eligible for a QALY weight multiplier of 1.2, and the post-cBTKi population is eligible for a QALY weight multiplier of 1.0.

Table 90: Summary features of QALY shortfall analysis

Factor	Parameter	Reference to section in submission
Post-cBTKi population		
Sex distribution, female	30.3%	Section 3.3.1
Mean patient age, years	67.0	Section 3.3.1
Dual-exposed population		
Sex distribution, female	40.0%	Section 3.3.1
Mean patient age, years	66.8	Section 3.3.1

Abbreviations: QALY: quality-adjusted life years.
Source: Eli Lilly (Data on File). CSR Addendum 2.[103]

Table 91: Summary of QALY shortfall analysis

General population QALYs	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Post-cBTKi population			
9.74	7.74	79.6%	1.0
Dual-exposed population			
9.89	8.57	86.7%	1.2

Abbreviations: QALY: quality-adjusted life year

3.7 Uncertainty

As with any economic model, there are several limitations to the analysis that should be noted. The design of the BRUIN-CLL-321 benefited patients randomised to the investigator's choice arm as the majority (75.86% of those eligible) of participants crossed over following disease progression to receive pirtobrutinib and benefited from the treatment. However, the design hindered the ability to conduct unbiased OS analyses and impacted the data available post-progression for subsequent treatments.

As discussed in Sections 2.4.2.3 and 3.3.2.2, attempts were made to adjust for the crossover impact, but due to the limited sample size of non-crossover patients, these adjustments led to unlikely parametric survival predictions – given the observed PFS benefit of pirtobrutinib – with OS hazards increasing faster than Investigator's choice values toward the end of Kaplan-Meier follow-up for many OS survival curves. Multiple crossover adjustment methods were employed, but they were unable to accurately reflect the OS of the Investigator's choice arm. Many studies

and NICE TSDs note that with high crossover, both the two-stage AFT and IPCW methodologies likely underestimate the true treatment benefit, likely leading to conservative differences in OS between pirtobrutinib and the control arm.

Given the clinical implausibility of the PFS curves continuing their separation while the OS curves cross in many cases, in the base-case investigator's choice, OS was modelled by applying the HR from the crossover-adjusted Cox models to the unbiased pirtobrutinib OS curve in each analysis, allowing for continued treatment benefit. High correlations in the published literature between PFS and OS support modelling of a continued OS benefit over time rather than the converging and subsequent crossing of arms observed in the BRUIN CLL-321 parametric analyses. Although applying the HR does assume proportional hazards for OS over time, the HR applied was likely conservative given the inability of the crossover methods to capture the true treatment effect where non-crossover participants are a minority.

Crossover plus follow-up time and data collected in the trial (e.g., only if a subsequent anticancer therapy was used, not when and for how long and in what combination, and also if it is reflective of UK clinical practice) impacted the ability to model post-progression costs.

In addition to the above, clinical effectiveness data for IdelaR in the model was represented by a basket comparator of Investigator choice of IdelaR and BR, as per the control arm of BRUIN CLL-321. As the majority of patients randomised to the control arm were treated with Investigator choice of IdelaR (see Section 2.3.2 and 3.2), it was assumed that the data for the overall control arm would be broadly generalisable to the subgroup of patients who were treated with IdelaR. This assumption was validated as acceptable by UK clinical experts.

3.8 Managed access proposal

As discussed in Section 1.1 and Section 1.3.3.3, it is anticipated that pirtobrutinib will be positioned as a treatment across three patient sub-populations. Data to support robust economic analyses of pirtobrutinib against the relevant comparators of interest, conducive to the routine commissioning of pirtobrutinib, are available for the dual-exposed and post-cBTKi, but cannot receive current SoC sub-populations, with details discussed in Section 3 of this submission.

However, as discussed in Section 1.3.3.3 (supported further by the FA detailed in Section 2.10), there is an absence of robust data to accommodate any direct or indirect comparisons of efficacy and safety between VenR and the covalent BTKis which are considered relevant comparators for the post-cBTKi, but can receive SoC population. As such the only reliable proxy analysis for this population is the one versus IdelaR in the ITT population.

Lilly remain open to discussing a managed access approach for the post-cBTKi sub-population that can receive current SoC.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 92.

Table 92: Summary of variables applied in the economic model

Variable	Post-cBTKi population	Dual-exposed population	Reference to section in submission
Model settings			
Population	BRUIN CLL-321		Section 3.2.2
Perspective	Healthcare payer (NHS/PPS)		
Time horizon	Lifetime		
Half-cycle correction	Yes		
Discount rate (costs and benefits)	3.5%		
Model IV drug wastage	Yes		Section 3.5.1
Crossover adjustment for Investigator's choice of OS	Two Stage AFT method		Section 3.3.2.2
Population Characteristics			
Mean age, years (SD)	67.0	66.8	Section 3.3.1
Proportion females, %	30.3	40.0	
Body surface area, m^2 (SD)	1.92 (0.24)	1.93 (0.26)	
Clinical inputs			
PFS (pirtobrutinib)	Gamma	Gamma	Section 3.3
OS (pirtobrutinib)	Gamma	Gamma	
TTD (pirtobrutinib)	Gompertz	Gompertz	
Utility inputs			
Utility for PF, mean (SE)	0.814 (0.018)		Section 3.4
Utility for PD, mean (SE)	0.600 (0.060)		
AE disutilities, mean (SE)			
Alanine aminotransferase increased	0.05 (0.01)		Section 3.4.4
Anaemia	0.09 (0.02)		
Cardiac failure	0.02 (0.00)		
COVID-19	0.22 (0.04)		
Diarrhoea	0.20 (0.04)		
Febrile neutropenia	0.20 (0.04)		
Hyperkalaemia	0.02 (0.00)		
Hypertension	0.02 (0.00)		
Infusion-related reaction	0.20 (0.04)		
Lymphocyte count increased	0.11 (0.02)		
Lymphopenia	0.11 (0.02)		
Neutropenia	0.16 (0.03)		
Neutrophil count decreased	0.16 (0.03)		
Platelet count decreased	0.11 (0.02)		
Pneumonia	0.20 (0.04)		

Thrombocytopenia	0.11 (0.02)	
WBC count decreased	0.11 (0.02)	
AE incidence (pirtobrutinib, Investigator's choice), %		
Alanine aminotransferase increased	0.9, 9.2	Section 3.3.3
Anaemia	11.2, 7.4	
Cardiac failure	2.6, 0.0	
COVID-19	0.0, 3.7	
Diarrhoea	0.0, 5.5	
Febrile neutropenia	1.7, 4.6	
Hyperkalaemia	2.6, 0.0	
Hypertension	2.6, 0.9	
Infusion-related reaction	0.0, 2.8	
Lymphocyte count increased	2.6, 0.9	
Lymphopenia	0.0, 2.8	
Neutropenia	14.7, 11.9	
Neutrophil count decreased	5.2, 12.9	
Platelet count decreased	1.7, 2.8	
Pneumonia	15.5, 8.3	
Thrombocytopenia	6.9, 4.6	
WBC decreased	0.9, 4.6	
Cost inputs		
Drug acquisition costs		
Pirtobrutinib (oral, 50 mg, 28 tablets per pack)	[redacted]	Section 3.5.1
Pirtobrutinib (oral, 100 mg, 56 tablets per pack)	[redacted]	
Idelalisib (oral, 100 mg, 60 tablets per pack)	£3,114.75	
Idelalisib (oral, 150 mg, 60 tablets per pack)	£3,114.75	
Rituximab (IV, 100 mg/10 mL, 2 vials)	£314.33	
Rituximab (IV, 500 mg/50 mL, 1 vial)	£785.84	
Distribution of use, %		
Pirtobrutinib	N/A	Section 3.5.1
IdelaR	100.0%	
Drug administration costs		
Pirtobrutinib	£0	Section 3.5.1
IdelaR (Cycles 1–2)	£499.10	
IdelaR (Cycles 3–6)	£203.98	
Active treatment following progressive disease drug acquisition costs		

Acalabrutinib (oral, 100 mg, 60 tablets per pack)	£5,059.00	Section 3.5.1
Cyclophosphamide (IV, 500 mg, 1 vial)	£11.18	
Cyclophosphamide (IV, 1,000 mg, 1 vial)	£13.11	
Cyclophosphamide (IV, 2,000 mg, 1 vial)	£27.50	
Fludarabine (SC, 50 mg/^{2} mL, 1 vial)	£105.93	
Lenalidomide (oral, 25 mg, 21 tablets per pack)	£28.27	
Obinutuzumab (IV, 1,000 mg, 1 vial)	£3,312.00	
Venetoclax (oral, 10 mg, 14 tablets per pack)	£59.87	
Venetoclax (oral, 50 mg, 7 tablets per pack)	£149.67	
Venetoclax (oral, 100 mg, 7 tablets per pack)	£299.34	
Venetoclax (oral, 100 mg, 112 tablets per pack)	£4,789.47	
Zanubrutinib (oral, 80 mg, 120 tablets per pack)	£4,928.65	
Healthcare resource costs		
Full blood count	£3.10	Section 3.5.2
Lactate dehydrogenase	£1.53	
X-ray	£101.10	
Bone marrow exam	£452.43	
Haematologist visit	£192.53	
Inpatient visit (medical)	£561.69	
Blood transfusion	£386.96	
Annual costs		
On treatment health state, mean	£400.49	Section 3.5
Off treatment health state, mean	£8,337.84	
End-of-life costs	£12,187.14	
AE costs		
Alanine aminotransferase increased	£767.65	Section 3.5.3
Anaemia	£766.57	
Cardiac failure	£718.05	
COVID-19	£701.51	
Diarrhoea	£564.22	

Febrile neutropenia	£567.22	
Hyperkalaemia	£584.31	
Hypertension	£404.67	
Infusion-related reaction	£549.10	
Lymphocyte count increased	£752.52	
Lymphopenia	£752.52	
Neutropenia	£752.52	
Neutrophil count decreased	£752.52	
Platelet count decreased	£752.52	
Pneumonia	£679.80	
Thrombocytopenia	£752.52	
WBC decreased	£752.52	

Abbreviations: AE: adverse event; AFT: accelerated failure time; cBTKi: covalent Bruton's tyrosine kinase inhibitor; IV: intravenous; NHS: National Health Service; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; PSS: Personal Social Services; SD: standard deviation; SE: standard error; TTD: time to treatment discontinuation; WBC : white blood cells.

3.9.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 93.

Table 93: Key assumptions made in the model

Parameter	Assumption	Justification
Patient body surface area is normally distributed	The model assumes that body surface area follows a normal distribution, which affects the amount of drug being used in each cycle for IV medications when IV drug wastage is modelled. Mean body surface area for the modelled population is assumed to be equal to the mean from the BRUIN CLL-321 trial.	The modelling of mean body surface area using that observed in the BRUIN CLL-321 trial ensures that the model reflects the characteristics of the studied population, enhancing its validity and applicability to the target indication.
Oral drug administration	Oral drugs are assumed to incur no administration costs.	This assumption was in line with past appraisals in R/R CLL.
AE occurrence	AEs were based on the grade 3/4 events reported in BRUIN CLL-321. In the model, these are assumed to occur once in the treatment course.	Adverse event costs were conservatively assumed to occur once throughout the model because AEs are typically experienced early in the treatment course.[91] This approach was taken despite noting a more favourable AE profile for pirtobrutinib when considering exposure-adjusted AEs.
OS extrapolation	OS extrapolations selected were considered to provide plausible long-term projections without the need for additional assumptions, which were instead investigated in sensitivity analyses.	Extrapolations were validated by clinical experts consulted for this submission and were deemed appropriate and clinically plausible long-term projections.
Crossover adjustment for OS	The Two-Stage AFT model was assumed to be sufficient in capturing treatment switching within the model, to capture OS outcomes for crossover patients.	The two-stage method was selected as the base-case approach as TSD 24 notes that "when switching proportions are high IPCW results can be prone to substantial bias, especially when sample sizes are small," both of which are present in BRUIN CLL-321. This method estimates survival outcomes in patients that have progressed in the control arm for those that switched to pirtobrutinib versus those that did not switch. The data for this part of the model are based on observational data and therefore may be affected by unknown confounders and correlated data. This method can be underpowered when a high proportion of eligible

		patients switch treatment. Therefore, this method is likely conservative and potentially underestimates the OS treatment effect of pirtobrutinib. However, the two-stage method has the lowest HR and 95% CI as shown in Table 59, and was considered the most clinically plausible option by the clinical experts consulted for this submission, making it the most appropriate method to represent treatment switching in the model.[35]
OS estimation method	Investigator's choice overall survival (OS) is modelled by applying the HR from the Cox models to the unbiased pirtobrutinib OS curve in each analysis, allowing for continued treatment benefit.	This approach is supported by high correlations between PFS and OS and avoids the implausible convergence and subsequent crossing of arms seen in the BRUIN CLL-321 parametric analyses.
Post-progression costs	It is assumed that once patients enter the progressive disease health state or upon treatment discontinuation, patients switch to active/systemic therapies or best supportive care until death, where they will incur an end-of-life care cost. It was assumed that post-progression costs for patients receiving pirtobrutinib and Investigator's choice are assumed to differ both in terms of total cost and cost per cycle, reflecting differences in treatment patterns and resource use following progression.	Differing post-progression costs between treatment arms were modelled to reflect variations in treatment patterns and resource utilisation following progression. This assumption aligns with clinical expert opinion and the BSH guidelines, which specify that treatment sequencing depends on treatment history, clinician judgment, and experience.[25, 35]

Abbreviations: AEs: adverse events; AFT: accelerated failure time; AR: adverse reaction; BSH: British Society for Haematology; CLL: chronic lymphocytic leukaemia; HR: hazard ratio; IPCW: inverse probability of censoring weighting; IV: intravenous; OS: overall survival; PFS: progression-free survival; R/R CLL: relapsed/refractory chronic lymphocytic leukaemia; TSD: technical support document.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

A summary of the probabilistic base case analysis for the dual-exposed and post-cBTKi populations are presented in Table 94 and Table 95 below, respectively.

At its list price, the base case probabilistic ICER for pirtobrutinib versus IdelaR was [redacted] per QALY gained in the post-cBTKi population and [redacted] per QALY gained in the dual-exposed population. A PAS discount for pirtobrutinib is currently under consideration and will be communicated to the PASLU shortly. Cost-effectiveness results with pirtobrutinib at its PAS price will be shared with NICE as soon as possible following its acceptance by PASLU.

Based on the severity calculations conducted in Section 3.6, a 1.2x severity modifier was applicable for patients in the dual-exposed population in the model. As a result of these analyses, the QALYs for treatment with pirtobrutinib in the dual-exposed population are upweighted to 2.055 from 1.713. This results in an amended ICER of [redacted] per QALY gained between pirtobrutinib and IdelaR; ICERs from the severity analysis were calculated in the model deterministically. Results from this severity analysis are presented in Table 96.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix H.

Table 94: Probabilistic base-case results in patients with R/R CLL: post-cBTKi population, currently suitable and unsuitable for standard of care (at pirtobrutinib list price)

Comparator	Total costs	Total LYG[a]	Total QALYs	NMB	Incremental costs	Incremental LYG[a]	Incremental QALYs	ICER (£/QALY)
Pirtobrutinib	[redacted]	[redacted]	2.576	[redacted]	[redacted]	[redacted]	0.539	[redacted]
IdelaR	[redacted]	[redacted]	2.037	[redacted]				

Footnote: [a] Calculated deterministically.
Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; ICER: incremental cost-effectiveness ratio; Inv. Choice: investigator's choice; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year.

Table 95: Probabilistic base-case results in patients with R/R CLL: dual-exposed population (at pirtobrutinib list price)

Comparator	Total costs	Total LYG[a]	Total QALYs	NMB	Incremental costs	Incremental LYG[a]	Incremental QALYs	ICER (£/QALY)
Pirtobrutinib	[redacted]	[redacted]	1.760	[redacted]	[redacted]	[redacted]	0.386	[redacted]
IdelaR	[redacted]	[redacted]	1.374	[redacted]				

Footnote: [a] Calculated deterministically.
Abbreviations: ICER: incremental cost-effectiveness ratio; Inv. Choice: investigator's choice; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year.

Table 96: Summary of QALY shortfall analysis (dual-exposed population)

Proportional QALY shortfall	QALY weight	Upweighted pirtobrutinib QALYs	ICER (£/QALY)[a]
86.7%	1.2	2.055	[redacted]

Footnote: [a] Calculated deterministically.
Abbreviation: QALY: quality-adjusted life year.

3.11 Exploring uncertainty

To address uncertainty in model inputs and assumptions, several sensitivity analyses were conducted, including PSA (Section 3.11.1), deterministic sensitivity analysis (DSA; Section 3.11.2) and scenario analyses (Section 3.11.3). The PSA was performed to analyse the joint uncertainty of the model parameters, and the DSA and scenario analyses were used to identify model drivers or test alternative data sources.

3.11.1 Probabilistic sensitivity analysis

PSA was conducted to assess the impact of parameter uncertainty on the results of the analysis in the model base case; 1,000 simulations were performed, and for each simulation, a value was drawn at random for each variable from its uncertainty distribution simultaneously, and the resulting costs, outcomes, and incremental results were recorded. Table 97 presents distributions selected for various model parameter categories. Uncertainty values were extracted from data were possible. When uncertainty was not reported, standard errors were assumed to be 20% of the mean value.

Table 97: Distributions for model parameters in the PSA

Parameter	Distribution
Hazard ratios	Log-normal
Survival curves	Multivariate normal with parameter correlation considered via Cholesky decomposition
Costs	Gamma
Adverse event incidence	Beta
Utility weights	Beta
Adverse event disutilities	Gamma

Abbreviations: PSA: probabilistic sensitivity analysis.

Post-cBTKi population

Use of 1,000 iterations was deemed appropriate based on the results of a PSA stabilisation plot, as shown in Figure 49. The results of the base-case PSA for the post-cBTKi population are presented in Table 94 (at pirtobrutinib list price), and the cost-effectiveness plane scatterplot is presented in Figure 50. Based on the PSA, treatment with pirtobrutinib in the post-cBTKi sub-population was associated with a mean ICER of [redacted] per QALY gained. With a WTP threshold of £30,000, [redacted]% of all iterations fall below the cost-effectiveness line. The probabilistic results are consistent with the deterministic results, indicating the robustness of the analyses to parameter uncertainty.

Figure 49: Stabilisation plot for pirtobrutinib versus IdelaR: post-cBTKi population

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

Figure 50: Scatter plot for pirtobrutinib versus IdelaR: post-cBTKi population

Abbreviations: cBTKi; covalent Bruton's tyrosine kinase inhibitor; ICER: incremental cost effectiveness ratio; IdelaR: idelalisib with rituximab; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

Dual-exposed population

Use of 1,000 iterations was deemed appropriate based on the results of a PSA stabilisation plot, as shown in Figure 51. The results of the base-case PSA for the dual-exposed population are presented in Table 95 (at pirtobrutinib list price), and the cost-effectiveness plane scatterplot is presented in ICER: incremental cost effectiveness ratio; IdelaR: idelalisib with rituximab; QALY: quality-adjusted life year.

Figure 52. Based on the PSA, treatment with pirtobrutinib in dual-exposed patients was associated with a mean ICER of [redacted] per QALY gained. At a WTP threshold of £30,000, [redacted]

of all iterations fall below the cost-effectiveness line. The probabilistic results are consistent with the deterministic results, indicating the robustness of the analyses to parameter uncertainty.

Figure 51: Stabilisation plot for pirtobrutinib versus IdelaR: dual-exposed population

Abbreviations: ICER: incremental cost effectiveness ratio; IdelaR: idelalisib with rituximab; QALY: quality-adjusted life year.

Figure 52: Scatter plot for pirtobrutinib versus IdelaR: dual-exposed population

Abbreviations: ICER: incremental cost effectiveness ratio; IdelaR: idelalisib with rituximab; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

3.11.2 Deterministic sensitivity analysis

In addition to the PSA, deterministic one-way sensitivity analyses were performed to assess the effect on the results when key input parameter values are varied by 20%.

Post-cBTKi population

The 10 most influential variables on the ICER (£ per QALY gained) in the DSA for the analysis of pirtobrutinib versus IdelaR in the post-cBTKi population are presented as a tornado plot in Figure 53. The most influential parameters were the HR used to adjust the OS Investigator's choice curve, post-progression drug acquisition costs, and the progression-free utility weight.

Figure 53: Tornado diagram for pirtobrutinib versus IdelaR (post-cBTKi population)

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; HR: hazard ratio; Inv.: Investigator; QALY: quality-adjusted life year.

Dual-exposed population

The 10 most influential variables on the ICER (£ per QALY gained) in the DSA for the analysis of pirtobrutinib versus IdelaR in the dual-exposed population are presented as a tornado plot in Figure 54. As for the post-cBTKi population, the most influential parameters were the HR used to adjust the OS investigator's choice curve, post-progression drug acquisition costs, and the progression-free utility weight.

Figure 54: Tornado diagram for pirtobrutinib versus IdelaR (dual-exposed population)

Abbreviations: HR: hazard ratio; Inv.: Investigator; QALY: quality-adjusted life year.

3.11.3 Scenario analysis

In addition to the DSA and PSA, a number of scenario analyses were explored in which model assumptions or parameters were altered. Pairwise probabilistic results of the scenario analyses for the post-cBTKi and dual-exposed sub-populations are presented in Table 98. Please note, the scenario-analyses for the dual-exposed population were run without the severity modifier applied.

Table 98: Scenario analyses (probabilistic) for the post-cBTKi and dual-exposed sub-populations (at pirtobrutinib list price)

Scenario	Base case	Scenario analysis	Incremental costs	Incremental QALYs	ICER (£/QALY)
Post-cBTKi population					
PFS endpoint (IRC)	PFS endpoint (Investigator's choice)	IRC PFS is used to assess the impact on survival estimates	[redacted]	0.495	[redacted]
PFS curve (Weibull)	PFS curve (Gamma)	Weibull distribution modelled for BRUIN CLL-321 PFS	[redacted]	0.517	[redacted]
OS curve (Weibull)	OS curve (Gamma)	Weibull distribution modelled for BRUIN CLL-321 OS	[redacted]	0.520	[redacted]
IPCW crossover method for OS	Two stage AFT	OS for Inv. Choice from BRUIN CLL-321 is adjusted using the IPCW analysis	[redacted]	0.324	[redacted]
TTD curve (Weibull)	TTD curve (Gompertz)	Weibull distribution modelled for BRUIN CLL-321 TTD	[redacted]	0.539	[redacted]
TTD equal PFS	TTD curve (Gompertz)	TTD is modelled equal to PFS curve	[redacted]	0.542	[redacted]
Post-progression (100% BSC)	Post-progression (different in each regard)	—	[redacted]	0.564	[redacted]
Post-progression (Equivalent per cycle)	Post-progression (different in each regard)	—	[redacted]	0.549	[redacted]
Post-progression (Equivalent in total)	Post-progression (different in each regard)	—	[redacted]	0.522	[redacted]
Exclude AE disutilities	Include AE disutilities	The impact of AEs on QALYs is included in the analysis	[redacted]	0.527	[redacted]
Investigator's choice as comparator	IdelaR as comparator	—	[redacted]	0.541	[redacted]

Dual-exposed population					
PFS endpoint (IRC)	PFS endpoint (Investigator's choice)	IRC PFS is used to assess the impact on survival estimates	[redacted]	0.363	[redacted]
PFS curve (Weibull)	PFS curve (Gamma)	Weibull distribution modelled for BRUIN CLL-321 PFS	[redacted]	0.389	[redacted]
OS curve (Weibull)	OS curve (Gamma)	Weibull distribution modelled for BRUIN CLL-321 OS	[redacted]	0.374	[redacted]
IPCW crossover method for OS	Two stage AFT	OS for Inv. Choice from BRUIN CLL-321 is adjusted using the IPCW analysis	[redacted]	0.259	[redacted]
TTD curve (Weibull)	TTD curve (Gompertz)	Weibull distribution modelled for BRUIN CLL-321 TTD	[redacted]	0.379	[redacted]
TTD equal PFS	TTD curve (Gompertz)	Weibull distribution modelled for BRUIN CLL-321 TTD	[redacted]	0.388	[redacted]
Post-progression (100% BSC)	Post-progression (different in each regard)	—	[redacted]	0.384	[redacted]
Post-progression (Equivalent per cycle)	Post-progression (different in each regard)	—	[redacted]	0.386	[redacted]
Post-progression (Equivalent in total)	Post-progression (different in each regard)	—	[redacted]	0.363	[redacted]
Exclude AE disutilities	Include AE disutilities	The impact of AEs on QALYs is included in the analysis	[redacted]	0.389	[redacted]
Investigator's choice as comparator	IdelaR as comparator	—	[redacted]	0.393	[redacted]

Abbreviations: AE: adverse event; BSC: best supportive care; cBTKi: covalent Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; IdelaR: idelalisib in combination with rituximab; IRC: independent review committee; PFS: progression-free survival; QALYs: quality-adjusted life years; TTD: time to treatment discontinuation.

3.12 Subgroup analysis

N/A – cost-effectiveness results for all sub-populations suitable for modelling (dual-exposed and post-cBTKi,but cannot receive SoC sub-populations) in this submission have been addressed in the sections above. No additional subgroup analyses were conducted.

3.13 Benefits not captured in the QALY calculation

While patient utilities are modelled in the base case, the model does not account for the potential reduction in caregiver burden or the impact on caregiver utilities. Given that CLL predominantly affects elderly patients, those with R/R disease often require significant additional care and support from family, friends, and caregivers.[34] Effective treatment could alleviate some of this burden, thereby improving caregiver quality of life and overall wellbeing. Including these effects in the model would offer a more comprehensive assessment of the treatment's broader, less direct benefits that are not captured by the QALY calculation alone.

The economic analysis also does not take into account patient preferences for orally administered treatments, and the preferences of clinical experts and patients for treatments which do not require the same level of hospitalisation and monitoring as a number of other comparators to pirtobrutinib discussed in this submission. Of note, this includes venetoclax-containing regimens for patients in the post-cBTKi, but can receive SoC sub-population where monitoring requirements for serious AEs (e.g., TLS) preclude any blanket recommendations over the alternatives within this sub-population. Should pirtobrutinib be recommended for use by NICE, it is anticipated to fulfil the need for a therapy with less stringent monitoring requirements, due the tolerable safety profile discussed in Section 2.11. This anticipated benefit of pirtobrutinib is not captured in the QALY calculation.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

External input from health economists and clinicians was sought during the development of the cost-effectiveness model, to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice.

In alignment with best practice, validation of the economic model was conducted by an independent health economist prior to the submission. The health economist documented any programme code and checked to ensure all model code was functioning accurately. Additionally, a series of diagnostic tests were conducted to ensure that all formulas and model functionality were working, alongside and in-depth review of all input data to ensure accuracy compared to the source data.

3.15 Interpretation and conclusions of economic evidence

3.15.1 Summary of the cost-effectiveness evidence

The cost-effectiveness of pirtobrutinib as a treatment for patients with R/R CLL – across the post-cBTKi and dual-exposed sub-populations – was evaluated versus IdelaR.

For the post-cBTKi population, the results of the probabilistic cost-effectiveness analysis demonstrate that the total costs associated with pirtobrutinib and IdelaR – at their list prices – are [redacted] and [redacted], respectively. The total QALYs associated with pirtobrutinib and IdelaR are 2.576 and 2.037, respectively. The resulting pairwise ICER is [redacted] per QALY for pirtobrutinib versus IdelaR in the post-cBTKi population.

For the dual-exposed population, the results of the probabilistic cost-effectiveness analysis demonstrate that the total costs associated with pirtobrutinib and IdelaR – at their list prices – are [redacted] and [redacted], respectively. The total QALYs associated with pirtobrutinib and IdelaR are 2.380 and 1.941, respectively. The resulting pairwise ICER is [redacted] per QALY for pirtobrutinib versus IdelaR in the dual-exposed population. However, as noted in Section 3.6, pirtobrutinib in the dual-exposed population is eligible for a 1.2x severity modifier versus IdelaR. The severity-adjusted pairwise ICER (deterministic) for pirtobrutinib versus IdelaR using a 1.2x modifier was [redacted] per QALY gained.

The PSA and DSA analyses demonstrated that the model is robust to variation. The DSA results identified a number of key influential parameters – namely the HR used to adjust the OS Investigator's choice curve, post-progression drug acquisition costs, pirtobrutinib acquisition cost, and the progression-free utility weight. Based on findings from the PSA, – at the list price for pirtobrutinib – [redacted] and [redacted] of iterations fell below the WTP threshold of £30,000, for the post-cBTKi and dual-exposed populations respectively. A PAS is currently under discussion and will be communicated to the PASLU shortly. Therefore, the ICERs for decision-making are not yet final and will be shared with NICE following submission.

Overall, pirtobrutinib is associated with meaningful QALY gains over IdelaR and would be a valuable treatment for patients who otherwise face a severe unmet need and a poor prognosis.

3.15.2 Strengths and limitations of the analysis

The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to capture fully all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%. The model structure was deemed appropriate for this decision problem, as it captures the clinical benefits associated with pirtobrutinib and aligned with previous NICE evaluations in R/R CLL.[27, 37, 69]

The clinical evidence presented within this submission has been derived primarily from the pivotal BRUIN CLL-321 Phase 3 trial, investigating the efficacy and safety of pirtobrutinib in R/R CLL adults who have previously been treated with at least one BTKi. BRUIN CLL-321 is a methodologically robust clinical trial in the patient populations of interest to this submission. A notable strength is the comprehensive long-term follow-up of primary, secondary, and safety analyses conducted on August 29, 2024, with a median follow-up of 19.35 months for the pirtobrutinib arm and 17.74 months for the comparator arm, providing robust insights into treatment efficacy and safety. Where inputs were not available from BRUIN CLL-321, inputs and assumptions from previous cost-effectiveness analyses and NICE evaluations in R/R CLL were used.

A limitation within the economic model arose due to the design of the BRUIN CLL-321 trial, which benefited patients randomised to the Investigator's choice arm as several (75.86% of those eligible) patients crossed over to receive pirtobrutinib following disease progression; ORR data demonstrated a benefit from pirtobrutinib treatment in patients who crossed-over from

Investigator choice. However, the design hindered the ability to conduct unbiased OS analyses and impacted the data available post-progression for subsequent treatments.

Attempts were made to adjust for the crossover impact, and multiple crossover adjustment methods were employed (detailed in Section 2.4.2.3 and Section 3.3.2.2). While adjustments were made within the model to account for these limitations, the literature, and NICE TSDs, highlight challenges regarding the cross-over analyses used (AFT two-stage and IPCW analyses) in the context of trials with a high proportion of cross-over. As such it was considered that the crossover analyses would likely underestimate the true treatment benefit of pirtobrutinib, leading to conservative differences in OS between pirtobrutinib and the control arm.[135]

Additionally, clinical effectiveness data in the model for IdelaR are sourced from a basket comparator of Investigator choice of IdelaR and BR, in line with the comparator arm of patients in BRUIN CLL-321. Clinical effectiveness data for the comparator arm were not segregated by choice of comparator therapy to maintain trial randomisation, and to maintain a large sample size for conducting efficacy analyses versus pirtobrutinib. This approach was confirmed as appropriate by clinical experts approached for this submission given that a majority of patients in the comparator arm received IdelaR (68.9%); clinical experts also agreed that the results for the basket comparator would be broadly generalisable to patients treated with IdelaR in UK clinical practice.

Despite the above, BRUIN CLL-321 is considered a robust Phase 3 trial with a suitably appropriate study design to assess the efficacy and safety of pirtobrutinib against the key comparator of relevance in this submission, IdelaR. This is evidenced by low risk of bias in the trial as assessed through the Cochrane tool for RCTs, and alignment from UK clinical experts. Consequently, the economic analyses in this submission are therefore backed by data from this strong evidence base.

Overall results from the economic analysis demonstrate that pirtobrutinib is associated with significant and clinically meaningful treatment benefit, in terms of PFS and OS (following crossover adjustment), compared with IdelaR, and extensive scenario analyses have been conducted to explore the impact of any uncertainty in the survival estimates.

3.15.3 Conclusions

For patients with R/R CLL who have received prior BTKi therapy, pirtobrutinib offers a highly targeted, oral treatment option that enables durable responses, with clinically meaningful and statistically significant improvements in PFS and OS (after crossover adjustment). Moreover, pirtobrutinib provides a tolerable alternative, particularly in the dual-exposed population, who would otherwise only have access to less tolerable PI3Ki therapy following discontinuation of covalent BTKi or BCL2i, addressing the substantial unmet medical need for effective, well-tolerated therapies in this population.

In the post-cBTKi population, pirtobrutinib provides a tolerable, efficacious alternate treatment option, particularly in those who cannot receive current SoC, who, due to the limited availability of effective therapies, would be likely to re-initiate BCL2i or BTKi therapies in later lines of treatment, despite the associated risks.[35] In the post-cBTKi but can receive current SoC population, pirtobrutinib provides a well-tolerated alternative to current SoC, providing an option to bypass the barriers to access related with BCL2i therapies that many R/R CLL patients encounter.

The results of the economic analysis demonstrate that pirtobrutinib would introduce considerable QALY benefits compared to IdelaR in UK clinical practice and provide patients who otherwise face a poor prognosis with an effective alternative treatment option. Evidence presented in the economic analyses and corresponding scenario analyses substantially reduces the uncertainty associated with the clinical and cost-effectiveness estimates for pirtobrutinib in the sub-populations of interest and provides compelling evidence for pirtobrutinib to become available via routine commissioning in UK clinical practice.

References

1. National Institute for Health and Care Excellence. Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors. [ID6269] Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta11298 [Accessed: 01 February 2025].
2. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 2021;397:892-901.
3. De SK. Pirtobrutinib: First Non-covalent Tyrosine Kinase Inhibitor for Treating Relapsed or Refractory Mantle Cell Lymphoma in Adults. Curr Med Chem 2024;31:4757-4762.
4. European Medicines Agency. Jaypirca. SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/jaypirca-epar-product-information_en.pdf [Accessed: 01 May 2025].
5. Eli Lilly USA L. Jaypirca. Prescribing Information. Available at: https://pi.lilly.com/us/jaypirca-uspi.pdf [Accessed: February 2025], 2023.
6. Follows G, Burke JM, Grosicki S, et al. BRUIN CLL-321: A phase 3 open-label, randomized study of pirtobrutinib versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma. Journal of Clinical Oncology 2023;41:TPS7582-TPS7582.
7. Mukkamalla SKR, Taneja A, Malipeddi D, et al. Chronic Lymphocytic Leukemia. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC., 2025.
8. Lymphoma Action. Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL). Available at: https://lymphoma-action.org.uk/types-lymphoma/chronic-lymphocytic-leukaemia-cll-and-small-lymphocytic-lymphoma-sll [Accessed: 01 February 2025].
9. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56.
10. Byrd JC, Stilgenbauer S, Flinn IW. Chronic lymphocytic leukemia. ASH Education Program Book 2004;2004:163-183.
11. Ghia P, Ferreri AJM, Caligaris-Cappio F. Chronic lymphocytic leukemia. Critical Reviews in Oncology/Hematology 2007;64:234-246.
12. Leukaemia UK. Chronic lymphocytic leukaemia. Available at: https://www.leukaemiauk.org.uk/about-leukaemia/types-of-leukaemia/chronic-lymphocytic-leukaemia-cll/ [Accessed: 01 February 2025].
13. Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. The European Journal of Health Economics 2013;14:749-759.
14. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll#heading-Zero [Accessed: 01 February 2025].
15. Burger JA. Treatment of chronic lymphocytic leukemia. New England Journal of Medicine 2020;383:460-473.
16. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.
17. Sagatys EM, Zhang L. Clinical and laboratory prognostic indicators in chronic lymphocytic leukemia. Cancer Control 2012;19:18-25.
18. Oscier D, Dearden C, Erem E, et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. British journal of haematology 2012;159.
19. Binet J, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.
20. Cancer Research UK. Symptoms of chronic lymphocytic leukaemia. Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/symptoms [Accessed: 01 February 2025].
21. Cancer Research UK. Staging chronic lymphocytic leukaemia (CLL). Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-

cll/staging#:~:text=The%20Binet%20staging%20system%20for,red%20blood%20cells%20or%20platelets [Accessed: 01 February 2025].
22. Leukaemia & Lymphoma Society. CLL Staging. Available at: https://www.lls.org/leukemia/chronic-lymphocytic-leukemia/diagnosis/cll-staging [Accessed: 01 February 2025].
23. Shanafelt T. Treatment of older patients with chronic lymphocytic leukemia: key questions and current answers. Hematology 2013, the American Society of Hematology Education Program Book 2013;2013:158-167.
24. Molica S, Shanafelt TD, Giannarelli D, et al. The chronic lymphocytic leukemia international prognostic index predicts time to first treatment in early CLL: Independent validation in a prospective cohort of early stage patients. Am J Hematol 2016;91:1090-1095.
25. Walewska R, Parry-Jones N, Eyre TA, et al. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology 2022;197:544-557.
26. Bhayat F, Das-Gupta E, Smith C, et al. The incidence of and mortality from leukaemias in the UK: a general population-based study. BMC Cancer 2009;9:252.
27. National Institute for Health and Care Excellence. Acalabrutinib for treating chronic lymphocytic leukaemia. [TA689] Available at: https://www.nice.org.uk/guidance/ta689 [Accessed: 01 February 2025].
28. CollaborativeGroup CT. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. Journal of the National Cancer Institute 1999;91:861-868.
29. Leukaemia Care. Left to #WatchWaitWorry Available at: https://www.leukaemiacare.org.uk/our-campaigns/watch-wait-worry/ [Accessed: 01 February 2025].
30. Buzaglo JS, Miller MF, Zaleta AK, et al. Chronic lymphocytic leukemia patient reported outcomes and quality of life: findings from the cancer experience registry. Blood 2017;130:2122.
31. National Institute for Health and Care Excellence. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. [TA663]. Available at: https://www.nice.org.uk/guidance/ta663. [Accessed: 01 February 2025].
32. Morrison EJ, Flynn JM, Jones J, et al. Individual differences in physical symptom burden and psychological responses in individuals with chronic lymphocytic leukemia. Ann Hematol 2016;95:1989-1997.
33. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. British journal of haematology 2007;139:255-264.
34. Else M, Cocks K, Crofts S, et al. Quality of life in chronic lymphocytic leukemia: 5-year results from the multicenter randomized LRF CLL4 trial. Leukemia & lymphoma 2012;53:1289-1298.
35. Eli Lilly and Company. Data on File. Clinical Validation Meeting Minutes.
36. Thurmes P, Call T, Slager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leukemia & lymphoma 2008;49:49-56.
37. National Institute for Health and Care Excellence. Zanubrutinib for treating chronic lymphocytic leukaemia. [TA931] Available at: https://www.nice.org.uk/guidance/ta931 [Accessed: 01 February 2025].
38. Youron P, Singh C, Jindal N, et al. Quality of life in patients of chronic lymphocytic leukemia using the EORTC QLQ-C30 and QLQ-CLL17 questionnaire. European journal of haematology 2020;105:755-762.
39. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood 2016;127:208-215.
40. Kutsch N, Busch R, Bahlo J, et al. FCR front-line therapy and quality of life in patients with chronic lymphocytic leukemia. Leukemia & lymphoma 2017;58:399-407.
41. Perkins JG, Flynn JM, Howard RS, et al. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma. Cancer 2002;94:2033-2039.
42. Moreira J, Rabe K, Cerhan JR, et al. The Prevalence of Serious Infectious Complications in a Cohort of Non-Referred Patients with Newly Diagnosed Chronic Lymphocytic Leukemia (CLL) Compared to Controls: Results of a Cohort Study. Blood 2011;118:4610.

43. Williams AM, Baran AM, Meacham PJ, et al. Analysis of the risk of infection in patients with chronic lymphocytic leukemia in the era of novel therapies. Leukemia & Lymphoma 2018;59:625-632.
44. Mauro FR, Frustaci AM, Visentin A, et al. Severe infections in patients with chronic lymphocytic leukemia included in trials investigating BTK and BCL2 inhibitors. Critical Reviews in Oncology/Hematology 2024;201:104408.
45. The Haematological Malignancy Research Network. Survival. Chronic lymphocytic Leukaemia. Available at: https://hmrn.org/statistics/survival [Accessed: 01 February 2025].
46. Delgado J, Rossi D, Forconi F, et al. Characterising the Burden of Chronic Lymphocytic Leukemia in Fludarabine-Ineligible Patients in Spain, Italy, and the United Kingdom (UK): A Retrospective Observational Study. Blood 2014;124:2646.
47. Blankart CR, Koch T, Linder R, et al. Cost of illness and economic burden of chronic lymphocytic leukemia. Orphanet J Rare Dis 2013;8:32.
48. Priyadarshini M, Deshpande G, Tiwana S, et al. P1696: Economic burden in chronic lymphocytic leukemia (CLL) for patients with ≥2 prior lines of therapy including a Bruton tyrosine kinase inhibitor (BTKI) and/or B-cell lymphoma 2 inhibitor (BCL2I). HemaSphere 2023;7:e8677199.
49. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32:23-33.
50. Eichhorst B, Ghia P, Niemann C, et al. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Annals of Oncology 2024;35:762-768.
51. Eli Lilly and Company. Data on File. CLL BOI Update.
52. Parry H, Damery S, Mudondo N, et al. Primary care management of early stage chronic lymphocytic leukaemia is safe and effective. QJM: An International Journal of Medicine 2015;108:789-794.
53. Electronic Medicines Consortium. Brukinsa (zanubrutinib) Available at: https://www.medicines.org.uk/emc/product/14001/smpc/print [Accessed: 01 February 2025].
54. Electronic Medicines Consortium. Venclyxto (venetoclax) Available at: https://www.medicines.org.uk/emc/product/2267/smpc/print [Accessed: 01 February 2025].
55. Medicines E, Compendium. Calquence (Acalabrutinib) SmPC. Available at: https://www.medicines.org.uk/emc/product/14853/smpc/print [Accessed: 01 February 2025].
56. Electronic Medicines Consortium. Imbruvica (ibrutinib) Available at: https://www.medicines.org.uk/emc/product/10041/smpc/print [Accessed: 01 February 2025].
57. Electronic Medicines Consortium. Zydelig (Idelalisib) SmPC. Available at: https://www.medicines.org.uk/emc/product/3330/smpc/print. [Accessed: 01 February 2025].
58. Electronic Medicines Consortium. Bendamustine hydrochloride. SmPC. Available at: https://www.medicines.org.uk/emc/product/7302/smpc/print [Accessed: 01 February 2025].
59. Electronic Medicines Consortium. Chlorambucil. SmPC. Available at: https://www.medicines.org.uk/emc/product/4656/smpc/print [Accessed: 01 February 2025].
60. Electronic Medicines Consortium. Gazyvaro (obinutuzumab). SmPC. Available at: https://www.medicines.org.uk/emc/product/3279/smpc/print [Accessed: 01 February 2025].
61. Electronic Medicines Consortium. MabThera (rituximab) SmPC. Available at: https://www.medicines.org.uk/emc/product/3801/smpc/print [Accessed: 01 February 2025].
62. National Institute for Care and Excellence. Rituximab for the first-line treatment of chronic lymphocytic leukaemia. [TA174] Available at: https://www.nice.org.uk/guidance/ta174/chapter/1-Recommendations [Accessed: February 2025].
63. National Institute for Care and Excellence. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. [TA216] Available at: https://www.nice.org.uk/guidance/ta216 [Accessed: February 2025].
64. National Institute for Health and Care Excellence. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia. [TA891] Available at: https://www.nice.org.uk/guidance/ta891 [Accessed: 01 February 2025].
65. National Institute for Care and Excellence. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia. [TA343] Available at: https://www.nice.org.uk/guidance/ta343 [Accessed: 01 February 2025].

66. National Institute for Health and Care Excellence. Idelalisib for treating chronic lymphocytic leukaemia. [ID359] Available at: https://www.nice.org.uk/guidance/ta359 [Accessed: 01 February 2025].
67. National Institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation. [TA429] Available at: https://www.nice.org.uk/guidance/ta429 [Accessed: February 2025].
68. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia. [TA796] Available at: https://www.nice.org.uk/guidance/ta796 [Accessed: 01 February 2025].
69. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. [TA561] Available at: https://www.nice.org.uk/guidance/ta561 [Accessed: 01 February 2025].
70. Puła B, Salomon-Perzyński A, Prochorec-Sobieszek M, et al. Immunochemotherapy for Richter syndrome: current insights. ImmunoTargets and therapy 2019:1-14.
71. Ding W. Richter transformation in the era of novel agents. Hematology 2014, the American Society of Hematology Education Program Book 2018;2018:256-263.
72. Wang Y, Tschautscher MA, Rabe KG, et al. Clinical characteristics and outcomes of Richter transformation: experience of 204 patients from a single center. Haematologica 2020;105:765-773.
73. Electronic Medicines Consortium. Venclyxto (venetoclax) Available at: https://www.medicines.org.uk/emc/product/2267/smpc/print [Accessed: 09 May 2025].
74. Eyre TA, Roeker LE, Fox CP, et al. The efficacy and safety of venetoclax therapy in elderly patients with relapsed, refractory chronic lymphocytic leukaemia. Br J Haematol 2020;188:918-923.
75. Shustik C, Bence-Bruckler I, Delage R, et al. Advances in the treatment of relapsed/refractory chronic lymphocytic leukemia. Annals of Hematology 2017;96:1185-1196.
76. Eek D, Krohe M, Mazar I, et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. Patient Prefer Adherence 2016;10:1609-21.
77. Molica S, and Mauro FR. The new life of ibrutinib therapy in CLL: enhancing personalized approaches. Expert Review of Anticancer Therapy 2024;24:789-792.
78. Smolewski P, Robak T. Current treatment of refractory/relapsed chronic lymphocytic leukemia: a focus on novel drugs. Acta Haematologica 2021;144:365-379.
79. Hus I, Puła B, Robak T. PI3K inhibitors for the treatment of chronic lymphocytic leukemia: current status and future perspectives. Cancers 2022;14:1571.
80. Woyach JA, Furman RR, Liu T-M, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. New England Journal of Medicine 2014;370:2286-2294.
81. Mato AR, Hess LM, Chen Y, et al. Outcomes for patients with chronic lymphocytic leukemia (CLL) previously treated with both a covalent BTK and BCL2 inhibitor in the United States: a real-world database study. Clinical Lymphoma Myeloma and Leukemia 2023;23:57-67.
82. Lin K, Huynh L, Yang X, et al. Clinical Characteristics, Treatment Patterns, and Outcomes of Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Refractory to Covalent Bruton's Tyrosine Kinase Inhibitor (BTKi) and Exposed to B-Cell Lymphoma 2 Inhibitor (BCL2i). Blood 2023.
83. Sharman JP, Munir T, Grosicki S, et al. Phase III Trial of Pirtobrutinib Versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor–Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321). Journal of Clinical Oncology 2025:JCO-25-00166.
84. Coiffier B, Altman A, Pui C-H, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. Journal of clinical oncology 2008;26:2767-2778.
85. Walewska R, Martinez-Calle N, Hickey J, et al. Epic: A Second Interim Analysis of the Non-Interventional, Observational Multi-Centre Cohort Study of Patients with Chronic Lymphocytic Leukaemia Treated with First-Line Acalabrutinib through the UK Early Access Programme. Blood 2023;142.

86. Kittai AS, Skarbnik A, Miranda M, et al. A matching-adjusted indirect comparison of acalabrutinib versus zanubrutinib in relapsed or refractory chronic lymphocytic leukemia. American Journal of Hematology 2023;98:E387-E390.
87. Roberts K, Dowell A, Nie J-B. Attempting rigour and replicability in thematic analysis of qualitative research data; a case study of codebook development. BMC medical research methodology 2019;19:1-8.
88. Hampel H, Elhage A, Cho M, et al. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. Brain 2023;146:4414-4424.
89. Scarfo L, Albi E, Quaglia FM, et al. An Observational Study on Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia Treated with Venetoclax-Based Regimens Outside Clinical Trials in Italy (GIMEMA CLL1920). Blood 2021;138:3746.
90. ClinicalTrials.gov. Phase I/II, FIH, Dose Escalation Trial of TL-895 and Expansion of TL-895 Monotherapy and Combination Therapy With Navtemadlin in Tx-Naïve and R/R CLL/SLL Subjects (NCT02825836). Available at: https://clinicaltrials.gov/study/NCT02825836 [Accessed: 20 June 2025].
91. Eli Lilly and Company. Data on File. BRUIN CLL-321 CSR.
92. ClinicalTrials.gov. Study of LOXO-305 Versus Investigator's Choice (IdelaR or BR) in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) (BRUIN CLL-321). Available at: https://clinicaltrials.gov/study/NCT04666038 [Accessed: 01 February 2025].
93. Eli Lilly and Company. Data on File. BRUIN CLL-321 Protocol Data.
94. Eli Lilly and Company. Data on File. Statistical Analysis Plan.
95. Latimer N. Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data. Report by the Decision Support Unit. Available at: https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis. [Accessed: March 2025], 2013.
96. Latimer N. The role of treatment crossover adjustment methods in the context of economic evaluation [PhD thesis]. Available at: https://etheses.whiterose.ac.uk/3720/1/Thesis_Final_with_corrections.pdf. [Accessed: March 2025], 2012.
97. Latimer N, White I, Tilling K, et al. Improved two-stage estimation to adjust for treatment switching in randomised trials: g-estimation to address time-dependent confounding. Statistical methods in medical research 2020;29:2900-2918.
98. Jones JA, Robak T, Brown JR, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial (NCT01659021). The Lancet Haematology 2017;4:e114-e126.
99. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia (ALPINE). New England Journal of Medicine 2023;388:319-332.
100. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial (ELEVATE RR). Journal of clinical oncology 2021;39:3441-3452.
101. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. Journal of Clinical Oncology 2020;38:2849-2861.
102. Eli Lilly and Company. Data on File. Clinical SLR Report (update SLR 1).
103. Eli Lilly and Company. Data on File. BRUIN CLL-321 CSR Addendum 2.
104. Sharman JP, Munir T, Grosicki S, et al. BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib versus Idelalisib plus Rituximab (IdelaR) or Bendamustine plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma ASH Annual Meeting, 2025.
105. Eli Lilly and Company. Data on File. BRUIN CLL-321 Clinical Evidence Module.
106. US Food and Drug Administration. FDA approval of lymphoma medicine Ukoniq (umbralisib) is withdrawn due to safety concerns. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approval-lymphoma-medicine-ukoniq-umbralisib-withdrawn-due-safety-concerns. [Accessed: 18 June 2025].

107. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia (MURANO). New England Journal of Medicine 2018;378:1107-1120.
108. Gribben JG, Jurczak W, Jacobs RW, et al. Umbralisib plus ublituximab (U2) is superior to obinutuzumab plus chlorambucil (O+ Chl) in patients with treatment naïve (TN) and relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): results from the phase 3 Unity-CLL study. Blood 2020;136:37-39.
109. Burger JA, Sivina M, Jain N, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia (NCT02007044). Blood, The Journal of the American Society of Hematology 2019;133:1011-1019.
110. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood, The Journal of the American Society of Hematology 2018;132:2446-2455.
111. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. American journal of hematology 2019;94:1353-1363.
112. Chanan-Khan A, Liu T, Yang K, et al. Network meta-analysis of progression free survival in the treatment of relapsed or refractory chronic lymphocytic leukemia: American Society of Clinical Oncology, 2022.
113. Sorensen S, Wildgust M, Sengupta N, et al. Indirect treatment comparisons of ibrutinib versus physician's choice and idelalisib plus ofatumumab in patients with previously treated chronic lymphocytic leukemia. Clinical Therapeutics 2017;39:178-189. e5.
114. Diels J, van Sanden S. Bayesian network meta-analysis to assess relative efficacy of ibrutinib versus idelalisib+ ofatumumab and physician's choice in relapsed/refractory CII patients. Value in Health 2015;18:A432.
115. Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. Journal of Clinical Oncology 2019;37:1391-1402.
116. Kater AP, Arslan Ö, Demirkan F, et al. Activity of venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia: Analysis of the VENICE-1 multicentre, open-label, single-arm, phase 3b trial. The Lancet Oncology 2024;25:463-473.
117. Al-Sawaf O, Jen M, Hess LM, et al. MATCHING-ADJUSTED INDIRECT COMPARISON OF PIRTOBRUTINIB VS VENETOCLAX CONTINUOUS MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY CLL PREVIOUSLY TREATED WITH A COVALENT BTK INHIBITOR. Hematology, Transfusion and Cell Therapy 2023;45:S162.
118. NHS England. 2023/24 National Cost Collection Data Publication. Available at: https://www.england.nhs.uk/publication/2023-24-national-cost-collection-data-publication/. [Accessed: 22 May 2025].
119. eMIT. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT); Pharmex data for the period of 1 July 2023 to 30 June 2024. Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [Accessed: 01 June 2025].
120. MIMS. Monthly Index of Medical Specialties. Available at: https://www.mims.co.uk/drugs/cancer/antineoplastics/tecartus. [Accessed: 01 June 2025].
121. NICE. Guide to the methods of technology appraisal 2013: The reference case. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case [Last accessed: 19/08/20].
122. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. Palliative Medicine 2015;29:899-907.
123. Jones K WH, Birch S, Castelli A, Chalkley M, Dargan A, et al. . University of Kent. Unit Costs of Health and Social Care 2023 Manual. 2024. Available at: https://www.pssru.ac.uk/unitcostsreport/. [Accessed: 22 May 2025].
124. Holzner B, Kemmler G, Kopp M, et al. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. European journal of haematology 2004;72:381-389.
125. Dretzke J, Barton P, Kaambwa B, et al. Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia. Health Technology Assessment 2010;14:19-26.
126. Eli Lilly and Company. Data on File. BRUIN CLL-321 PRO report.

127. British National Formulary (BNF). Fezolinetant. Medicinal Forms. Available at: https://bnf.nice.org.uk/drugs/fezolinetant/medicinal-forms/ [Accessed: 24 June 2024].
128. Cramer P, Isfort S, Bahlo J, et al. Outcome of advanced chronic lymphocytic leukemia following different first-line and relapse therapies: a meta-analysis of five prospective trials by the German CLL Study Group (GCLLSG). Haematologica 2015;100.
129. Bloehdorn J, Krzykalla J, Holzmann K, et al. Integrative prognostic models predict long-term survival after immunochemotherapy in chronic lymphocytic leukemia patients. Haematologica 2022;107:615-624.
130. Alrawashdh N, Sweasy J, Erstad B, et al. Survival trends in chronic lymphocytic leukemia across treatment eras: US SEER database analysis (1985-2017). Ann Hematol 2021;100:2501-2512.
131. Seung SJ, Hurry M, Hassan S, et al. Examining treatment patterns and real-world outcomes in chronic lymphocytic leukemia using administrative data in Ontario. Curr Oncol 2021;28:4832-4844.
132. Schlosser P, Schiwitza A, Klaus J, et al. Conditional survival to assess prognosis in patients with chronic lymphocytic leukemia. Ann Hematol 2024;103:1613-1622.
133. NICE. Acalabrutinib for treating chronic lymphocytic leukaemia [TA689]: National Institute for Health and Care Excellence, 2021.
134. Latimer NR, Dewdney A, Campioni M. A cautionary tale: an evaluation of the performance of treatment switching adjustment methods in a real world case study. BMC Med Res Methodol 2024;24:17.
135. Gorrod H LN, Abrams K,. NICE Decision Support Unit. NICE DSU Technical Support Document 24: Adjusting survival time estimates in the presence of treatment switching: An update to TSD 16. Available at: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. [Accessed: 05 June 2025].
136. Guyot P, Ades AE, Beasley M, et al. Extrapolation of survival curves from cancer trials using external information. Medical Decision Making 2017;37:353-366.
137. Vickers A. An evaluation of survival curve extrapolation techniques using long-term observational cancer data. Medical Decision Making 2019;39:926-938.
138. Jackson CH. survextrap: a package for flexible and transparent survival extrapolation. BMC Medical Research Methodology 2023;23:282.
139. Deng L, Hsu C-Y, Shyr Y. Power and sample sizes estimation in clinical trials with treatment switching in intention-to-treat analysis: a simulation study. BMC Medical Research Methodology 2023;23:49.
140. Simon F, Ligtvoet R, Robrecht S, et al. End point surrogacy in first-line chronic lymphocytic leukemia. Journal of Clinical Oncology 2025;43:381-391.
141. Maheshwari V BA, Takyar J, Saini P, Hall A, Gandra S,. Correlation between progression-free survival and overall survival among patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: A clinical trial-based approach. EHA Library. 2024.
142. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. 2023. Available at: https://www.nice.org.uk/process/pmg36/chapter/the-scope-2. [Accessed: 01 April 2025].
143. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. Pharmacoeconomics 2023;41:199-207.
144. National Institute for Care and Excellence. Venetoclax for treating chronic lymphocytic leukaemia. [TA487] Available at: https://www.nice.org.uk/guidance/ta487/ [Accessed: 01 February 2025].
145. NHS England. 2023/25 NHS Payment Scheme (amended). Annex B: Guidance on currencies. Available at: https://www.england.nhs.uk/wp-content/uploads/2023/03/23-25NHSPS-amended_Annex-B-Guidance-on-currencies.pdf. [Accessed: 09 May 2025].
146. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under. [TA975] Available at: https://www.nice.org.uk/guidance/ta975 [Accessed: 19 June 2025].
147. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med 2015;29:899-907.
148. Schneider P, McNamara S, Love-Koh J, et al. QALY Shortfall Calculator. Available at: https://shiny.york.ac.uk/shortfall. [Accessed: 01 April 2025]. 2021.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia after 1 or more BTK inhibitors [ID6269]

Summary of Information for Patients (SIP)

June 2025

File name	Version	Contains confidential information	Date
[ID6269] Pirtobrutinib in CLL_NICE_SIP_02Jul2025 [NoCON].docx	V1.1	**No**	24th June 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Pirtobrutinib **Brand name:** Jaypirca®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

There are three populations in whom this treatment is anticipated to be used: • For people living with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with at least one type of medicine known as a **Bruton's tyrosine kinase inhibitor (BTKi)**, and who are unsuitable for treatment with current **standard of care (SoC)** • For people living with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with at least one type of medicine known as a **BTKi**, and who are suitable for treatment with current **SoC** • For people living with relapsed or refractory CLL who have received at least two prior lines of therapy including at least one BTKi and one **B-cell lymphoma 2 inhibitor (BCL2i)** either sequentially or in combination

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **marketing authorisation** (licence) for pirtobrutinib in the UK is currently pending. More information on this can be found in Section 1.2 of the Company submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Table 1 below shows support from Eli Lilly to relevant patient advocacy groups in the United Kingdom (UK), and how the company engages or supports these charities and/or patients who use them. Financial support varies from annual corporate memberships to services provided to support individual patients and/or staff to attend events.

Table 1: Existing collaborations between Eli Lilly and patient groups relevant to pirtobrutinib

Patient Group	Year	Financial support provided:	Engagement/activity with each group:
Blood Cancer UK	2024	£10,000	Sponsorship of Blood Cancer UK Clinical Trials Support Service
	2025	£10,000	Sponsorship of Blood Cancer UK Clinical Nurse Specialist Programme of Support
Lymphoma Action	2022	£10,000	Annual Corporate Membership
	2022	£1,000	Sponsorship of virtual Lymphoma Management webinar series
	2023	£2,200	Services provided by Lymphoma action developing and attending patient experience workshop
Leukaemia Care	2022	£5,000	Annual Corporate Membership
	2024	£10,000	Sponsorship of Leukaemia Care Blood Cancer Awareness Month programme
CLL Support Association	2024	£3,690	Services provided by CLL Support Association to develop and participate in patient experience workshop
	2025	£20,000	Sponsorship of CLL Support Association well-being and advocacy programme for 2025

Abbreviations: CLL: Chronic Lymphocytic Leukaemia; UK: United Kingdom.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Pirtobrutinib is being considered for the treatment of CLL in adults who have previously been treated with at least one BTKi

What is CLL?

CLL is a type of blood cancers that are caused by the excessive production of **white blood cells** called **CD5+ B lymphocytes** (**B cells)**, that undergo genetic changes which impairs the body's ability to fight infections.[1, 2] These cells accumulate in areas like the blood, **bone marrow** (the soft centre of bones), and the **lymph nodes** (small nodules which contain millions of infection-fighting cells).[3]

What are the signs and symptoms of CLL?

CLL may vary greatly in how it manifests, with some people showing no symptoms of their disease.[4-6] Others may experience symptoms like swollen lymph nodes, **fatigue** (extreme tiredness and exhaustion), frequent infections, weight loss, night sweats, and fever, as shown in **Figure 1**.[6] In more severe cases, people might have enlarged organs like the liver or **spleen** (an organ which filters blood and helps protect against infection).[6]

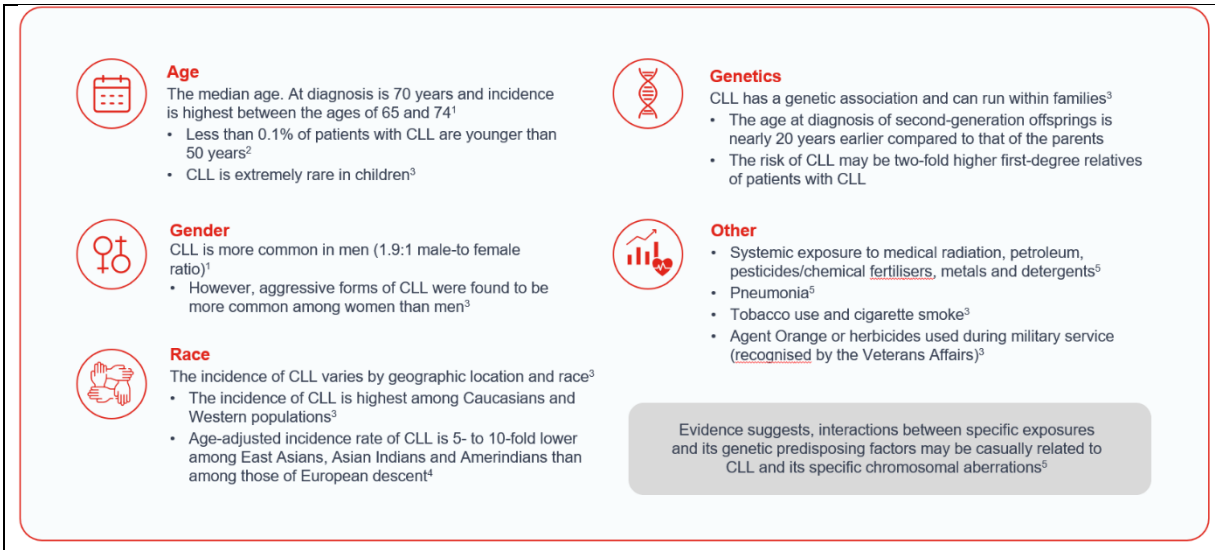
Figure 1: CLL signs and symptoms

Abbreviations: CLL: chronic lymphocytic leukaemia.
Source: Lilly Data on File.

How many people have CLL?

It is estimated that approximately 4,000 people yearly are affected by CLL in the UK.[6] CLL is most commonly diagnosed in older adults.[7-9] There are several factors, known as risk factors, that can result in an increased likelihood of a person developing CLL (**Figure 2**).

Figure 2: CLL risk factors



Abbreviations: CLL: Chronic lymphocytic leukaemia
Source: 1. National Cancer Institute (2025);[10] 2. National Cancer Institute (2025);[11] 3. Mukkamalla SKR *et al.* (2025);[1] 4. Yang *et. al* (2021); [12] 5. Karakosta *et. al* (2016).[13]

What is the impact of CLL?

Impact on quality of life

Initiating treatment when symptoms are not showing has not been shown to provide any added benefit to people living with CLL.[14] This means many patients live with the disease in a monitoring phase called "Watch and Wait," where regular check-ups are required. Following diagnosis, this phase can be a source of anxiety and depression to people living with the disease. In 2024, around 13,000 people in the UK were being watched, with half expressing feelings of increased concern and anxiety.[15-17]

People living with CLL often face a worse **quality of life** compared to the general population, experiencing fatigue, anxiety, depression, sleep disturbance and pain more frequently.[6, 18, 19] Research shows that fatigue levels are notably higher in people living with CLL, and worsen as the condition progresses, affecting peoples' everyday life and emotional well-being significantly.[20]

As the disease advances, it places a growing emotional and physical burden on peoples' families and carers, as the person's need for support increases due to a loss of independence.[21] Evidence suggests that family members and friends who care for a person with CLL, have a lower quality of life compared to those who do not care for a person with CLL.[22]

The choice of treatment also has a large impact on a person's quality of life, especially for those with CLL that does not get better with treatment or disease that returns after a period of improvement (**relapsed or refractory disease**). Limited options can create anxiety due to the uncertainty as to whether another treatment will be available if the current treatment is not well-tolerated or does not work.[23] This increases the psychological burden on people during an already challenging time.

Symptom burden

People who begin treatment with **chemoimmunotherapy** (**CIT**; a combination of **chemotherapy** and **immunotherapy** [please refer to Section 2c for further details]) often experience more

severe symptoms like nausea, appetite loss, and physical discomfort compared to the general population.[24]

Infections are a major concern for people living with CLL, due to their compromised immune systems and increased susceptibility to infection.[6, 25] Over half of those undergoing treatment experience infections, which contribute to a significant proportion of CLL-related deaths.[20] Novel therapies have reduced infection risks, but a high susceptibility remains, especially in people who have been previously treated with **fludarabine** and **ibrutinib.**[20, 26]

CLL can lead to various complications, such as an increased risk of secondary cancers and conditions like **Richter's transformation** (an aggressive type of blood cancer) or **tumour lysis syndrome** (which can result in kidney failure).[27] Elderly people, who often have other health issues, face additional treatment challenges as they commonly manage multiple medications, complicating their condition further.[28]

Life expectancy

The life expectancy of people living with CLL varies by age and how **advanced** (severe) their CLL is at diagnosis (**disease state**); younger people with CLL tend to have better chances of living longer (**Table 1**). Factors like **genetic mutations** and **the Binet stage** (refer to Section 2b) of the disease also influence outcomes, with people who are considered **high-risk** having lower chances of living longer compared to those with lower-risk CLL.[29]

Table 1: Five-year outlook for CLL in England in 2022[30]

	<60 years	**60 to 69 years**	**70 to 79 years**	**≥80 years**
5-year chance of survival (%)	95	90.8	83.6	69.4

Abbreviations: CLL: chronic lymphocytic leukaemia.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is CLL diagnosed?

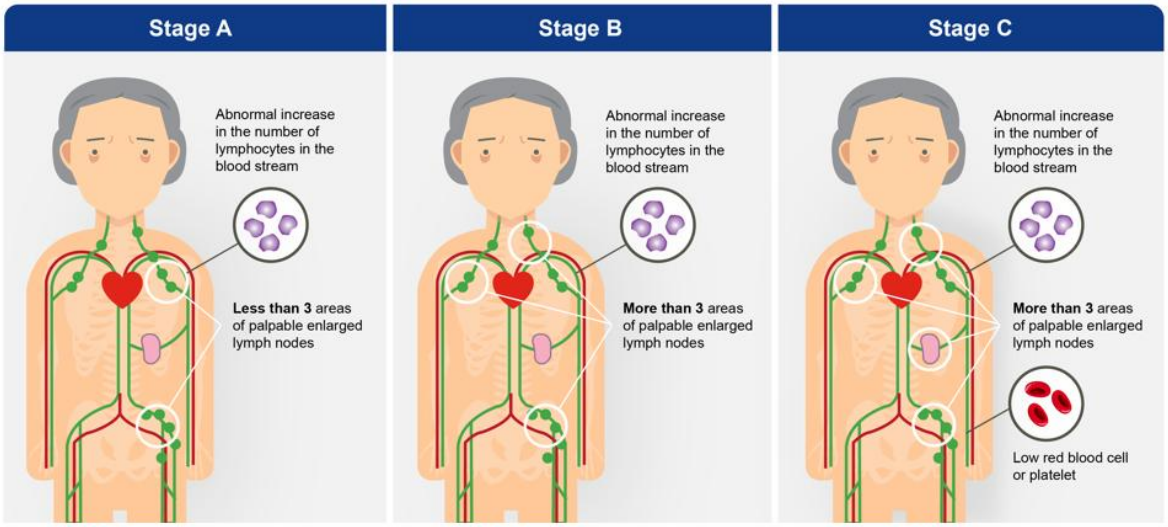
CLL is often diagnosed after having a routine blood test for something else. Referral to a specialist depends on a person's symptoms and blood test results; additional tests may be needed to determine how advanced the disease is.

In people who are exhibiting signs and symptoms of the disease when diagnosed, treatment will be initiated immediately. In many cases however, CLL is diagnosed prior to visible signs and symptoms.

What is disease staging?

Upon disease diagnosis, the clinician will ascertain how advanced the disease is by determining the **stage of the disease**. This can help to predict how a person's disease could progress or respond to treatment and support the development of an appropriate treatment plan. The staging system most commonly used in the UK is called the 'Binet Staging System', shown in **Figure 4**. This measures a person's **platelet count,** number of enlarged lymph nodes and blood **haemoglobin** levels.

Figure 4: Summary of the Binet staging system for CLL



Abbreviations: CLL: chronic lymphocytic leukaemia
Source: Adapted from Chronic Lymphocytic Leukaemia Ireland (CLLI) (2025).[31]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Watch and Wait

To manage early-stage CLL, where people are not showing signs and symptoms of disease, a 'Watch and Wait' strategy is recommended in the UK.[32] Regular checkups take place every three months following diagnosis of CLL to monitor the disease progression until a symptom is identified.[15] Many people living with CLL may never require treatment in their lifetime.

How do doctors choose the most appropriate treatment?

Where a patient starts to show signs or symptoms of CLL, or where a doctor finds evidence of more advanced disease, it is necessary to treat CLL to prevent the patient from getting worse. For the most effective **first-line** treatment doctors will take into account age, fitness level and the presence of 'high-risk' indicators in determining the best possible course of treatment for the patient. **Screening** (checking to see if someone shows signs or symptoms of disease) for these 'high risk' indicators is advised prior to each following line of treatment.

'High risk' CLL indicators

The most important indicators doctors look for are changes in parts of a gene called *TP53*, missing parts of chromosome 17 called 17p (referred to as 17p deletion), and the presence, or lack thereof, of mutations in the immunoglobulin heavy chain variable genes (*IGHV;* found in the B cell).

Treatments for CLL target the abnormal B cells to either kill them or stop their creation and multiplication. Current first-line treatments are either CITs or **targeted therapies** (treatments that directly target parts of the cancer cell), which in some cases are given in combination with an immunotherapy.

Targeted therapy

BTKi, BCL2i, and phosphoinositide 3 kinase inhibitors (PI3Ki) are the main types of targeted therapies used to treat CLL.[33] They work by targeting something in or around the cancer cell that is helping it to grow and survive, and have less effect on healthy cells than other treatments.[34]

Chemotherapy

Chemotherapy uses anti-cancer (**cytotoxic**) drugs to destroy or damage leukaemia cells; cells which grow and multiply quickly (an example of this being the abnormal B cells responsible for CLL).[35] Chemotherapy drugs can be taken orally or injected into a vein (**intravenously**) and then move around the body via the bloodstream to reach the leukaemic cells. Chemotherapy is given in **cycles** of treatment; a cycle is made up of a period where treatment is administered and a rest period.

Chemotherapy can also destroy or damage healthy cells and as a result of this, side effects include fatigue, hair loss, skin changes, nausea, bruising, bleeding and more.[35]

Immunotherapy

Immunotherapy uses our immune system to combat cancer, by helping the immune system to recognise and attack cancer cells.[36] Immunotherapies are also given in cycles of

treatment. They are most commonly given **intravenously** (into a vein) or via an injection under the skin (**subcutaneously**), however in some cases can be in the form of tablets or injected into an area of cancerous cells.[37]

The most common side effect of immunotherapy is skin reactions, including rash, itchiness, and redness, particularly at the injection site.[38] Other common side effects include **diarrhoea** (frequent, loose, or watery bowel movements), fever, chills, and **fatigue** (extreme tiredness and exhaustion).[38]

What are the current treatment options for people with previously untreated CLL?

The 2022 guidelines from the British Society for Haematology (BSH), and the 2018 International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) guidelines inform the current treatment pathway in the UK. A summary of the UK clinical care pathway in previously untreated CLL is shown in **Figure 5**.[32, 33]

To identify people living with CLL who are 'fit and young', doctors look for patients who are aged 65 years or below, have a **cumulative illness rating** (a scale ranging from 0 to 56 points that quantifies how much disease affects an elderly person's overall health) of less than 6 (indicating a lower burden of illness), have a **creatinine clearance** of above 70 ml/min (indicating a kidney that is working optimally), and who show genetic mutations in the *IGHV*.[32] Those with mutated *IGHV* have a better prognosis and slower disease progression compared to those with unmutated *IGHV*. If a patient is defined as being 'fit and young', they have the potential to better tolerate CITs to treat their disease.[32] If a patient is defined as 'fit and older', they have the potential to achieve benefits from targeted therapies, and targeted therapies in combination with immunotherapies.[32]

Chemoimmunotherapy

Chemotherapies are often used in combination with immunotherapies to increase the effectiveness of treatment, compared to chemotherapies alone.[39] CITs include:

- Fludarabine, cyclophosphamide, and rituximab (FCR)

This therapy is recommended only to those who are identified as 'young and fit', who do not have other health conditions, who do not have 17p deletion, *TP53* mutations or unmutated *IGHV*.[40, 41] FCR is not suitable in elderly people with CLL, with several other health conditions, as it can cause severe side-effects such as infections, lowered blood cell counts (which can cause people to feel tired and weak, or to experience increased bruising), or organ damage, which can contribute to the worsening of existing problems.[40, 41]

- Bendamustine and rituximab (BR)

This therapy is given to those who cannot receive FCR due to **contraindications** (when a medication should not be used if it is harmful to a person) or where people are over the age of 65 and deemed fit.[42] Side-effects include pain or swelling at the injection site, fever, sweats, muscle and joint pain and headaches.[43]

- Chlorambucil and obinutuzumab (O-Clb)

This therapy is recommended for people who are not suitable to FCR or BR.[44] Common side-effects include infections, low blood cell counts, **tumour lysis syndrome** (a condition that causes kidney issues, heart rhythm changes, and muscle cramps), diarrhoea, fatigue, insomnia and headaches.[45]

Targeted therapies

- BTKi

The most common therapies of this type used to treat CLL are named zanubrutinib, acalabrutinib, and ibrutinib.[39] These therapies target proteins on the cancerous cells to kill them.[39] BTKi are taken as tablets by the mouth.[39] Common side effects on BTKi include higher risk of infection, bruising and bleeding, **nausea** (can cause discomfort in the stomach and make you feel like vomiting), and diarrhoea.[46-48]

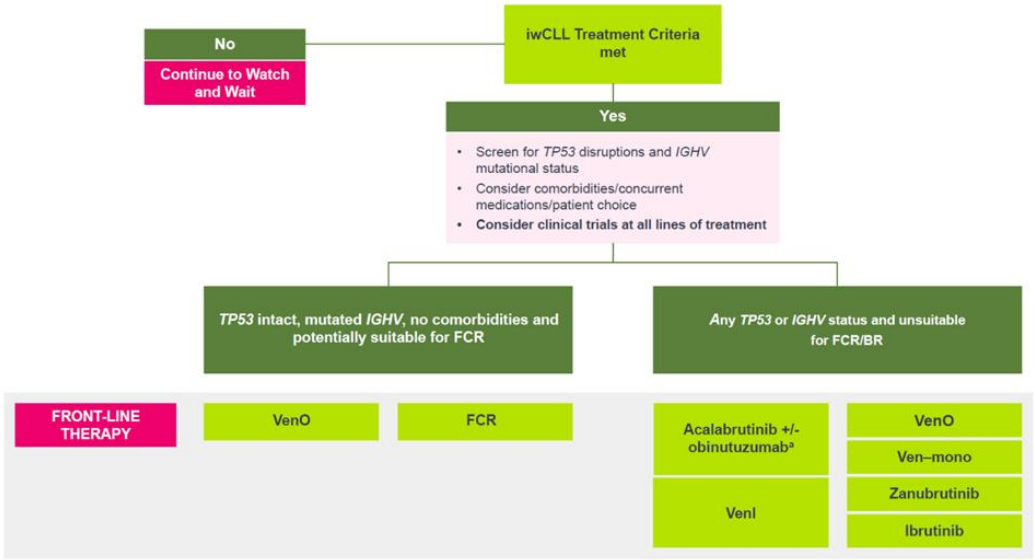
- BCL2i

The most common therapy of this type used to treat CLL in the UK is venetoclax.[49] Venetoclax is used alone or in combination with obinutuzumab or ibrutinib.[17, 50] Common side effects of these therapies include a reduction in the number of white blood cells which increases risk of infection (**neutropenia**), diarrhoea**,** and tiredness.[51]

- PI3Ki

The most common therapy of this type used to treat CLL is named idelalisib, and it is often given in combination with rituximab.[52] This is recommended to people with a 17p depletion or *TP53* mutation. However, it is linked with a higher risk of infection and death.[53, 54]

Figure 5: Overview of the UK clinical care pathway for front-line therapy



Abbreviations: BR: Bendamustine and rituximab; FCR: Fludarabine, cyclophosphamide, and rituximab**;** IGHV: immunoglobulin heavy chain variable region; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; NICE: National Institute for Health and Care Excellence; Ven: venetoclax; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.
Source: Adapted from Walewska *et al.* (2022).[32]

Current treatment option for relapsed or refractory CLL

If a patient relapses but shows no signs or symptoms of disease, then the disease is managed via a 'Watch and Wait' approach.[32] Once the disease becomes active (**symptomatic**), clinicians will first consider:[32]

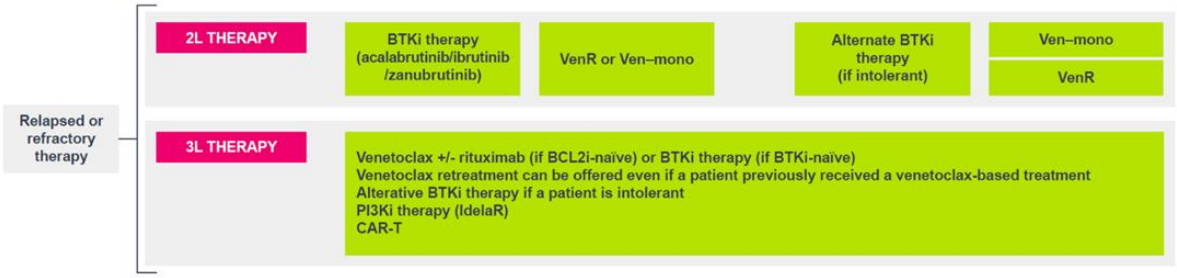
- The number of previous therapies
- The intensity of previous therapies (such as intensive CIT therapies)
- The duration of response to previous therapies
- Whether the patient has 'high-risk' CLL
- The number of patient **comorbidities** (when a patient has more than one health condition at the same time)

The licensed therapies for relapsed or refractory CLL are listed below and a diagrammatical representation is outlined in **Figure 6.**

Targeted therapies

As detailed above for untreated CLL, targeted therapies for relapsed or refractory CLL include BTKi (commonly zanubrutinib, acalabrutinib and ibrutinib), BCL2i (commonly venetoclax alone or in combination with rituximab) and PI3Ki (commonly idelalisib alone or in combination with rituximab).[39,49, 55]

Figure 6: Overview of the UK clinical care pathway for relapsed or refractory CLL



Abbreviations: 2L: second-line; 3L: third-line; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton's tyrosine kinase inhibitor; CAR-T: Chimeric antigen receptor T-cell; PI3Ki: phosphoinositide 3 kinase inhibitors; Ven: venetoclax; VenR: venetoclax with rituximab
Source: Adapted from Walewska *et al.* (2022).[32]

Treatment sequencing

For people with relapsed or refractory CLL, the sequencing of treatments involves choosing the best next therapy when the disease returns after initial treatment.[32] The ideal treatment sequence suggested by the BSH is presented in **Table 3**. The below approaches are suggested as they consider prior treatment responses and aim to maximise the effectiveness of each stage of therapy while managing potential side effects.

Table 3: Treatment sequencing options for people with relapsed CLL

Relapsed therapy	Suggested sequence
BTKi	BCL2i or PI3Ki[a]
PI3Ki	BTKi or BCL2i
BCL2i/BTKi	PI3Ki or AlloSCT

BCL2i/BTKi/PI3Ki	AlloSCT
Venetoclax Obinutuzumab	BTKi or Venetoclax with Rituximab[b] or PI3Ki[a]
Venetoclax monotherapy	BTKi or PI3Ki[a]
Venetoclax with Rituximab	BTKi or venetoclax monotherapy or PI3Ki[a]

Footnotes: [a]BTKi or BCL2i are the preferred options for people who have not tried these treatments before. [b]Only used if a person's illness has not returned while on venetoclax in combination therapy, and they have been in remission for at least 12 months.
Abbreviations: AlloSCT: allogeneic stem cell transplant; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton tyrosine kinase inhibitor; PI3Ki: phosphoinositide 3-kinase inhibitor.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

CLL from the patient perspective

People with CLL experience substantially worse **health-related quality of life** (HRQoL) in terms of fatigue, anxiety, physical functioning, social functioning, depression, sleep disturbance and pain.[6, 18, 19] An international survey found that 80% of respondents experienced a higher severity of fatigue compared to that of people living without the disease, with emotional well-being also scoring lower in people living with CLL.[20]

The Lymphoma Coalition conducted an international Global Patient Survey, with 1,204 respondents based in the UK (approximately 90% patients and 10% caregivers). It found that key side effects from treatment were fatigue (76%), hair loss (48%), constipation (42%), numbness/tingling sensations (39%) and lack of concentration (32%).[56] Many people felt that they did not receive the support they needed from their healthcare team to manage their side effects.[56] More than 80% reported experiencing an emotional impact attributable to their diagnosis and fear of progression and relapse being of most concern.[56]

As CLL progresses, it can have an increasingly negative impact on people's families and carers HRQoL, as their ability to remain independent decreases.[21] Choice of treatment has a large impact on a patient's HRQoL, especially in those with relapsed or refractory CLL, as there are limited effective targeted treatment options available. This can lead to feelings of anxiety due to uncertainty as to whether another treatment will be available if the treatment is not well-tolerated.[23] The survey conducted by Lymphoma Action, found that 95% of caregivers suffer emotional impacts due to the CLL diagnosis of a loved one.[56]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

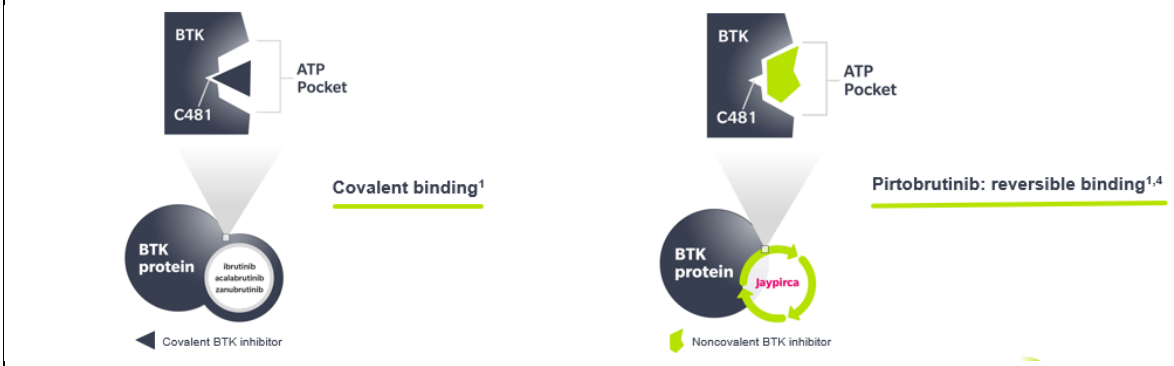
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Pirtobrutinib

Pirtobrutinib is a new and innovative type of BTKi. Like other BTKi it works by binding and blocking the BTK protein (BTK C481S), blocking the abnormal B cells from multiplying (**Figure 7**).[57, 58] However, pirtobrutinib is a **non-covalent** BTKi which means it binds differently, that is reversibly, to the BTK protein than other BTKi which bind **covalently** (irreversibly), as demonstrated in pre-clinical studies. Therefore, pirtobrutinib often works where other covalent BTKi may not.

Figure 7: Mechanism of action of pirtobrutinib



Abbreviations: ATP: adenosine triphosphate; BTK: Bruton tyrosine kinase.
Source: Eli Lilly Data on File.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- **No**

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Pirtobrutinib is not intended to be used with any other treatments for CLL.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Dosing and method of administration

People are required to take 200 mg of pirtobrutinib, taken as four 50 mg tablets or two 100 mg tablets, once daily (at approximately the same time every day).[59] Tablets should be swallowed with a glass of water and should not be chewed, crushed or split before swallowing.[59] It can be taken with or without food.[59]

This differs to existing treatments used to treat those with relapsed or refractory CLL, notably idelalisib in combination with rituximab, where rituximab is given intravenously. Intravenous infusions necessitate regular in-person appointments, which can be challenging for people with CLL as they may find it difficult to travel to a hospital for treatment if these services are not available nearby. Regular attendance at hospitals may also impair their ability to work and be productive.[15] Orally administered treatments are therefore often preferred by people living with CLL due the convenience of administration, allowing them to take the treatment at home without needing frequent hospital visits.[60]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

BRUIN CLL-321 is an ongoing trial studying people who have been treated with pirtobrutinib. The BRUIN CLL-321 is a **Phase 3 trial**, this means it that looks at how well pirtobrutinib works to treat relapsed or refractory CLL (its **efficacy**), and how safe the medicine is compared to the standard treatment. It also looks at the impact of pirtobrutinib on a person's quality of life.

Key results from this trial are available and therefore this trial is being used to support the marketing authorisation application for pirtobrutinib in adults with relapsed or refractory CLL who have previously been treated with a BTKi. Please find the key details of the trial below (**Table 4**).

Patients were **randomised** to receive either pirtobrutinib or Investigator's choice of idelalisib in combination with rituximab (IdelaR) or bendamustine in combination with rituximab (BR); the **comparator**.

To be eligible to participate in the trial, people had to meet the criteria presented in **Table 5**.

Table 4: BRUIN CLL-321 trial details

Clinical trial name and number	Location	CLL patient group	Number of people included	Expected completion date
Phase 3 BRUIN CLL-321 NCT04666038[61, 62]	Europe North America Asia-Pacific	People who had previously treated CLL	238	2027

Abbreviations: CLL: chronic lymphocytic leukaemia.

Table 5: Key eligibility criteria in BRUIN CLL-321

Key Inclusion Criteria	Key Exclusion Criteria
Patients must have a confirmed CLL diagnosis (as per criteria detailed in the 2018 iwCLL guidelines[33])	Patients CLL must not have experienced Richter transformation to **diffuse large B-cell lymphoma**, **prolymphocytic leukaemia**, or **Hodgkin's lymphoma** at any time before joining the study
Patients must have been previously treated with a covalent BTKi, and may have received multiple prior treatments	Patients must not have experienced major bleeding on a prior BTKi
Patients must have known 17p depletion status	Patients could not have had a major surgery within four weeks of study starting
Patients must have had normal organ function before starting the study	Patients must not have had ongoing liver issues
Any side effects from previous treatment must have resolved or recovered to a mild severity	Patients must not have had recent stem cell (cells that can develop into different cell types) or **CAR-T** cell (a type of immune cell) therapy in the last 60 days

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor; CAR-T: chimeric antigen receptor T-cell therapy; CLL: chronic lymphocytic leukaemia; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

In the BRUIN CLL-321 trial, the efficacy of pirtobrutinib was measured according to how well it improved a number of outcomes, including:

- **Progression free survival (PFS)**

Patients who were treated with pirtobrutinib in BRUIN CLL-321 had a 46% lower risk of their disease getting worse compared to those who were treated with the comparator. On average (**median**), those on pirtobrutinib went about 14 months without their disease getting worse i.e., they were progression-free, while those on the comparator therapy experienced about 8.7 months before their condition worsened.

- **Overall survival (OS)**

On average (median), people treated with pirtobrutinib lived for approximately 2.5 years after starting treatment.

- **Time to next treatment (TTNT)**

On average, people treated with pirtobrutinib stayed without needing further treatment or passing away for approximately 2 years, while those in the other group needed more treatment after 10.9 months.

Figure 8 shows the key efficacy results of the BRUIN CLL-321 trial after treatment with pirtobrutinib and investigator's choice of IdelaR or BR. Further efficacy results can be found in **Section 2 of the Company's submission**.

Figure 8: Key efficacy results for BRUIN CLL-321

Abbreviations: BR: bendamustine with rituximab; CLL; chronic lymphocytic leukaemia; IdelaR: idelalisib with rituximab
Source: EMA. Pirtobrutinib Summary of Product Characteristics;[59] Sharman et al. (2025).[63]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The BRUIN CLL-321 trial assessed the quality of life of people with relapsed or refractory CLL through several measures:

- The **EORTC QLQ-C30** questionnaire asked people how difficult they found it to take part in activities of normal daily life such as walking, carrying bags, eating or getting dressed, and asked questions concerning symptoms experienced during the past week
- The **EQ-5D-5L** questionnaire compromises mobility, self-care, usual activities, pain/discomfort and anxiety/depression

Pirtobrutinib impact on quality of life

During the BRUIN CLL-321 trial, the quality of life of individuals was assessed through several measures:

- The **EORTC QLQ-C30 physical function (PF) scale**
- CLL/SLL-related symptoms scale
- Fatigue scale expanded from the **QLQ-C30 fatigue scale**
- **EQ-5D-5L** quality of life questionnaire

Overall, people treated with pirtobrutinib reported significantly lower CLL/SLL-related symptoms, lower fatigue, and better physical functioning, therefore an overall improvement in quality of life compared with people receiving Investigator's choice of IdelaR or BR.[64]

Further details are presented in **Section 2 of the Company's submission**.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own **side effects,** and the same medicine can produce different reactions in different people.

In the BRUIN CLL-321 trial, pirtobrutinib was generally better tolerated than standard treatments used to treat relapsed or refractory CLL. No new side effects were discovered for pirtobrutinib compared to the known side effects of standard therapies. Side effects were experienced in both groups being treated by pirtobrutinib or Investigator's choice of IdelaR or BR (the comparator), as shown in **Table 1**.

The most common side effect in those treated with pirtobrutinib were **pneumonia** (a lung infection that can cause shortness of breath and cause coughing and a fever)**, anaemia** (a

condition leading to tiredness and weakness due to a lack of **red blood cells**), and neutropenia.

The most common side effects in those being treated with Investigators choice of IdelaR or BR were diarrhoea, fever, nausea, and fatigue.

As pirtobrutinib is administered orally, there were no infusion-related reactions in the pirtobrutinib group of BRUIN CLL-321. Infusion-related reactions are the most common side effect experienced by people who are treated with rituximab-containing treatment regimens; infusion-related side effects were experienced by 11.7% participants in the comparator arm.

Overall, discontinuation of treatment due to side effects experienced when receiving pirtobrutinib were low, as shown in **Table 1.**

Table 1: Adverse drug reactions of patients treated with pirtobrutinib[1]

Type of reaction	Adverse drug reaction	Frequency category[a] (%) (All grades)	Grade ≥ 3[c] (%)
Infections and infestations	Pneumonia	Very common (13.8)	9.0
	Upper respiratory tract infection	Very common (10.1)	0.1
	Urinary tract infection	Common (9.9)	1.4
Blood and lymphatic system disorders	Neutropenia[b]	Very common (27.7)	23.9
	Anaemia[b]	Very common (20.7)	11.2
	Thrombocytopenia[b]	Very common (16.8)	9.7
	Lymphocytosis[b]	Common (6.4)	3.9
Nervous system disorders	Headache	Very common (12.6)	0.7
Cardiac disorders	**Atrial fibrillation/atrial flutter**	Common (3.8)	1.7
Vascular disorders	**Haemorrhage[b]**	Very common (20.3)	2.8
	Epistaxis	Common (5.2)	0
	Haematuria	Common (4.5)	0.1
	Haematoma	Common (1.7)	0.1
	Conjunctival haemorrhage	Common (1.7)	0.1
	Bruising[b]	Very common (19.7)	0.3
	Contusion	Very common (17.8)	0.1
	Petechiae	Common (5.7)	0
Gastrointestinal disorders	Diarrhoea	Very common (23.8)	1.0
	Nausea	Very common (16.7)	0.4
	Abdominal pain	Very common (10.4)	1.0
Skin and subcutaneous tissue disorders	Rash[b]	Very common (18.4)	1.2

Musculoskeletal and connective tissue disorders	**Arthralgia**	Very common (14.6)	1.2
General disorders and administration site conditions	Fatigue	Very common (26.2)	1.9
General disorders and administration site conditions	**Oedema peripheral**	Very common (11.6)	0.3

Footnotes: a Frequencies are derived from Jaypirca exposure in patients with B-cell malignancies. b Includes multiple adverse reaction terms. c Severity grade assignment based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
Source: 1. EMA. Pirtobrutinib Summary of Product Characteristics.[59]

Managing side effects

The most common side effects of pirtobrutinib are pneumonia, anaemia, and neutropenia, which can be managed by reducing the doses of treatment or stopping the medication.[65]

Your doctor may prescribe additional medication to reduce your risk of infection.[65] Additionally, it is important to take active precautions to prevent infection such as, washing your hands regularly, avoiding large crowds and people who are sick, and ensuring cuts or scratches are kept clean.[66]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of pirtobrutinib to patients with relapsed or refractory CLL include:

A greater likelihood to live longer without their disease getting worse, compared to those on current standard treatments

Improvement to patients quality of life, as pirtobrutinib therapy is associated with reduced levels of fatigue, fever and diarrhoea

It is administered orally, which may be preferred to patients, and means that there are no infusion-related reactions, which are the most common side effect experienced on immunotherapies

It is generally well-tolerated and has an improved safety profile to that of existing therapies for the treatment of CLL

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Pirtobrutinib is generally well-tolerated and effective in extending a person's time of progression free survival, however, some things people may want to consider before starting treatment include:

Side effects

Like all medicines, some people may experience side effects while they are taking intervention. A summary of side effects can be found in **Section 3g) Safety of the medicine and side effects** The most common side effects for people treated with pirtobrutinib were pneumonia, anaemia, and neutropenia, however, they are usually manageable, and most people do not stop treatment because of side effects.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Introduction for patient groups

Healthcare administrators need to get the most value from limited budgets. To do this, they need to check whether a new medicine provides good value for money compared to other medicines. They will look at the costs of the new medicine and how the health of people is likely to improve if they take it. The pharmaceutical company that makes the medicines provides this information to healthcare administrators using a **health economic model.**

How the model reflects the condition

The health economic model simulates people with relapsed or refractory CLL with characteristics similar to those of people who would receive pirtobrutinib treatment in the NHS.

The effect of treatment is assessed by modelling the proportion of people within a defined **health state.** The three heath states are **progression free disease** (people whose disease has not become worse on treatment), **progressed disease** (people whose disease has become worse on treatment), and **death** (arising due to CLL or another cause).

The aim of the model is to sum the total costs and quality of life increases over a person's lifetime whilst on pirtobrutinib and compare this to currently available treatment options. If pirtobrutinib is deemed **cost-effective** then it is considered a beneficial use of NHS resources, to be recommended for patient access.

Modelling how much a treatment extends life

The model extrapolates results taken from the trial over the period of a person's lifetime to predict the total life extending benefits of the therapy. The main **outcomes** used in the model are progression free survival, overall survival, and side effects experienced on treatment.

The model concludes that pirtobrutinib helps people to sustain progression free disease for a longer time period compared to other treatment options.

Modelling how much a treatment improves quality of life

People who partook in the BRUIN CLL-321 trial were asked about their quality of life at the start of the trial, whilst they were on treatment, and shortly after stopping treatment. Their responses were collected using questionnaires including the **EQ-5D** and the **EORTC-QLQ-C30** questionnaires. The data gathered from these questionnaires were used to model HRQoL in the economic analyses discussed further in **Section 3 of the Company's submission**. Further inputs on patient HRQoL were also sourced from the literature, in the absence of relevant data from BRUIN CLL-321.

Modelling how the costs of treatment differ with the new treatment

Various costs are included in the model for the different treatments that were analysed. These costs include:

- The cost to purchase the medicine itself and how much it costs to administer the medicine (e.g., healthcare professional time dedicated to injections in clinic)
- The costs of clinician time, covering both initial consultation on treatment initiation and subsequent check-ups

- The costs of healthcare resource use including any laboratory investigations or patient examinations
- The costs to provide end-of-life care for patients who succumb to their disease while on treatment

Model results suggest that treatment with pirtobrutinib may be more costly than comparator therapies over a patient's lifetime, however this is balanced by the increased survival and quality of life provided by pirtobrutinib. Moreover, pirtobrutinib may be the cheaper medicine to administer, compared to IdelaR, as it associated with lower administration fees owing to its fully oral method of administration, and the decreased healthcare resource usage associated with pirtobrutinib. Further details on these costs are discussed in **Section 3 of the Company's submission.**

Uncertainty

Extrapolating clinical trial data beyond observed periods inherently introduces uncertainty into model results. When data uncertainty exists within the model, assumptions are made and varied to assess their impact on outcomes. Predicted outcomes are validated by clinical experts or through comparison with other clinical trials whenever possible, ensuring they align with expected clinical reality.

Results of the economic analysis

All of these considerations affect whether pirtobrutinib represents good value for money and a good use of NHS resources. The cost effectiveness results of the economic analysis are presented in **Section 3 of the Company's submission.**

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Pirtobrutinib is an innovative treatment which would represent an important advancement in the treatment of CLL

More than 50% of people living with CLL discontinue covalent BTKi therapy due to progression or intolerance.[67] With covalent BTKi becoming the standard of care in both the first-line and relapsed/refractory setting, **treatment resistance** and contraindications are concerns, particularly for those with 'high-risk' CLL.[33]

Pirtobrutinib is the first-and-only reversible BTKi that re-establishes BTK inhibition even when covalent BTKi are no longer an option. This is vital as the development of resistance or intolerance to existing therapies is a concern. BTKi resistance is caused by mutations in the BTK protein, which prevent covalent BTKi from binding to the site.[68] Pirtobrutinib as a non-covalent BTKi, is able to bind to both **wild-type** (unchanged versions on the BTKi proteins) and mutated BTK proteins.[69]

Pirtobrutinib provides an efficacious new treatment with an improved safety profile, for people with relapsed or refractory disease, who have tried at least one BTKi or both BTKi and BCL2i, and to those who cannot tolerate current therapeutic options. Non-covalent BTKi, such as pirtobrutinib, are crucial for overcoming resistance mediated by BTK mutation at C481, offering these people an additional treatment option.[68]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

There are no equality issues associated with CLL and pirtobrutinib treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on CLL:

- What is chronic lymphocytic leukaemia? https://www.nhs.uk/conditions/chronic-lymphocytic-leukaemia/
- Small lymphocytic lymphoma: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/non-hodgkin/types/small-lymphocytic
- Chronic lymphocytic leukaemia: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll

Further information on the BRUIN CLL-321 trial:

- https://clinicaltrials.gov/study/NCT04666038
- https://pmc.ncbi.nlm.nih.gov/articles/PMC9429640/
- https://ash.confex.com/ash/2024/webprogram/Paper198147.html
- JP Sharman et al. (2025) Manuscript submitted for publication

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

The glossary explains terms that are in **bold** within this document. In some instances, an explanation for a term might mean you need to read other terms to understand the meaning of the original term.

- **Advanced** – Advanced is used to describe cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to other parts of the body.

- **Anaemia** – A condition where the blood doesn't have enough health red blood cells to carry oxygen around the body, which can cause tiredness, weakness and paleness.

- **Arthralgia** – This is the medical term for joint pain, which can cause discomfort or ache in one or more joints.

- **Atrial fibrillation/atrial flutter** – This is a condition where the heart beats irregularly or very quickly, which can cause feelings of fluttering in the chest, shortness of breath, or dizziness.

- **B cells** - A type of white blood cell in the immune system that help to fight infections. Also called B-lymphocytes.

- **B-cell lymphoma 2 inhibitor (BCL2i)** – These are a type of targeted therapy that block a protein called BCL-2 which allows cancer cells to survive and continue to multiply.

- **Bone marrow** – This is a soft, spongy tissue inside most bones where blood cells (red blood cells, white blood cells and platelets) are made.

- **Bruton's tyrosine kinase inhibitor (BTKi)** – These are a type of targeted therapy that block a protein called BTK, which helps cancer cells to survive and continue to multiply.

- **Cancer** – A disease where abnormal cells in the body grow uncontrollably, which can form tumours and spread to other parts of the body.

- **CD5+ B lymphocytes** – These are a subset of B cells that express the CD5 protein on their surface. They are involved in the immune response and can be associated with certain types of blood cancers like CLL.

- **Chemotherapy** – A type of cancer therapy that uses drugs to kill cancer cells.

- **Chemoimmunotherapy (CIT)** – Chemotherapy in combination with immunotherapy.

- **Circulating tumour DNA** – This is tiny pieces of genetic material (DNA) from cancer cells that are found in the blood. Testing for this can help find and monitor cancer.

- **Clinical trial** – A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.

- **Comorbidities** – This is when more than one illness or disease is present in one person at the same time.

- **Comparator** – The standard (for example, another medicine or usual care) against which a medicine is compared in a study. The comparator can be no intervention (for example, best supportive care).

- **Conjunctival haemorrhage** – This is bleeding underneath the clear tissue (conjunctiva) that covers the white part of the eye, causing it to look red or bloodshot.

- **Contraindications** – These are specific reasons or conditions that make it unsafe or inappropriate to use a particular medicine or treatment.

- **Contusion** – A contusion is a bruise, which is bleeding under the skin caused by a bump or injury, resulting in discolouration and swelling.

- **Cost-effective** – This means that a treatment provides good results or benefits relative to the money spent, making it a good use of resources.

- **Covalent** – This refers to a type of chemical bond where atoms share electrons to form a strong connection, holding molecules together.

- **Creatinine clearance** – This is a test that measures how well kidneys are working by estimating how quickly they can clear a waste called creatinine from the blood.

- **Cumulative illness rating** – This is a way to measure how many and how severe other health problems or illnesses a person has, which can affect their overall health and how they respond to treatment.

- **Cycles** – Many cancer treatments are given in cycles. Each cycle is often divided into a period where you receive a treatment, followed by a period of rest from treatment to allow your body to recover from any side effects. The length of each cycle and the split between treatment and rest periods depend on the type of cancer you have, where it is in your body, if it has spread and where to.

- **Cytotoxic** – This refers to substances or cells that are capable of killing or damaging other cells, often used as drugs to destroy cancer cells.

- **Disease stage/stage of the disease** – This refers to how advanced or widespread a disease, like cancer, is in the body, helping doctors decide on the best treatment and predict outcomes.

- **Diarrhoea** – This is frequent, water, or loose bowel movements, which can cause dehydration and discomfort.

- **Efficacy** – The ability of a medicine to produce a desired positive effect on your disease or illness in a clinical trial.

- **Epistaxis** – This is the medical term for a nosebleed, which occurs when blood flows from the inside of the nose due to broken blood vessels.

- **EQ-5D-5L** – This is a questionnaire that helps measure a person's overall health and quality of life by asking about different areas like mobility, self-care, usual activities, pain and anxiety.

- **EORTC QLQ-C30** – This is a questionnaire used to assess the quality of life of cancer patients, covering areas like physical, emotional, and social functioning, as well as symptoms of overall health.

- **Fatigue** – This is when you feel very tired, exhausted and lacking energy. It can be a symptom of the cancer or a side effect of treatment.

- **First-line** – This is the first treatment given for your disease or illness.

- **Fludarabine** – This is a chemotherapy drug used to treat certain blood cancers, including CLL, by helping to kill or stop the growth of cancer cells.

- **Genetic mutations** – Our genes pick up mistakes that happen when cells divide. These mistakes are called genetic mutations or mutations. It is usual for cells to repair faults in their genes or for the faults to be removed by the body. Cancer happens when cells with genetic mutations are not repaired or removed from the body and instead multiply out of control.

- **Haematoma** – This is a collection of blood outside the blood vessels, usually caused by injury, leading to a swollen, tender, and sometimes discoloured area under the skin.

- **Haematuria** – This is the medical term for blood in the urine.

- **Haemoglobin** – This is a protein in red blood cells that carries oxygen from the lungs to tissues around the body and helps remove carbon dioxide.

- **Haemorrhage** – This refers to severe bleeding, which can occur internally or externally and may require medical attention to stop the bleeding and prevent complications.

- **Health-related quality of life** – This is a measure of how well a person functions in daily life and feels physically, emotionally, and socially, especially in relation to their health and wellbeing.

- **Health state** – A description of someone's health.

- **Health economic model** – A way to predict the cost and effects of a technology over time or in patient groups not covered in a clinical trial.

- **High-risk** – This refers to patients who have factors such as genetic mutations or advanced disease stages that are associated with a lower likelihood of longer survival compared to lower-risk patients.

- **Hospitalisation** – This is when a person stays in a hospital overnight for a period of time to receive medical care or treatment.

- **Ibrutinib** – This is a targeted medication used to treat certain types of blood cancers, like CLL, by blocking specific proteins that help cancer cells grow.

- **Immunotherapy** – A type of cancer therapy that uses the body's own immune system to fight cancer.
- **Intravenously** - This is when you are given medicine through an injection or drip (see 'intravenous drip') into one of your veins.
- **Lymph nodes** – These are small organs that are part of the immune system and help fight infections and filter harmful substances from the body.
- **Lymphocytosis** – This is a condition where there are an increased number of lymphocytes, a type of white blood cell, in the blood.
- **Marketing authorisation** – The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
- **Median** – A term used to describe the middle value in a set of measurements.
- **Nausea** – Sickness in the stomach with an urge to vomit.
- **Neutropenia** – A condition in which there is a lower-than-normal number of neutrophils in the blood.
- **Non-covalent** – This is a type of chemical bond or interaction that do not involve sharing electrons, which are generally weaker than covalent bonds.
- **Oedema peripheral** – This is swelling in the limbs or other parts of the body caused by fluid build-up.
- **Outcomes** – This refers to the results or effects of different treatments, interventions, or decisions, often measured in terms of costs, benefits, or health benefits to help inform decision making.
- **Patient preference information** – This refers to the insights and values of patients regarding different treatment options, helping healthcare providers make decisions that align with what patients value most.
- **Patient-reported outcomes** – Measures of a person's quality of life.
- **Petechiae** – These are small, pinpoint spots of bleeding under the skin, often caused by broken blood vessels, and can look like tiny red or purple dots.
- **Phase 3 trial** – This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects.
- **Platelet count** – This is a blood test that measures the number of platelets, which are tiny, disc-shaped cells that are found in the blood and spleen that help form blood clots to slow or stop bleeding and help wounds heal.
- **Pneumonia** – A severe inflammation of the lungs that can reduce the amount of oxygen that blood can be absorbed from air.

- **Progressed disease** – This refers to a cancer or illness that has worsened or spread to new areas, meaning it has advanced despite previous treatment.

- **Progression free disease** – This means that the cancer or illness has not grown or spread further during a specific period of time.

- **Quality of life** – The overall enjoyment of life. Many clinical trials assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.

- **Randomised** – Patients are randomly allocated to one treatment group in a clinical trial.

- **Red blood cells** – A type of blood cell that is made in the bone marrow and found in the blood. It has a range of functions in the body, including the transport of oxygen.

- **Relapsed or refractory disease** – This is when a cancer has returned after treatment (relapsed) or doesn't respond to treatment (refractory), making it more challenging to treat.

- **Richter's transformation** – This is a rare condition where CLL changes into a more aggressive type of lymphoma, usually diffuse large B-cell lymphoma, which progresses more quickly and requires different treatment.

- **Screening** – This is checking to see if someone shows signs or symptoms of disease, in order to inform treatment decisions.

- **Side effects** – These are unwanted or unexpected problems, symptoms or reactions that can occur when taking a medicine or undergoing treatment.

- **Small cell lymphoma** – This is a type of cancer that begins in the lymph nodes and involves a small, abnormal growth of lymphocytes, which are a type of white blood cell.

- **Spleen** – An organ behind the rib cage that helps filter blood and helps fight infection.

- **Stabilisation** – This is when a disease or condition stops getting worse and remains kept under control, without further progression or decline.

- **Standard of care** – The typical treatment that is widely accepted and used by medical professionals for a certain condition. It represents the best-known method to treat a disease based on current evidence and practice.

- **Subcutaneously** – This means injecting or delivering medication into the tissue just under the skin using a short needle.

- **Symptomatic** – Symptomatic disease is where a patient experiences symptoms or signs of the disease or condition.

- **Targeted therapies** – Treatments that directly target parts of the cancer cell.

- **The Binet stage** – This is a system used to classify the severity of CLL based on the number of affected lymphoid tissue groups and the presence of anaemia or low platelet counts, helping to guide treatment decisions.
- **Thrombocytopenia** – This is a condition where the number of platelets in the blood is lower than normal, which can increase the risk of bleeding or bruising.
- **Treatment resistance** – This is when a disease, such as cancer, no longer responds to the treatments that were previously effective.
- **Tumour lysis syndrome** - A side effect of some treatments. Tumour lysis syndrome happens when lots of cancer cells are destroyed very quickly. As cancer cells break down, they release a chemical called uric acid, which is removed from the body by the kidneys. When cancer cells get destroyed very quickly, the kidneys cannot cope with the high levels of uric acid. This can cause serious problems affecting the kidneys and the heart.
- **White blood cells** – These are cells in the body that fight disease and infection by attacking and killing germs.
- **Wild-type** – This is the normal version of a gene, without any mutations.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Mukkamalla SKR, Taneja A, Malipeddi D, et al. Chronic Lymphocytic Leukemia. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC., 2025.
2. Lymphoma Action. Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL). Available at: https://lymphoma-action.org.uk/types-lymphoma/chronic-lymphocytic-leukaemia-cll-and-small-lymphocytic-lymphoma-sll [Accessed: 01 February 2025].
3. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56.
4. Oscier D, Dearden C, Erem E, et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. British journal of haematology 2012;159.
5. Binet J, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.
6. Cancer Research UK. Symptoms of chronic lymphocytic leukaemia. Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/symptoms [Accessed: 01 February 2025].

7. Byrd JC, Stilgenbauer S, Flinn IW. Chronic lymphocytic leukemia. ASH Education Program Book 2004;2004:163-183.

8. Leukaemia UK. Chronic lymphocytic leukaemia. Available at: https://www.leukaemiauk.org.uk/about-leukaemia/types-of-leukaemia/chronic-lymphocytic-leukaemia-cll/ [Accessed: 01 February 2025].

9. Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. The European Journal of Health Economics 2013;14:749-759.

10. National Cancer Institute (NCI). Surveillance, Epidemiology, and End Results Program (SEER). Cancer Stat Facts: Leukemia — Chronic Lymphocytic Leukemia (CLL). Available at: https://seer.cancer.gov/statfacts/html/clyl.html [Accessed: 01 June 2025], 2025.

11. National Cancer Institute (NCI). Surveillance, Epidemiology, and End Results Program (SEER). Cancer Statistics Explorer Network. Available at: https://seer.cancer.gov/statistics-network/explorer/application.html [Accessed: 01 June 2025], 2025.

12. Yang S, Varghese AM, Sood N, et al. Ethnic and geographic diversity of chronic lymphocytic leukaemia. Leukemia 2021;35:433-439.

13. Karakosta M, Delicha EM, Kouraklis G, et al. Association of various risk factors with chronic lymphocytic leukemia and its cytogenetic characteristics. Arch Environ Occup Health 2016;71:317-329.

14. Shadman M. Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Review. Jama 2023;329:918-932.

15. Leukaemia Care. Left to #WatchWaitWorry Available at: https://www.leukaemiacare.org.uk/our-campaigns/watch-wait-worry/ [Accessed: 01 February 2025].

16. Buzaglo JS, Miller MF, Zaleta AK, et al. Chronic lymphocytic leukemia patient reported outcomes and quality of life: findings from the cancer experience registry. Blood 2017;130:2122.

17. National Institute for Health and Care Excellence. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. [TA663]. Available at: https://www.nice.org.uk/guidance/ta663. [Accessed: 01 February 2025].

18. Morrison EJ, Flynn JM, Jones J, et al. Individual differences in physical symptom burden and psychological responses in individuals with chronic lymphocytic leukemia. Ann Hematol 2016;95:1989-1997.

19. National Institute for Health and Care Excellence. Acalabrutinib for treating chronic lymphocytic leukaemia. [TA689] Available at: https://www.nice.org.uk/guidance/ta689 [Accessed: February 2025].

20. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. British journal of haematology 2007;139:255-264.

21. Else M, Cocks K, Crofts S, et al. Quality of life in chronic lymphocytic leukemia: 5-year results from the multicenter randomized LRF CLL4 trial. Leukemia & lymphoma 2012;53:1289-1298.

22. Li H, Lian Q, Wang P, et al. Assessment of Quality of Life in Chinese Patients with Chronic Lymphocytic Leukemia. Blood 2021;138:5028-5028.

23. National Institute for Health and Care Excellence. Zanubrutinib for treating chronic lymphocytic leukaemia. [TA931] Available at: https://www.nice.org.uk/guidance/ta931 [Accessed: 01 February 2025].

24. Youron P, Singh C, Jindal N, et al. Quality of life in patients of chronic lymphocytic leukemia using the EORTC QLQ-C30 and QLQ-CLL17 questionnaire. European journal of haematology 2020;105:755-762.

25. Perkins JG, Flynn JM, Howard RS, et al. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma. Cancer 2002;94:2033-2039.

26. Williams AM, Baran AM, Meacham PJ, et al. Analysis of the risk of infection in patients with chronic lymphocytic leukemia in the era of novel therapies. Leukemia & Lymphoma 2018;59:625-632.

27. Leukaemia & Lymphoma Society. Complications of CLL or CLL Treatment. Available at: https://www.lls.org/leukemia/chronic-lymphocytic-leukemia/treatment/complications-cll-or-cll-treatment [Accessed: 10 June 2025].

28. Thurmes P, Call T, Slager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leukemia & lymphoma 2008;49:49-56.

29. Network THMR. Survival. Chronic lymphocytic Leukaemia. Available at: https://hmrn.org/statistics/survival [Accessed: February 2025].

30. The Haematological Malignancy Research Network. Survival. Chronic lymphocytic Leukaemia. Available at: https://hmrn.org/statistics/survival [Accessed: 01 February 2025].

31. Chronic Lymphocytic Leukaemia Ireland (CLLI). Staging CLL. Available at: https://clli.ie/treatment/staging-cll/ [Accessed: June 2025], 2025.

32. Walewska R, Parry-Jones N, Eyre TA, et al. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology 2022;197:544-557.

33. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.

34. Macmillan Cancer Support. Target therapy for chronic lymphocytic leuakemia (CLL). Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/targeted-therapies-for-cll. [Accessed: 01 March 2025].

35. Macmillan Cancer Support. Chemotherapy for chronic lymphocytic leukaemia (CLL). Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/chemotherapy-for-cll. [Accessed: 01 March 2025].

36. Cancer Research UK. What is immunotherapy? Available at: https://www.cancerresearchuk.org/about-cancer/treatment/targeted-cancer-drugs-immunotherapy/what-is-immunotherapy. [Accessed: 01 March 2025].

37. Macmillan Cancer Support. Immunotherapy. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatment/types-of-treatment/immunotherapy. [Accessed: 01 March 2025].

38. Cancer Research Institute. Immunotherapy Side Effects. Available at: https://www.cancerresearch.org/immunotherapy-side-effects [Accessed: 01 March 2025].

39. Leukaemia Care. Treatments for CLL. Available at: https://www.leukaemiacare.org.uk/support-and-information/information-about-blood-cancer/blood-cancer-information/leukaemia/chronic-lymphocytic-leukaemia/treatments-for-cll/. [Accessed: 01 March 2025].

40. Eichhorst B, Fink A-M, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. The lancet oncology 2016;17:928-942.

41. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164-74.

42. National Institute for Care and Excellence. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. [TA216] Available at: https://www.nice.org.uk/guidance/ta216 [Accessed: February 2025].

43. eviQ. Patient information - Lymphoma - Bendamustine and Rituximab. Available at: https://www.eviq.org.au/haematology-and-bmt/lymphoma/3794-lymphoma-bendamustine-and-rituximab/patient-information#:~:text=pain%2C%20stinging%2C%20swelling%20or%20redness,any%20way%20(allergic%20reaction). [Accessed: 01 April 2025].

44. National Institute for Care and Excellence. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia. [TA343] Available at: https://www.nice.org.uk/guidance/ta343 [Accessed: 01 February 2025].

45. Electronic Medicines Consortium. Gazyvaro (obinutuzumab). SmPC. Available at: https://www.medicines.org.uk/emc/product/3279/smpc/print [Accessed: 01 February 2025].

46. Electronic Medicines Consortium. Imbruvica (ibrutinib) Available at: https://www.medicines.org.uk/emc/product/10041/smpc/print [Accessed: 01 February 2025].

47. Medicines E, Compendium. Calquence (Acalabrutinib) SmPC. Available at: https://www.medicines.org.uk/emc/product/14853/smpc/print [Accessed: 01 February 2025].

48. Electronic Medicines Consortium. Brukinsa (zanubrutinib) Available at: https://www.medicines.org.uk/emc/product/14001/smpc/print [Accessed: 01 February 2025].

49. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia. [TA796] Available at: https://www.nice.org.uk/guidance/ta796 [Accessed: 01 February 2025].

50. National Institute for Health and Care Excellence. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia. [TA891] Available at: https://www.nice.org.uk/guidance/ta891 [Accessed: 01 February 2025].

51. Electronic Medicines Consortium. Venclyxto (venetoclax) Available at: https://www.medicines.org.uk/emc/product/2267/smpc/print [Accessed: 01 February 2025].

52. National Institute for Health and Care Excellence. Idelalisib for treating chronic lymphocytic leukaemia. [ID359] Available at: https://www.nice.org.uk/guidance/ta359 [Accessed: 01 February 2025].

53. Electronic Medicines Consortium. Zydelig (Idelalisib) SmPC. Available at: https://www.medicines.org.uk/emc/product/3330/smpc/print. [Accessed: February 2025].

54. Electronic Medicines Consortium. MabThera (rituximab) SmPC. Available at: https://www.medicines.org.uk/emc/product/3801/smpc/print [Accessed: 01 February 2025].

55. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. [TA561] Available at: https://www.nice.org.uk/guidance/ta561 [Accessed: 01 February 2025].

56. Lymphoma Action. Lymphoma Coalition Global Patient Survey 2024. Available at: https://lymphoma-action.org.uk/lymphoma-coalition-global-patient-survey-2024. [Accessed: March 2025].

57. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 2021;397:892-901.

58. De SK. Pirtobrutinib: First Non-covalent Tyrosine Kinase Inhibitor for Treating Relapsed or Refractory Mantle Cell Lymphoma in Adults. Curr Med Chem 2024;31:4757-4762.

59. European Medicines Agency. Jaypirca. SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/jaypirca-epar-product-information_en.pdf [Accessed: May 2025].

60. CLL Society. Patient Preferences for Fixed vs Continuous Therapies in CLL. Available at: https://cllsociety.org/2024/07/patient-preferences-for-fixed-vs-continuous-therapies-in-cll/. [Accessed: 01 April 2025].

61. ClinicalTrials.gov. Study of LOXO-305 Versus Investigator's Choice (IdelaR or BR) in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) (BRUIN CLL-321). Available at: https://clinicaltrials.gov/study/NCT04666038 [Accessed: 01 February 2025].

62. Eli Lilly and Company. Data on File. BRUIN CLL-321 CSR.

63. Sharman JP, Munir T, Grosicki S, et al. Phase III Trial of Pirtobrutinib Versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor–Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321). Journal of Clinical Oncology 2025:JCO-25-00166.

64. European Hematology Association (EHA). PATIENT REPORTED OUTCOMES FROM BRUIN CLL-321: A RANDOMIZED PHASE 3 TRIAL COMPARING PIRTOBRUTINIB TO IDELALISIB/RITUXIMAB OR BENDAMUSTINE/RITUXIMAB IN COVALENT BTKI PRETREATED CLL/SLL. Available at:

https://library.ehaweb.org/eha/2025/eha2025-congress/4161356/paolo.ghia.patient.reported.outcomes.from.bruin.cll-321.a.randomized.phase.3.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dpirtobrutinib. [Accessed: 13 June 2025].

65. Medical News Today. Jaypirca side effects: What you should know. Available at: https://www.medicalnewstoday.com/articles/drugs-jaypirca-side-effects. [Accessed: 01 March 2025].

66. University of Pennsylvania. Pirtobrutinib (Jaypirca). Available at: https://www.oncolink.org/print/pdf/27679?print_27337_pirtobrutinib_jaypirca.pdf. [Accessed: 01 March 2025].

67. Smolewski P, Robak T. Current treatment of refractory/relapsed chronic lymphocytic leukemia: a focus on novel drugs. Acta Haematologica 2021;144:365-379.

68. Woyach JA, Furman RR, Liu T-M, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. New England Journal of Medicine 2014;370:2286-2294.

69. Roeker LE. A fresh look at covalent BTK inhibitor resistance. Blood 2024;144:1029-1031.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID6269 pirtobrutinib EAG Clarification Response [CON].docx	1.1	No	04 August 2025

Section A: Clarification on effectiveness data

Population

A1. Priority question. Two intended positions of pirtobrutinib in NHS clinical practice are currently described in the company submission (CS):

- **"pirtobrutinib is positioned in this submission as a treatment for patients with [chronic lymphocytic leukaemia] CLL who have previously had at least one [Bruton tyrosine kinase inhibitor] BTKi" (CS, Table 1)**
- **"pirtobrutinib is positioned after patients relapse or become refractory to covalent BTKi therapy." (CS, Section 1.3.3.3)**

Please clarify the intended position of pirtobrutinib in NHS clinical practice.

Lilly apologise for any confusion caused due to the differences in the wording of the positioning in the Company submission (CS) as highlighted above. As noted in the main CS, pirtobrutinib is anticipated to receive marketing authorisation in the United Kingdom (UK) as a treatment for adult patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi). The treatment position for pirtobrutinib in the clinical care pathway in England is anticipated to reflect the full marketing authorisation above i.e., for adult patients with R/R CLL who have been previously treated with a BTKi.

It is noted that this position wording is aligned with that presented in the "Population" row of CS Table 1, under the column "Decision problem addressed in the company submission", wherein it is further noted that the submission addresses the full marketing authorisation through three sub-populations; the necessity for these sub-populations are detailed further in the main CS but – in brief – were due to variations in relevant comparators and available direct and indirect evidence within the sub-populations:

- Adults with CLL who have previously been treated with a covalent BTKi (cBTKi) i.e., a post-cBTKi population, but can receive current standard of care (SoC)
- Adults with CLL who have previously been treated with a cBTKi but are currently unsuitable for a BCL2i or another cBTKi, i.e., a post-cBTKi population, but cannot receive current SoC
- Adults with CLL who have previously been exposed to a cBTKi *and* BCL2i (either sequentially or in combination) i.e., the dual-exposed population

Lilly confirm that the wording within the first bullet highlighted in Question A1 should have been reported as follows, in line the anticipated licence wording for pirtobrutinib in the UK:

- "…pirtobrutinib is positioned in this submission as a treatment for **adult** patients with **R/R** CLL who have **been** previously **treated with a** BTKi…"

This positioning is also in line with the inclusion criteria for the pivotal Phase III BRUIN CLL-321 clinical trial, which included a requirement for patients to have undergone prior treatment with a cBTKi (CS, Table 14). In contrast, there was no requirement for patients to be refractory to cBTKi treatment specifically for inclusion in BRUIN CLL-321. This is evidenced by the small minority of patients who did not report relapse or refractoriness to at least one previous cBTKi at BRUIN CLL-321 baseline (11.8% and 9.2% of patients in Arms A and B of BRUIN CLL-321, respectively; CS, Table 17). It should be noted that this population of patients i.e., those who have been previously treated with a BTKi and who are in the R/R stage of CLL but are not refractory to cBTKi, are addressed within the "post-cBTKi population, but can receive current SoC" sub-population in the submission, and therefore Lilly consider the wording highlighted in the second statement to be a typographical error within the CS. The correct position wording should have been noted in the CS as follows:

- "…pirtobrutinib is positioned after patients **have been previously treated with a** covalent BTKi therapy…"

To conclude, neither of the statements highlighted in Question A1 fully reflected the true anticipated positioning of pirtobrutinib in the UK clinical care pathway. Rather, pirtobrutinib is positioned as a treatment for adult patients with R/R CLL who have been previously treated with a BTKi. This represents the full anticipated marketing authorisation for pirtobrutinib in the UK.

Comparators

A2. Priority question. Please describe BSC for patients with R/R CLL who have previously been treated with one or more BTKis.

In general practice, best supportive care (BSC) encompasses the range of supportive treatments that aim to alleviate patient symptoms and improve quality of life but does not actively treat the underlying cause of a disease. Within the context of CLL more broadly, supportive treatments may include those given for the treatment of infections, treatments to manage anaemia or thrombocytopenia, pain relief medications or treatments for autoimmune conditions.[1] Ultimately, BSC focuses on managing complications arising from disease or its treatment, thereby improving patient quality of life without directly treating the disease itself.

However, despite the above, there are no standard definitions of BSC for patients with R/R CLL in UK clinical practice, including for those patients who have previously received one or more BTKi. This is evidenced by the lack of discussion and emphasis of BSC within more recent guidelines, such as the 2022 British Society for Haematology (BSH) clinical guidelines as well as the interim 2024 update to the European Society for Medical Oncology guidelines for CLL.[2, 3] Older guidelines such the 2018 BSH clinical guidelines also do not offer a standardised definition of BSC for patients with R/R, highlighting instead the need for a patient-specific approach to supportive care, considering the individual's history of previous therapies and existing co-morbidities.[4]

UK clinical experts, who were approached for comment alongside this response, highlighted the challenges in defining BSC in the R/R post-cBTKi population. In line with the discussion above, experts noted that BSC included blood and platelet transfusions, antibiotics and palliation in hospital or the community. This supports a definition of BSC as non-anticancer treatments used in conjunction with active treatment for the purpose of alleviating complications of the active treatment i.e., as a concomitant medication or as a last resort in the clinical pathway without an

active treatment as a supportive palliative measure only. However, clinical experts were unable to define standard regimens of BSC, noting that it is highly individualised to the patient. The clinical experts also noted that no standard approach exists for when a patient is deemed to be for palliation. It was also considered unlikely that patients would receive BSC as the sole therapy in R/R CLL due to the availability of a range of efficacious active treatments in the UK clinical care pathway.

Therefore, in the absence of any well-defined descriptions for BSC in UK clinical guidelines or clinical practice for patients with R/R CLL who have previously been treated with a BTKi, Lilly is unable to present a standard description of BSC or define a standard approach for the target indication for this submission within this response.

A3. Priority question. Please provide clinical effectiveness evidence for the comparison of pirtobrutinib versus best supportive care (BSC) for patients with relapsed/refractory (R/R) CLL who have previously been treated with one or more BTKis.

As noted in the response to Question A2, Lilly maintain that BSC cannot be accurately defined for patients with R/R CLL who have been previously treated with a BTKi. This position is supported by UK clinical experts, who noted that BSC broadly encompass any concomitant or palliative care offered to patients with R/R CLL.

It is important to note that this description of BSC generally aligns with the use of concomitant therapy in BRUIN CLL-321 (Eli Lilly, Data on File, BRUIN CLL-321 CSR), and therefore does not represent an active anti-cancer intervention. Rather the relevant comparators to pirtobrutinib in patients with R/R CLL who have been previously treated with a BTKi include the active treatment regimens of idelalisib with rituximab (IdelaR), as discussed in Table 1 of the main CS. This is also in line with precedence from the technology appraisal (TA) of VenR for previously treated CLL (TA561), wherein the Company noted that BSC was not an appropriate comparator when there are treatment options for which efficacy has been demonstrated that are being used in UK clinical practice.[5] This description of BSC is consistent with the clinical expert opinion elicited for comment along with the response provided to Question A2.

Given the above, Lilly do not consider BSC to represent a relevant comparator to pirtobrutinib in the target indication and therefore Lilly do not believe it to be appropriate to include clinical effectiveness evidence for pirtobrutinib versus BSC in the target indication.

However, it is important to note that clinical effectiveness comparisons for pirtobrutinib against BSC in patients with R/R CLL who have been previously treated with a BTKi are not possible. As per the systematic literature review (SLR) conducted for this submission (CS Section 2.1; detailed further in Appendix B), there were no head-to-head clinical effectiveness studies identified that compared treatment with pirtobrutinib against BSC – or placebo as a proxy for BSC – in patients with R/R CLL. Neither were any studies identified comparing BSC or placebo against other anti-cancer therapies in patients with R/R CLL who have been previously treated with a BTKi. Therefore, neither direct nor indirect treatment comparisons (ITC) to estimate the comparative effectiveness of pirtobrutinib versus BSC are considered feasible in the target indication.

Section B: Clarification on cost-effectiveness data

Additional cost effectiveness analyses

B1. Priority question. The following question relates to people with R/R CLL which has previously been treated with a BTKi and that is B-cell lymphoma 2 inhibitor (BCL2i)-naïve. Please generate cost effectiveness results for pirtobrutinib versus the comparators specified below. Please use the progression free survival (PFS), overall survival (OS) and time to discontinuation (TTD) from the pirtobrutinib arm in the BL2Ci-naïve population of the BRUIN CLL-321 trial (August 2024 data cutoff (DCO)) for both pirtobrutinib and:

i. **people treated with venetoclax plus rituximab (VenR)**

ii. **people treated with a covalent (c)BTKi.**

Lilly acknowledge the request from the EAG to generate cost effectiveness results for pirtobrutinib versus venetoclax plus rituximab (VenR) and covalent BTKi (cBTKi) for the group of patients with R/R CLL who are naïve to treatment with B-cell lymphoma 2 inhibitors (BCL2i), using the progression free survival (PFS), overall survival (OS) and time to discontinuation (TTD) data from the pirtobrutinib arm in the BL2Ci-naïve population of the BRUIN CLL-321 trial for both pirtobrutinib and the requested comparators. This request is understood to be akin to a cost-comparison analysis of pirtobrutinib to VenR and cBTKi for patients with R/R CLL who have been previously treated with a BTKi and are also naïve to treatment with a BCL2i.

It is recognised that a comparative analysis is not feasible due to the limited Phase 3 trial data on the efficacy of VenR in post-BTKi populations; the MURANO trial included less than 3% of patients who had received prior BTKi treatment, restricting conclusions regarding its efficacy in this population. This assessment is supported by the comprehensive feasibility analysis detailed in Section 2.10 of the CS, which concludes that there is a lack of RCTs reporting on R/R CLL patients with prior BTKi treatment and those with prior BTKi and BCL2i treatments. As a result, conducting a Network Meta Analysis (NMA) or any other form of indirect treatment comparison in these groups is not feasible.

However, a previously published unanchored MAIC in the peer-reviewed literature aimed to estimate the treatment effect of pirtobrutinib versus venetoclax monotherapy in patients with R/R CLL who had been previously treated with a cBTKi.[6] This analysis, based on Phase 2 data comparing pirtobrutinib to venetoclax monotherapy, found that the efficacy of pirtobrutinib was comparable to that of continuously administered venetoclax monotherapy in patients with R/R CLL previously treated with a cBTKi, with a noted trend towards an overall survival benefit for pirtobrutinib. Additionally, pirtobrutinib was associated with an improved ORR (80% for pirtobrutinib, including PR-L, versus 65% for venetoclax monotherapy; p=0.01) and demonstrated a favourable overall safety profile, with fewer Grade ≥3 TEAEs – such as febrile neutropenia, neutropenia, anaemia, and thrombocytopenia – compared to venetoclax. The study raises important questions regarding the optimal treatment sequencing of pirtobrutinib and

venetoclax in cBTKi-treated CLL; however, the absence of prospective direct comparisons and limited long-term follow-up data preclude definitive conclusions.

Clinical experts consulted during this process also acknowledged that there is insufficient data to define the comparative effectiveness and comparative safety of pirtobrutinib and VenR or cBTKi in the target indications for this submission. When asked about their treatment decision-making in the absence of VenR efficacy data in the post-BTKi population, clinicians indicated that in practice, clinicians would value an alternative option to venetoclax, given that the efficacy of venetoclax is uncertain in this population. Current trials for venetoclax lack applicability to the post-BTKi population,as those data were derived from a BTKi-naïve cohort. Based on this input, along with concerns raised regarding venetoclax toxicity and its increased use of NHS resources, it was concluded that clinicians would be more inclined to use an alternative like pirtobrutinib over venetoclax therapy in this patient population.

A cost-comparison analysis between pirtobrutinib and VenR has been conducted, as requested by the EAG, and is discussed henceforth. However, in contrast to the request to conduct these analyses in a BCL2i-naïve population, this cost-comparison has been conducted for adult patients with R/R CLL who have been previously treated with a BTKi, i.e., the full post-BTKi population, in line with the anticipated marketing authorisation for pirtobrutinib in the UK and the intent-to-treat (ITT) population in BRUIN CLL-321.

The results from the cost-comparison analysis of pirtobrutinib and VenR in patients with R/R CLL who have been previously treated with a BTKi are presented in Table 1 (with pirtobrutinib at list price) and in Table 2 (with pirtobrutinib at Patient Access Scheme [PAS] price).

The analysis is predicated on an assumption of comparable efficacy between pirtobrutinib and VenR. Consequently, VenR survival data incorporated in the model (PFS, OS, and TTD) are derived from the pirtobrutinib arm of the BRUIN-321 study. Separate analyses have been conducted for both ITT (post-BTKi) and dual-exposed cohorts, aligning with the original CS. The analysis considers potential differences in the safety profiles of pirtobrutinib and VenR. Accordingly, the following assumptions were applied:

- Adverse event (AE) incidence rates for VenR are based on data from the MURANO study. In line with the base case, only Grade 3 or higher AEs with >2% incidence have been included
- Six AEs—fatigue, hyperuricemia, hypocalcaemia, leukopenia, lower respiratory tract infection, and upper respiratory tract infection—were not reported at >2% incidence in the BRUIN trial and are therefore considered ‘new’ additions to the model
- Associated costs for each newly added AE have been included

Rituximab administration costs are accounted for within the model for VenR, consistent with the dosing specified in the venetoclax SmPC and as observed in the MURANO study.[7] All other model parameters (e.g., utility values, health state costs) remain consistent with the cost-effectiveness model base case.

Table 1: Deterministic base case results for a lifetime horizon (pirtobrutinib list price; post-BTKi population)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	[redacted]
VenR	[redacted]	

Abbreviations: BTKi: Bruton’s tyrosine kinase inhibitor; VenR: venetoclax and rituximab.

Table 2: Base case results for a lifetime horizon (pirtobrutinib PAS price; post-BTKi population)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	−£16,140
VenR	[redacted]	

Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; PAS: patient access scheme; VenR: venetoclax and rituximab.

Lilly note that there are inherent weaknesses and limitations of the modelling of this analysis. A primary limitation of this analysis is the reliance on comparative efficacy, which remains uncertain due to the inability to perform an ITC versus VenR. Due to time constraints, certain simplifying assumptions were necessary. As such, not all relevant costs are reflected in the current model (e.g., TLS prophylaxis costs, accurate VenR TTD, subsequent therapy distributions). Additionally, the analysis utilises the VenR list price, as the confidential PAS price is not available.

However, in the absence of the efficacy data required for a comprehensive cost-effectiveness analysis of pirtobrutinib compared to VenR, the results from the cost-comparison analysis serve as a useful assessment. Results indicate that pirtobrutinib is comparably cost-efficient relative to VenR and can inform decision-making in scenarios where efficacy data are limited, thereby supporting a more comprehensive assessment of its overall value.

It is important to note that, cost-comparison analyses against cBTKi therapy have not been conducted as cBTKi therapy are not a relevant comparator to pirtobrutinib, as discussed in Table 1 and Section 1.3.3.3 of the CS. UK clinical experts agreed that they would be unlikely to consider cBTKi rechallenge in patients with clear evidence of disease progression as it is a hallmark of the development of cBTKi resistance mutations. For patients previously treated with cBTKi, BSH and ESMO guidelines recommend venetoclax-based therapies as the next line of treatment.[2] Treatment sequencing guidelines published by the BSH also recommend the use of BCL2i following relapse or disease refractory to treatment with cBTKi, should a patient be naïve to BCL2i therapy.

B2. Priority question. The following question relates to the dual-exposed population. Please generate cost effectiveness results for pirtobrutinib versus the comparator specified below, using results in the dual-exposed population of the BRUIN CLL-321 trial (August 2024 DCO) and applying:

a. **the PFS, OS and TTD from the idelalisib plus rituximab (IdelaR) arm for the following:**
   i. **people treated with VenR**
   ii. **people treated with a cBTKi**
   iii. **people treated with BSC.**

b. **the PFS, OS and TTD from the pirtobrutinib arm for the following:**
   i. **people treated with VenR**
   ii. **people treated with a cBTKi.**

As noted by the EAG during the clarification meeting, there is an error in part a) of question B2, as it had been intended to request cost effectiveness results for pirtobrutinib versus the requested comparators using data from the **'Investigator's choice of IdelaR or bendamustine in combination with rituximab (BR)'** arm of BRUIN CLL-321 in alignment with the efficacy results presented in Section 2.6 of the main CS.

Lilly does not believe it is appropriate to generate cost-effectiveness results for pirtobrutinib against the requested comparators using the data for Investigator's choice of IdelaR or BR as a proxy given existing evidence demonstrating that treatment with VenR is more effective than IdelaR and BR. For such a comparison, the analysis would rely on the assumptions that pirtobrutinib is superior to VenR, and that VenR is equivalent to IdelaR and BR. The latter assumption was found not to hold in a MAIC conducted for the NICE submission for VenR for CLL (TA561), where the company compared VenR to IdelaR. The results of the analysis indicated that VenR is superior to IdelaR.[5]

As such, cost effectiveness results generated using data from the Investigator choice arm of BRUIN CLL-321 would likely be biased in favour of pirtobrutinib and may not be conducive to inform decision making. Rather, the more conservative approach of conducting a cost-comparison between pirtobrutinib and VenR, using efficacy data from the pirtobrutinib arm of BRUIN CLL-321 as a proxy for the effectiveness of VenR in the dual-exposed population has been conducted in line with the request in Question B2b), the results for which are presented in Table 3 (with pirtobrutinib at list price) and Table 4 (with pirtobrutinib at PAS price).

It is important to note that, as discussed in the responses to Questions A3 and B1, respectively, BSC and cBTKi are not considered relevant comparators to pirtobrutinib in patients with R/R CLL who have been previously treated with a BTKi. As the dual-exposed population is a sub-set of this overall post-BTKi population (see response to Question A1 and detailed further in Section 1 of the main CS) by extension, BSC and cBTKi are also not considered to be relevant comparators to pirtobrutinib in the dual-exposed population. Cost-comparison analyses for pirtobrutinib against these comparators have therefore not been conducted.

Table 3: Deterministic base case results for a lifetime horizon (pirtobrutinib list price; dual-exposed population)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	[redacted]
VenR	[redacted]	

Abbreviations: VenR: venetoclax and rituximab.

Table 4: Base case results for a lifetime horizon (pirtobrutinib PAS price; dual-exposed population)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	[redacted]
VenR	[redacted]	

Abbreviations: PAS: patient access scheme; VenR: venetoclax and rituximab.

As discussed in the response to Question B1 above, while there are inherent limitations and uncertainties associated with the cost-comparison analysis due to the lack of direct comparative data and the necessary assumptions within the model, this analysis provides valuable insights to inform decision-making despite the inherent uncertainties.

B3. Priority question. As reported in Table 82 of the CS, 33.3% of the post-cBTKi population and 41.7% of the dual-exposed population are modelled to

have pirtobrutinib as a subsequent anti-cancer therapy after progression in the investigator's choice arm. Please provide cost effectiveness analyses (in both the post-cBTKi and dual-exposed populations) that do not include pirtobrutinib as a subsequent treatment using:

- **the company base case assumptions**
- **all scenarios requested by the EAG in questions B1 and B2.**

In line with the EAGs request to remove pirtobrutinib from consideration as a subsequent treatment for patients who progress on treatment with Investigator's choice of IdelaR or BR, Lilly have amended the Company economic model, and the Company base-case has been revised to take this into account. It should be noted that following additional dialogue with UK clinical experts, who highlighted the limited availability of therapies in clinical practice for the post-BTKi R/R CLL population, CAR T-cell treatments (particularly lisocabtagene maraleucel) were also removed as a subsequent treatment option from the model because they are not reimbursed in the UK for patients in the post-cBTKi population.[2, 8] This change has also been incorporated into the revised Company base-case analysis, results for which are discussed in the Appendices below. The subsequent treatment distributions have been reweighted accordingly based on the original trial data, and the assumptions for subsequent anticancer treatment distributions used in the revised Company base-case are presented in Table 17.

Utility values

B4. Priority question. Please provide the baseline average EQ-5D-3L mapped utility values from the BRUIN CLL-321 trial for the:

i. **post-cBTKi population**

ii. **dual-exposed population.**

The descriptive mapped baseline average EQ-5D-3L utility values from the BRUIN CLL-321 trial for the post-cBTKi population and the dual-exposed population are presented in Table 5. Utility weights (EQ-5D-3L index score) were calculated by mapping EQ-5D-5L to -3L using the algorithm published by Hernandez-Alava *et al.* (2023).[9]

The EQ-5D-3L utility values observed in the post-cBTKi population appear to demonstrate face validity. The mean utility score at baseline was [redacted] (standard deviation [SD]: [redacted]), with a median of [redacted]. The range spans from [redacted] to [redacted], which is consistent with expectations for a population with significant disease burden.[10, 11] These values align with those typically seen in advanced hematologic malignancies, suggesting that the data reflect plausible health-related quality of life outcomes and are appropriate for use in further analyses.

Additionally, the utility values observed in the dual-exposed population – patients who have received both covalent and non-covalent BTKi – further support the face validity of the baseline utility estimate. These patients often represent a heavily pretreated and clinically complex subgroup, typically associated with a lower quality of life, as supported by clinical expert

opinion.[10, 11] The alignment between the lower baseline utility in this subgroup and clinical expectations reinforces the credibility of the utility values used.

Table 5: Descriptive baseline average EQ-5D-3L utility values from the BRUIN CLL-321 trial (mapped from EQ-5D-5L)

Characteristic	Post-cBTKi population	Dual-exposed population
EQ-5D-3L utility weight, baseline		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; EQ-5D-3L: EuroQol five dimensions questionnaire, 3-level version; EQ-5D-5L: EuroQol five dimensions questionnaire, 5-level; Max: maximum; Min: minimum; SD: standard deviation.

B5. Priority question. Please provide the average PFS EQ-5D-3L mapped utility values for the dual-exposed population from the BRUIN CLL-321 trial.

The mixed model repeated measures (MMRM) average PFS EQ-5D-3L mapped utility value for the dual-exposed population from the BRUIN CLL-321 trial are presented in Table 6. Utility weights (EQ-5D-3L index score) were calculated by mapping EQ-5D-5L to -3L using the algorithm published by Hernandez-Alava *et al* (2023).[9]

To appropriately account for repeated measures (i.e., the same patients completing the same assessments over time) during PFS, utility weights from the BRUIN CLL-321 trial were analysed using a linear mixed model. Utility weights mapped to the progression-free health state were included as the response variable. Additionally, centred baseline EQ-5D-5L utility scores (calculated as [mean population baseline utility] – [subject baseline utility]) and centred age ([mean population age] – [subject age]) were included as fixed-effect covariates to adjust for differences in baseline utility and age. Repeated measures were modelled using the unique subject identifier from BRUIN CLL-321 as a random effect to account for within-subject correlation across assessments. The model-based average progression-free EQ-5D-3L utility value corresponds to the fixed intercept of this model. A summary of model coefficients is provided in the Appendices.

The MMRM- average PFS EQ-5D-3L mapped utility value for the dual-exposed population appears to demonstrate face validity. The mean utility score of [redacted] (standard error [SE]: [redacted]) was higher than the utility value at baseline, which is consistent with expectations that there would be higher HRQoL in the progression-free state due to the psychological adaptation, optimism or response shift typically associated with a treatment response.[12]

However, for consistency, a single progression-free utility value of 0.814 was applied across both the post-cBTKi and dual-exposed health states, as the post-progression utility value was also the same between the post-cBTKi and dual-exposed health states. This is supported by UK clinical experts noting that patients with R/R CLL in the progression-free state for both the post-cBTKi and dual-exposed populations would have a similar health-related quality of life (HRQoL) to that of the general population. Notably, the average progression-free EQ-5D-3L utility value for the post-BTKi population was also derived from a similar linear mixed model.

Error! Reference source not found.**Table 6: MMRM average progression-free EQ-5D-3L utility value for the dual-exposed population from the BRUIN CLL-321 trial (mapped from EQ-5D-5L)**

Characteristic	Dual-exposed population
PF	
Mean (SE)	[redacted]

Abbreviations: EQ-5D-3L: EuroQol five dimensions questionnaire, 3-level version; EQ-5D-5L: EuroQol five dimensions questionnaire, 5-level version; PF: progression-free; SE: standard errer.

B6. Priority question. In the company model, PFS health state utility values are higher for patients aged 65 years who have had CLL for a mean of over 10 years (0.814) than the mean EQ-5D-3L utility value for people aged 65 in the UK (0.78).[13] Given that, in the CS (CS, Section 1.3.2.1), it is stated that patients with CLL "…*experience substantially worse health-related quality of life… The severity of fatigue is higher in CLL patients compared to published population norms and worsens as the disease progresses*", please comment on the generalisability of BRUIN CLL-321 trial EQ-5D-3L mapped data to the NHS CLL population.

The Company clarifies that while patients with CLL experience worse HRQoL in specific domains such as fatigue and emotional wellbeing, patients with CLL experience overall HRQoL scores that are similar or better than published population norms. This observation is supported by Shanafelt *et al.* (2007) wherein it was found that physical, social/family, functional well-being, and overall QoL scores of patients with CLL were comparable to or exceeded the published population norms.[10] This reflects a well-documented phenomenon in health outcomes research, where cancer patients experiencing a treatment response may report higher HRQoL scores due to psychological adaptation, optimism or response shift.[12] Additionally, the PFS health state utility value of 0.814 used in the model is not dissimilar to the value of 0.804 generated for the general population irrespective of health status (aged 65 to ≤70 years) by Ara and Brazier (2011), which is included in the appraisal for zanubrutinib (TA931).[14, 15] This study is more recent than the Kind *et al.* (1998) study, which is over 25 years old and consequently may not accurately reflect current population norms.[13] Thus, given its more recent publication date and inclusion in an R/R CLL appraisal from 2023, the Ara and Brazier (2011) study may be a more appropriate source of the utility value for the general population.[14, 15]

It is also important to note that, at baseline, the reported mean health state utility values in BRUIN CLL-321 were slightly lower than published population norms for both the post-cBTKi and dual-exposed patient populations ([redacted] and [redacted], respectively; see response to Question B4, Table 5). The modelled PFS health state utility value of 0.814 reflects the positive impact of treatment on patient HRQoL and was applied across both the post-cBTKi and dual-exposed health states for consistency, given that the post-progression utility value was also the same between the post-cBTKi and dual-exposed health states.

The generalisability of the BRUIN CLL-321 EQ-5D-3L mapped data to the NHS CLL population in particular is further supported by comments from UK clinical experts. It was noted that while a utility decrement would be expected for patients who are symptomatic and awaiting treatment for CLL, patients who are in remission following treatment could expect similar HRQoL to the general population.

On this basis, Lilly considers the utility value of 0.814 to be appropriate, as it reflects the disease when it is in remission and is supported by both observational and interventional evidence, and clinical opinion.

Section C: Textual clarification and additional points

Systematic literature review (SLR) methods

C2. Please clarify the dates that the original and updated clinical effectiveness searches were conducted:

- the original SLR date is reported as 26th September 2023 (CS, p44 and CS, Appendix B, p8) and as 27th September 2024 (CS, Appendix B, p14)
- the updated SLR1 search date is reported as 19th February 2025 (CS, p44 and CS, Appendix B, p9) and as 19th February 2019 (CS, Appendix B, p19)

The Company notes that the searches for the original clinical SLR were conducted on 26th September 2023, and on 19th February 2025 for SLR update 1. Deviation from these dates within the CS were made in error.

C3. The original SLR EMBASE search strategy (CS, Appendix B, Table 6, Line 42) was date restricted and only records published after 2021 were identified. However, the original SLR MEDLINE (CS, Appendix B, Table 7) and EBM review (CS, Appendix B, Table 8) search strategies were not date restricted. Please provide the reason for this discrepancy.

Since the EMBASE database (searched on the OvidSP® platform) indexes several congresses, the search retrieved a large volume of conference abstracts. To optimise the search results, a filter was applied to include only those conference abstracts published within the two most recent years. Specifically, the limit set in Line 42 (year 2021) applies only to conference abstracts (identified in Line 41).

Conference abstracts published two years prior to the EMBASE search run date were excluded, based on the assumption that any relevant/pertinent results or studies from these abstracts would likely have been published as full manuscripts by that time.

In addition to database searches, relevant congress websites were also hand searched as part of the grey literature sources, to ensure comprehensive capture of congress disclosures.

C4. For the updated SLR1, the EMBASE (CS, Appendix B, Table 9, Line 38) and MEDLINE (CS, Appendix B, Table 10, Line 38) databases were searched from 1st May 2024 to 19th February 2025, rather than from the end date of the original SLR search (i.e., 26th September 2023). Please clarify the date restrictions for the updated SLR1 and provide an explanation for any discrepancies.

Lilly apologise for any confusion caused due to the discrepancy here. For clarity, the searches for SLR Update 1 were executed in two parts:

- The first search was run on 21st May 2024, covering the period from 26th September 2023 to 21st May 2024
- The second search covered the timeframe from 1st May 2024 through 19th February 2025

The search strategy for the searches conducted on 21st May 2024 were erroneously omitted from Appendix B of the CS. These are presented below in Table 7, Table 8, and Table 9.

Table 7: MEDLINE® Search Terms (21st May 2024)

S.No.	Search Terms	Results
1	lymphoma, non-hodgkin/	36626
2	(chronic lymphocytic leukemia or chronic lymphocytic leukaemia).mp.	23702
3	chronic lymphatic leukemia.mp.	989
4	(chronic lymphocytic or CLL).mp.	28685
5	(small lymphocytic lymphoma or small-lymphocytic lymphoma).mp.	1676
6	small lymphocytic lymphoma.mp.	1676
7	(small lymphocytic or SLL).mp.	2831
8	((chronic or small) adj3 (lymph* or leuk* or NHL)).mp.	83791
9	(chronic lymphocytic leukemia or small lymphocytic lymphoma).mp.	20401
10	or/1-9	120109
11	exp salvage therapy/	16491
12	((salvage adj3 (chemotherap* or treatment* or therap*)) or (resistant adj3 (chemotherap* or treatment resistant))).mp.	46139
13	(second line or 2nd line or 2?nd line or second-line or (second adj4 line)).ti,ab.	34911
14	(third line or third-line or 3?rd line or 3rd line or (third adj4 line)).ti,ab.	7229
15	(refractory or refractor* or relaps* or recurrent or (((previously adj3 treated) or previous*) adj3 treat*) or (drug adj3 resistan*) or pre-treated or pretreated).ti,ab.	946526
16	((failed or failure or discontinue or discontinu* or progress*) and (treatment* or therap* or prior or previous)).mp.	1648708
17	((chemotherap* or treatmen* or regime* or medication* or therap*) adj7 (refractory or recurrent or resistant or rescue or salvage or failed or failure)).mp.	410029
18	or/11-17	2506181
19	10 and 18	27822
20	Bruton Tyrosine Kinase inhibitor.mp.	306
21	exp Agammaglobulinaemia Tyrosine Kinase/	2312
22	(ibrutinib or imbruvica or "cra 032765" or cra032765 or cra-032765 or "pci 32765" or pci32765 or "pci 32765-00" or "pci 32765 00" or pci3276500 or PC-32765 or PC32765 or "PC 32765").mp.	3917
23	(acalabrutinib or "calquence acp 196" or acp196 or acp-196 or Acp-196).mp.	498
24	(zanubrutinib or brukinsa or BGB-3111 or Bgb-3111 or "BGB 3111" or BGB3111).mp.	369
25	(Tirabrutinib or GS-4059 or Gs-4059 or "GS 4059" or GS4059 or ONO-4059 or Ono-4059 or ONO4059 or "ONO 4059").mp.	109
26	(pirtobrutinib or LOXO-305 or "LOXO 305" or Loxo-305 or "Loxo 305" or LY-3527727 or "LY 3527727" or LY3527727 or RXC-005 or RXC005 or "RXC 005").mp.	72
27	(B*cell lymphoma 2 inhibitor or BCL2* or venetoclax or ABT*199 or (venetoclax adj3 therapy) or (venetoclax adj3 regimen)).mp.	46420
28	(Anti*CD20 or rituximab or obinutuzumab or alemtuzumab).mp.	32544

29	(Phosphoinositide 3*kinase inhibitors or PI3Ki or idelalisib or duvelisib).mp.	1011
30	(CAR*T cell therap* or chimeric antigen receptor*T cell therapy).mp.	52
31	or/20-30	83530
32	19 and 31	3756
33	exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or child* or girl? or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.	5130402
34	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.	7596878
35	(nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	1884202
36	or/33-35	13236876
37	32 not 36	1833
38	limit 37 to english language	1761
39	limit 38 to "humans only (removes records about animals)"	1747
40	limit 39 to dt=20230926-20240521	81

Table 8: EMBASE® Search Terms (21st May 2024)

S.No.	Search Terms	Results
1	lymphoma, non-hodgkin/	1033
2	(chronic lymphocytic leukemia or chronic lymphocytic leukaemia).mp.	39869
3	chronic lymphatic leukemia.mp.	51086
4	(chronic lymphocytic or CLL).mp.	50376
5	(small lymphocytic lymphoma or small-lymphocytic lymphoma).mp.	3410
6	small lymphocytic lymphoma.mp.	3410
7	(small lymphocytic or SLL).mp.	5787
8	((chronic or small) adj3 (lymph* or leuk* or NHL)).mp.	152610
9	(chronic lymphocytic leukemia or small lymphocytic lymphoma).mp.	35477
10	or/1-9	159744
11	exp salvage therapy/	41914
12	((salvage adj3 (chemotherap* or treatment* or therap*)) or (resistant adj3 (chemotherap* or treatment resistant))).mp.	77254
13	(second line or 2nd line or 2?nd line or second-line or (second adj4 line)).ti,ab.	66907
14	(third line or third-line or 3?rd line or 3rd line or (third adj4 line)).ti,ab.	15715
15	(refractory or refractor* or relaps* or recurrent or (((previously adj3 treated) or previous*) adj3 treat*) or (drug adj3 resistan*) or pre-treated or pretreated).ti,ab.	1502285
16	((failed or failure or discontinue or discontinu* or progress*) and (treatment* or therap* or prior or previous)).mp.	2923871
17	((chemotherap* or treatmen* or regime* or medication* or therap*) adj7 (refractory or recurrent or resistant or rescue or salvage or failed or failure)).mp.	781330
18	or/11-17	4198820
19	10 and 18	54311
20	Bruton Tyrosine Kinase inhibitor.mp.	3949

21	exp Agammaglobulinaemia Tyrosine Kinase/	4439
22	(ibrutinib or imbruvica or "cra 032765" or cra032765 or cra-032765 or "pci 32765" or pci32765 or "pci 32765-00" or "pci 32765 00" or pci3276500 or PC-32765 or PC32765 or "PC 32765").mp.	13936
23	(acalabrutinib or "calquence acp 196" or acp196 or acp-196 or Acp-196).mp.	2482
24	(zanubrutinib or brukinsa or BGB-3111 or Bgb-3111 or "BGB 3111" or BGB3111).mp.	1446
25	(Tirabrutinib or GS-4059 or Gs-4059 or "GS 4059" or GS4059 or ONO-4059 or Ono-4059 or ONO4059 or "ONO 4059").mp.	386
26	(pirtobrutinib or LOXO-305 or "LOXO 305" or Loxo-305 or "Loxo 305" or LY-3527727 or "LY 3527727" or LY3527727 or RXC-005 or RXC005 or "RXC 005").mp.	381
27	(B*cell lymphoma 2 inhibitor or BCL2* or venetoclax or ABT*199 or (venetoclax adj3 therapy) or (venetoclax adj3 regimen)).mp.	70338
28	(Anti*CD20 or rituximab or obinutuzumab or alemtuzumab).mp.	123331
29	(Phosphoinositide 3*kinase inhibitors or PI3Ki or idelalisib or duvelisib).mp.	4583
30	(CAR*T cell therap* or chimeric antigen receptor*T cell therapy).mp.	264
31	or/20-30	202219
32	19 and 31	13340
33	exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or child* or girl? or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.	5948495
34	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.	5403559
35	(nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	9643987
36	or/33-35	18972593
37	32 not 36	8318
38	limit 37 to english language	8152
39	limit 38 to "humans only (removes records about animals)"	8135
40	limit 39 to dc=20230926-20240521	880

Table 9: EBM Reviews Search Terms (21st May 2024)

S.No.	Search Terms	Results
1	lymphoma, non-hodgkin/	1350
2	(chronic lymphocytic leukemia or chronic lymphocytic leukaemia).mp.	2023
3	chronic lymphatic leukemia.mp.	1076
4	(chronic lymphocytic or CLL).mp.	2453
5	(small lymphocytic lymphoma or small-lymphocytic lymphoma).mp.	361
6	small lymphocytic lymphoma.mp.	361
7	(small lymphocytic or SLL).mp.	531
8	((chronic or small) adj3 (lymph* or leuk* or NHL)).mp.	5407
9	(chronic lymphocytic leukemia or small lymphocytic lymphoma).mp.	1736
10	or/1-9	7017
11	exp salvage therapy/	1022

12	((salvage adj3 (chemotherap* or treatment* or therap*)) or (resistant adj3 (chemotherap* or treatment resistant))).mp.	7831
13	(second line or 2nd line or 2?nd line or second-line or (second adj4 line)).ti,ab.	8216
14	(third line or third-line or 3?rd line or 3rd line or (third adj4 line)).ti,ab.	1515
15	(refractory or refractor* or relaps* or recurrent or (((previously adj3 treated) or previous*) adj3 treat*) or (drug adj3 resistan*) or pre-treated or pretreated).ti,ab.	117466
16	((failed or failure or discontinue or discontinu* or progress*) and (treatment* or therap* or prior or previous)).mp.	264571
17	((chemotherap* or treatmen* or regime* or medication* or therap*) adj7 (refractory or recurrent or resistant or rescue or salvage or failed or failure)).mp.	95644
18	or/11-17	359599
19	10 and 18	4032
20	Bruton Tyrosine Kinase inhibitor.mp.	86
21	exp Agammaglobulinaemia Tyrosine Kinase/	46
22	(ibrutinib or imbruvica or "cra 032765" or cra032765 or cra-032765 or "pci 32765" or pci32765 or "pci 32765-00" or "pci 32765 00" or pci3276500 or PC-32765 or PC32765 or "PC 32765").mp.	867
23	(acalabrutinib or "calquence acp 196" or acp196 or acp-196 or Acp-196).mp.	211
24	(zanubrutinib or brukinsa or BGB-3111 or Bgb-3111 or "BGB 3111" or BGB3111).mp.	145
25	(Tirabrutinib or GS-4059 or Gs-4059 or "GS 4059" or GS4059 or ONO-4059 or Ono-4059 or ONO4059 or "ONO 4059").mp.	35
26	(pirtobrutinib or LOXO-305 or "LOXO 305" or Loxo-305 or "Loxo 305" or LY-3527727 or "LY 3527727" or LY3527727 or RXC-005 or RXC005 or "RXC 005").mp.	42
27	(B*cell lymphoma 2 inhibitor or BCL2* or venetoclax or ABT*199 or (venetoclax adj3 therapy) or (venetoclax adj3 regimen)).mp.	2270
28	(Anti*CD20 or rituximab or obinutuzumab or alemtuzumab).mp.	6441
29	(Phosphoinositide 3*kinase inhibitors or PI3Ki or idelalisib or duvelisib).mp.	335
30	(CAR*T cell therap* or chimeric antigen receptor*T cell therapy).mp.	2
31	or/20-30	9153
32	19 and 31	1455
33	exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or child* or girl? or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.	376474
34	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.	17680
35	(nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	64287
36	or/33-35	445717
37	32 not 36	1326
38	limit 37 to english language [Limit not valid in ACP Journal Club,CCA,CDSR,CLCMR,DARE; records were retained]	1317
39	limit 38 to yr="2023-Current" [Limit not valid in DARE; records were retained]	108
40	remove duplicates from 39	105

BRUIN CLL-321 trial quality assessment

C5. Please explain and provide evidence for each domain of the BRUIN CLL-321 trial Cochrane Risk of Bias assessment (CS, Table 23).

Please refer to Table 10 for the assessment of each bias domain, along with the rationale behind the risk assignment. The overall rating of ‘some risk concern’ is driven by inherent bias associated with the open-label design and the cross-over design, both addressed under the domain of bias due to deviations from intended interventions. All other domains are assessed as having a low risk of bias.

Table 10: The Cochrane Risk of Bias Assessment Tool for Randomised Trials

Bias domain and signalling question*	BRUIN CLL-321	Rationale (if applicable)
Bias arising from the randomisation process		
1.1 Was the allocation sequence random?	Y; Low risk of bias	Randomised trial design
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y; Low risk of bias	Centrally assigned using Interactive voice/web response system (IXRS) for randomisation
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N; Low risk of bias	Baseline patient characteristics were generally balanced between the two groups. The prevalence of high-risk features was similar between pirtobrutinib and IdelaR/BR groups, except for IGHV unmutated and complex karyotype, which appeared more prevalent in the pirtobrutinib group
Risk of bias judgment (low/high/some concerns)	**Low risk**	-
Bias due to deviations from intended interventions		
2.1 Were participants aware of their assigned intervention during the trial?	Y; High risk of bias	Open-label design
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y; High risk of bias	Open-label design
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Y; High risk of bias	Cross-over design
2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	PN; Low risk of bias	Minimal risk, as the primary endpoint analysis of PFS included data up until cross-over. Notably, the cross-over occurred upon confirmed disease progression, and only if patients met the eligibility criteria for treatment by iwCLL 2018
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA; Other	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y; Low risk of bias	The secondary endpoint OS was estimated using two adjustments methods: inverse probability of censoring weighting (IPCW) and the accelerated failure time (AFT) model
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA; Other	-
Risk of bias judgment (low/high/some concerns)	**Some concerns**	-

Bias due to missing outcome data		
3.1 Were data for this outcome available for all or nearly all participants randomised?	Y; Low risk of bias	Yes, data reported for ITT population, with results presented in accordance with the CONSORT guidelines
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA; Other	-
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA; Other	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI; Other	-
Risk of bias judgment (low/high/some concerns)	**Low risk**	-
Bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	N; Low risk of bias	Standard iwCLL 2018 criteria
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N; Low risk of bias	Outcomes ascertained by both IRC and investigator.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N; Low risk of bias	Blinded IRC
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA; Other	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA; Other	-
Risk of bias judgment (low/high/some concerns)	**Low risk**	-
Bias in selection of the reported result		
5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?	Y; Low risk of bias	Yes, the analyses followed the study protocol; with all revisions fully documented.
Is the numerical result being assessed likely to have been selected on the basis of the results from:		
5.2... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N; Low risk of bias	All results reported across all planned analyses.
5.3... multiple eligible analyses of the data?	N; Low risk of bias	All results reported across all planned analyses.
Risk of bias judgment (low/high/some concerns)	**Low risk**	-

Overall bias		
Risk of bias judgment (low/high/some concerns)	**Some concerns**	-

Footnotes: *Signalling questions for bias due to deviations from intended interventions relate to the effect of assignment to intervention.
Abbreviations: AFT: accelerated failure time; BR: bendamustine plus rituximab; CONSORT: Consolidated Standards of Reporting Trials; IdelaR: idelalisib plus rituximab; IGHV: immunoglobulin heavy chain variable region; IPCW: inverse probability of censoring weighting; IRC: independent review committee; ITT: intention-to-treat; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; NA: not applicable; NI: no information; OS: overall survival; PFS: progression-free survival; PN: probably no; PY: probably yes; Y: yes; N: no.

Appendices

Appendix 1: Revised Company base-case incremental cost-effectiveness analysis results

As discussed in the response to Question B3, a revised base-case analysis has been conducted to account for the amendments to the subsequent anticancer treatment distributions requested by the EAG, and as necessitated following clarification calls with UK clinical experts.

In conjunction with the updated company base case assumptions, Lilly can confirm that a simple PAS has been confirmed with the Patient Access Scheme Liaison Unit (PASLU). Consequently, the revised cost-effectiveness analyses have been presented at both the list price and the communicated PAS price of pirtobrutinib. Lilly understand that a confidential PAS is also applicable for IdelaR, however the details for this are unknown to Lilly and therefore cannot be explored in the revised base-case analysis.

The results of the revised Company base-case incremental cost-effectiveness analysis for patients within the post-cBTKi R/R CLL population are presented in Table 11 and Table 12 with pirtobrutinib at list and PAS price, respectively. Revised base-case results in the dual-exposed population are presented with pirtobrutinib at list price and PAS price in Table 13 and Table 14, respectively. Revised results incorporating the upweighted QALYs for the dual-exposed population are presented in Table 15 and Table 16, with pirtobrutinib at list price and PAS price, respectively.

Table 11: Revised probabilistic base-case results in patients with R/R CLL: post-cBTKi population, currently suitable and unsuitable for standard of care (at pirtobrutinib list price)

Comparator	Total costs	Total LYG[a]	Total QALYs	NMB	Incremental costs	Incremental LYG[a]	Incremental QALYs	ICER (£/QALY)
Pirtobrutinib	[redacted]	[redacted]	2.603	[redacted]	[redacted]	[redacted]	0.547	[redacted]
IdelaR	[redacted]	[redacted]	2.056	[redacted]				

Footnote: [a] Calculated deterministically.
Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; ICER: incremental cost-effectiveness ratio; Inv. Choice: investigator's choice; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year.

Table 12: Revised probabilistic base-case results in patients with R/R CLL: post-cBTKi population, currently suitable and unsuitable for standard of care (at pirtobrutinib PAS price)

Comparator	Total costs	Total LYG[a]	Total QALYs	NMB	Incremental costs	Incremental LYG[a]	Incremental QALYs	ICER (£/QALY)
Pirtobrutinib	[redacted]	[redacted]	2.574	[redacted]	[redacted]	[redacted]	0.557	£70,377
IdelaR	[redacted]	[redacted]	2.016	[redacted]				

Footnote: [a] Calculated deterministically.
Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; ICER: incremental cost-effectiveness ratio; Inv. Choice: investigator's choice; LYG: life-years gained; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life-year.

Table 13: Revised probabilistic base-case results in patients with R/R CLL: dual-exposed population (at pirtobrutinib list price)

Comparator	Total costs	Total LYG[a]	Total QALYs	NMB	Incremental costs	Incremental LYG[a]	Incremental QALYs	ICER (£/QALY)
Pirtobrutinib	[redacted]	[redacted]	1.726	[redacted]	[redacted]	[redacted]	0.392	[redacted]
IdelaR	[redacted]	[redacted]	1.334	[redacted]				

Footnote: [a] Calculated deterministically.
Abbreviations: ICER: incremental cost-effectiveness ratio; Inv. Choice: investigator's choice; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year.

Table 14: Revised probabilistic base-case results in patients with R/R CLL: dual-exposed population (at pirtobrutinib PAS price)

Comparator	Total costs	Total LYG[a]	Total QALYs	NMB	Incremental costs	Incremental LYG[a]	Incremental QALYs	ICER (£/QALY)
Pirtobrutinib	[redacted]	[redacted]	1.726	[redacted]	[redacted]	[redacted]	0.392	£14,978
IdelaR	[redacted]	[redacted]	1.334	[redacted]				

Footnote: [a] Calculated deterministically.

Abbreviations: ICER: incremental cost-effectiveness ratio; Inv. Choice: investigator's choice; LYG: life-years gained; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life-year.

Table 15: Summary of revised QALY shortfall analysis results (dual-exposed population, at pirtobrutinib list price)

Proportional QALY shortfall	QALY weight	Upweighted pirtobrutinib QALYs	ICER (£/QALY)[a]
86.7%	1.2	2.064	[redacted]

Footnote: [a] Calculated deterministically.
Abbreviation: QALY: quality-adjusted life year.

Table 16: Summary of revised QALY shortfall analysis results (dual-exposed population, at pirtobrutinib PAS price)

Proportional QALY shortfall	QALY weight	Upweighted pirtobrutinib QALYs	ICER (£/QALY)[a]
86.7%	1.2	2.064	[redacted]

Footnote: [a] Calculated deterministically.
Abbreviation: PAS: patient access scheme; QALY: quality-adjusted life year.

Appendix 2: Revised Company base-case anticancer therapy distribution and treatment duration

As discussed in the response to Question B3, the updated assumptions for subsequent anticancer treatment distributions used in the revised Company base case are presented in Table 17.

Table 17: Anticancer therapy distribution and treatment duration (revised Company base-case)

Treatment	Post-cBTKi population			Dual-exposed population		
	Post-progression use		Mean 28-day cycles	Post-progression use		Mean 28-day cycles
	Pirtobrutinib	Inv. choice		Pirtobrutinib	Inv. choice	
Covalent BTK inhibitor						
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Noncovalent BTK inhibitor						
Pirtobrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCL2i						
Venetoclax						
Weeks 1 to 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 5+			[redacted]			[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy						
FCR						
Fludarabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide						
Rituximab						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles 2-6			[redacted]			[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 antibody						
Rituximab						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles 2-6			[redacted]			[redacted]
Obinutuzumab						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles 2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PI3K agent						
Idelalisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IMID/immunomodulator						

Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAR-T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stem cell transplant						
AlloSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic therapy						
Other systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other molecular pathways/small molecule inhibitors						
Other molecular pathways/small molecule inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AlloSCT: allogeneic stem cell transplant; BCL2i: B-cell lymphoma 2 inhibitor; BTK: Bruton tyrosine kinase; CAR-T: chimeric antigen receptor T-cell therapy; FCR: fludarabine, cyclophosphamide, and rituximab; IMID: immunomodulatory drug; Inv. choice: investigator's choice; PI3K: phosphoinositide 3-kinase.
Source: Eli Lilly (Data on File). Revised Company cost-effectiveness model

Appendix 3: Model Coefficients Used for the Calculation of Utility Values

Table 18: Summary of model coefficients for the calculation of the MMRM average PFS EQ-5D-3L mapped utility value (post-cBTKi population)[a]

Effect	Group	Term[b]	Estimate	SE	Statistic	DF[c]	P value
Fixed	N/A	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixed	N/A	bl_utility_cent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixed	N/A	bl_age_cent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random	SUBJID	SD of intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random	Residual	SD of observation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Utility weight (EQ-5D-3L index score) was calculated by mapping EQ-5D-5L to 3L using Hernández *et al.* (2023).[9] All patient assessments included were on progression-free. [b] bl_age_cent = baseline age centered; bl_utility_cent = baseline utility centered; DF = degrees of freedom. [c] Kenward-Roger's method was used to compute the degree of freedom.
Abbreviations: DF: degrees of freedom; N/A: not applicable; PF: progression-free; SD: standard deviation; SE: standard error; SUBJID: unique subject identifier from BRUIN CLL-321 trial.

Table 19: Summary of model coefficients for the calculation of the MMRM average PFS EQ-5D-3L mapped utility value (dual-exposed population)[a]

Effect	Group	Term[b]	Estimate	SE	Statistic	DF[c]	P value
Fixed	N/A	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixed	N/A	bl_utility_cent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fixed	N/A	bl_age_cent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random	SUBJID	SD of intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random	Residual	SD of observation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Utility weight (EQ-5D-3L index score) was calculated by mapping EQ-5D-5L to 3L using Hernández *et al.* (2023).[9] [b] bl_age_cent = baseline age centered; bl_utility_cent = baseline utility centered. [c] Kenward-Roger's method was used to compute the degree of freedom.
Abbreviations: DF: degrees of freedom; N/A: not applicable; PF: progression-free; SD: standard deviation; SE: standard error; SUBJID: unique subject identifier from BRUIN CLL-321 trial.

References

1. Cancer Research UK. Supportive treatments for chronic lymphocytic leukaemia (CLL), Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/treatment/supportive [Accessed: 22 July 2025].
2. Walewska R, Parry-Jones N, Eyre TA, et al. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology 2022;197:544-557.
3. Eichhorst B, Ghia P, Niemann C, et al. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Annals of Oncology 2024;35:762-768.
4. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. British journal of haematology 2018;182:344-359.
5. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. [TA561] Available at: https://www.nice.org.uk/guidance/ta561/documents/committee-papers [Accessed: 30 July 2025].
6. Al-Sawaf O, Jen MH, Hess LM, et al. Pirtobrutinib versus venetoclax in covalent Bruton tyrosine kinase inhibitor-pretreated chronic lymphocytic leukemia: a matching-adjusted indirect comparison. Haematologica 2024;109:1866-1873.
7. Electronic Medicines Consortium. Venclyxto (venetoclax) Available at: https://www.medicines.org.uk/emc/product/2267/smpc/print [Accessed: 09 May 2025].
8. Electronic Medicines Compendium. Breyanzi (lisocabtagene maraleucel) Available at: https://www.medicines.org.uk/emc/product/100499/smpc/print [Accessed: 25 July 2025].
9. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. Pharmacoeconomics 2023;41:199-207.
10. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. British journal of haematology 2007;139:255-264.
11. Else M, Cocks K, Crofts S, et al. Quality of life in chronic lymphocytic leukemia: 5-year results from the multicenter randomized LRF CLL4 trial. Leukemia & lymphoma 2012;53:1289-1298.
12. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507-15.
13. Kind P, Dolan P, Gudex C, et al. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998;316:736-41.
14. National Institute for Health and Care Excellence. Zanubrutinib for treating chronic lymphocytic leukaemia. [TA931] Available at: https://www.nice.org.uk/guidance/ta931 [Accessed: 01 February 2025].
15. Ara R, Brazier JE. Using Health State Utility Values from the General Population to Approximate Baselines in Decision Analytic Models when Condition-Specific Data are Not Available. Value in Health 2011;14:539-545.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	**Jackie Martin**
2. Name of organisation	Joint submission on behalf of: the following charities CLL Support, Blood Cancer UK, Leukaemia Care, Lymphoma Action and Leukaemia UK
3. Job title or position	CLL Support Associate Trustee and Patient Advocate
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Information supplied by the individual charities** **CLL Support -** is the UK's only charity dedicated to supporting CLL patients. There are approx. 3,500 members of the charity and approx. 12,000 UK members of the on line support forum on Health Unlocked (c 50% of the 24,000 members) https://healthunlocked.com/cllsupport Our mission is to support and empower Chronic Lymphocytic Leukaemia (CLL) patients, and Small Lymphocytic Leukaemia (SLL) patients, their families and supporters through education and access to reliable, relevant and current information. We also represent CLL patients in discussions with government, pharmaceutical companies, other leukaemia charities and the National Institute for Care and Health Excellence (NICE). **Lymphoma Action -** is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources; predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted

	income for the financial year (this includes donations, gifts in kind, sponsorship etc) and there is also a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. This policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. **Leukaemia UK:** Leukaemia UK is a leading leukaemia research and advocacy charity that believes research has the power to stop leukaemia devastating lives. We bring together the leukaemia community—patients, families, researchers, and advocates—to fund and drive the life-saving breakthroughs that matter most to those affected. We campaign for change, pushing for earlier diagnosis, better treatment options, improved care, and more investment in research to represent the nearly 60,000 people living with leukaemia in the UK and to make sure that the next person with leukaemia has the best possible experience and outcomes of diagnosis, treatment and care. Leukaemia UK receives income from a variety of sources (as detailed in the charity's 2023 Annual Report). **Leukaemia Care** Leukaemia Care is a UK leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected receives the best possible diagnosis, information, advice, treatment and support. Read more about our work, including the number of people supported, here: https://www.leukaemiacare.org.uk/about-us/our-impact-in-2024/. Blood Cancer UK Blood Cancer UK is the UK's biggest blood cancer research charity. We fund world-class research and provide information, support and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has around 100 employees and is funded primarily through donations and legacies

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**Information supplied by the individual charities** **CLL Support has received funding from companies bringing the treatment to NICE and the comparator treatment. The most recent figures as follows** **Abbvie: -** £20,000 educational grant and £337.50 advisory fees **Astra Zeneca:** £15,000 educational grant and £900 advisory fees **Johnson and Johnson**:- £5000 educational grant **Beigene:** - £20,000 educational grand and £212.44 advisory fees **Eli Lilly** - £3,960 advisory fees **Lymphoma Action has received the following funding** **Eli Lily** – no funding **Abbvie** (venetoclax) - £15000 in 2025 towards information provision, helpline and workshops. £25000 in 2024 Preparing for Treatment project, helpline and information provision **AstraZeneca** (acalabrutinib) - £15,000 in 2024 towards Preparing for Treatment project **BeiGene UK** (zanubrutinib) – £20,000 in 2025 towards TrialsLink and Lymphoma Management course. £20,561.34 in 2024 towards Lymphoma Essentials and Preparing for Treatment projects, sponsorship of Lymphoma Management course and payment for volunteer expenses to attend BeiGene event. **Gilead Sciences** (idelalisib) - £14,000 in 2025 towards Preparing for Treatment and Lymphoma Essentials projects and Lymphoma Information days. £40,000 in 2024 towards peer support services and our publications **Janssen-Cilag (**ibrutinib) - £5,000 in 2024 towards Lymphoma Essentials provision **Pfizer** (rituximab) - £4,000 in 2025 towards sponsorship of Lymphoma Information days

	Roche (rituximab) - £20,000 in 2025 towards our information provision and peer support services. £20,000 in 2024 towards our helpline, information provision and Preparing for Treatment project **Leukaemia Care has received the following funding in 2023, the most recently available year, funding included:** **AbbVie**: £15,800 for improving the accessibility of our patient information **AstraZeneca** - £15,000 for our work on early diagnosis We received no funding from the submitting company in 2023, but have since received a grant from them. **Leukaemia UK has received the following funding:** **Novartis** funding of £20,000 for a policy research project **Gilead Sciences** (idelalisib) - £10,451 in 2024 for community champions, new application going in this week for more funding **Janssen-Cilag (**ibrutinib) - £9,500 funding from Janssen this year for HEU data project **Abbvie** (venetoclax) - £10k grant in 2024 for HEU data analysis **Blood Cancer UK has received the following funding:** **Eli Lilly** - £10,000 for Clinical Trials Support Service and CNS Programme of Support **Abbvie** - £50,000 for Direct Referral service **AstraZeneca** - £15,000 for Direct Referral service **BeiGene UK** - £30,000 for Clinical Trials Support Service **Gilead Sciences** - £70,910 for the Blood Cancer Action Plan, Direct Referral and Blood Cancer Awareness Month Health info packs **Janssen (J&J)** - £45,910 - for the Blood Cancer Action Plan **Pfizer** - £33, 214.59 for Clinical Trials Support Service, Pfizer Patient Charter Consultancy, CEO consultancy and travel expenses

	Roche - £15,000 for CNS programme of support
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None of the charities have any direct or indirect links with the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	An on line survey of UK patients and carers was compiled and analysed, led by Leukaemia Care. In addition patients were consulted on the Health Unlocked on line platform of CLL Support and 2024 survey of CLL patients and carers. https://cllsupport.org.uk/wp-content/uploads/2024/09/Survey-results-2024.pdf All gave permission for their experiences to be shared in this HTA.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL patients experience varying degrees of fatigue, swollen lymph nodes, weight-loss, anaemia, infections and night-sweats which can be very distressing. As the CLL progresses, then the symptoms become progressively more severe, with greater fatigue, anaemia leading to shortness of breath, sometimes excessive bruising and bleeding, and a much greater risk of infection. The majority of patients will start with a period of watch and wait or active monitoring as treatment is delayed whilst the patient's disease is in the early stages and with few symptoms. However, once the disease progresses and the patient's condition is compromised then patients will start treatment. In addition, due to the physical symptoms that patients' have, their quality of life is reduced in many ways. Patients and carers suffer higher anxiety, even during the watch and wait period, almost living from one blood test or CT scan to the next with fears of progression, treatment failure and death. One patient survey found that 72% of patients expressed these fears and 96% stating that delaying disease progression was their priority with concerns that there will be a suitable treatment available for them when they relapse. Patients who are diagnosed at a younger age are even more likely to suffer from anxiety and depression as many have work and family responsibilities. Life insurance may be an issue. One patient said "***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***". Older patients are more likely to isolate themselves in order to avoid infections and this can exacerbate the anxiety, loneliness and depression. Patients' families, friends and caregivers are similarly affected with the same worries about their loved ones. As well as important emotional support because CLL affects mainly an older age group, often with comorbidities, then as symptoms progress patients often require support with everyday activities such as shopping, cooking and cleaning and may also need support dealing with any side effects of the treatment they are taking. Patients often need help travelling to appointments and carers may be needed to be with the patient to listen to the doctor, which can be difficult when trying to understand a medical diagnosis.

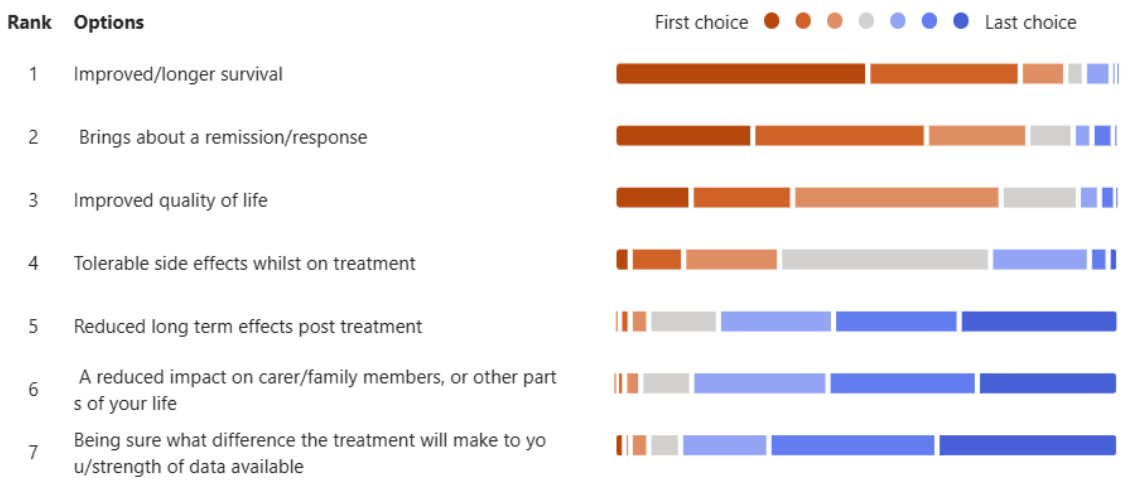
Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients are very appreciative of the range of current non chemotherapy (CIT) treatments for CLL which have been very successful in providing long term remissions for many patients. Despite this a greater range of treatment options are needed, especially for heavily pre treated patients. The range of treatments available means that almost every patient has access to a treatment appropriate for their personal CLL, previous treatments and existing comorbidities. However, younger patients suffer from treatment anxiety and worry about what effective treatment will be available to them when they need it. A patient's preferred treatment depends very much on their personal circumstances, both health and social but some of the things we are told that are considered are: Ability to adhere to treatment schedules Participating in normal activities including work and family life. Availability and affording travel and parking costs to attend appointments Anxiety about how well the treatment will work Their understanding of available treatment options Anxiety about disease progression and what might follow Ability to be able to manage potential side effects Degree of support and other resources available Many CLL/SLL patients eventually develop resistance to first-generation covalent BTK inhibitors (like ibrutinib or acalabrutinib), or are forced to stop due to side effects (e.g., atrial fibrillation, bleeding). Pirtobrutinib, a non-covalent (reversible) BTK inhibitor, works even in the presence of resistance mutations such as C481S, offering an important new option. Tam CS, Balendran S, Blombery P. Novel mechanisms of resistance in CLL: variant BTK mutations in second-generation and noncovalent BTK inhibitors. Blood. 2025 Mar 6;145(10):1005-1009. doi: 10.1182/blood.2024026672. PMID: 39808800

8. Is there an unmet need for patients with this condition?	Due to the heterogeneous nature of CLL there is still a significant unmet need in a small group of patients that have failed many treatments and for whom, allo stem cell transplant is not an option due to comorbidities and age. Those that are intolerant of other BTKi's or those that have developed resistant mutations of BTKi are another group of unmet need, especially if they have also been previously treated with Venetoclax. For those suitable for cellular therapies then Pirtobrutinib is a proven bridging treatment to obtain remission before SCT or CAR-T. For those unsuitable for cellular therapies then Pirtobrutinib offers an additional therapeutic option to try to obtain another response and extend their lives. It is worth noting that in clinical trials (notably the **BRUIN study**) Pirtobrutinib shows strong overall response rates in heavily pre-treated patients — including those who failed prior BTK and BCL2 inhibitor therapies. In the BRUIN trial, **response rates remained high** even in high-risk groups with TP53 mutations or unmutated IGHV. Disease control was durable, with many patients remaining progression-free beyond a year. https://investor.lilly.com/news-releases/news-release-details/phase-3-results-lillys-jaypircar-pirtobrutinib-covalent-btk

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients see this novel and importantly oral treatment as another lifeline that can extend their life but also give a good quality of life with few side effects. This is especially true for those that are double refractory or intolerant to Venetoclax and the co valent BTKi's Ibrutinib, Acalabrutinib and Zanubrutinib. In addition, Pirtobrutinib allows for outpatient management — important for improving quality of life and reducing NHS resource burden. Pirtobrutinib is a non covalent BTKi and offers an option for patients with BK mutations that confer resistance to co valent BTKI's. Patients value that it is a well tolerated, oral treatment. The BRUIN study showed excellent results in all groups of patients including heavily pretreated patients with BTKi mutations, unmutated IgHV and 17p del and TP53 patients. Disease control was durable, with numerous patients remaining progression-free beyond a year and a significant number for more than two years. The treatment is reported to have very few side effects and low rates of atrial fibrillation or bleeding make it a safer option for older or co-morbid patients. In a brief and limited survey of patients conducted by Leukaemia Care and of the patients on the CLL Support platform on Health Unlocked (https://healthunlocked.com/cllsupport/posts) revealed the following quotes are from patients: "*I had no side effects*." – said by the majority of patients *"*I had an almost immediate reduction in the size of the swollen cervical nodes, generally stable bloods but extreme fatigue, diarrhoea and a rapid fall in platelets (63 at their lowest). My consultant suggested I halve the recommended dose to 100 mg daily, which I've stayed with ever since. By mid September the unwanted side effects had gone, I was feeling good and the half dose Pirto seemed to be working fine"*. – from an 80 year old respondent. ***"***The results have been pretty dramatic with noticeable lymph node shrinkage by the end of week 1 and gone by the end of cycle 2. Start of Cycle 2 blood work was completely normal."* *"*I had a rash, now fine*" As one patient in the Leukaemia Care survey said – "*all treatments eventually stop working, so knowing a different type of treatment is available is comforting*". Patients gave the following priorities when asked what they felt were the most and least important features of a new treatment (ref: The Leukaemia Care Survey). This survey is in the people who have already had more than 1 treatment, so the group under consideration. People still want to survive even if they have not long left to live.

	22. What would you consider to be the most and least important features of a new treatment for CLL? (please rank the options from most important at the top to least important at the bottom) 189 Responses 

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients expressed no concerns of any disadvantages with this treatment. Although there are side effects known and reported for this treatment, reports were almost wholly positive in nature

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There is a significant unmet need in a small group of patients that have failed many treatments, particularly both covalent BTKi's and BCL2 inhibitors and also for those for whom an allo stem cell transplant or CAT-T is not an option due to comorbidities and age. Many CLL/SLL patients eventually develop resistance to first-generation covalent BTK inhibitors (like ibrutinib or acalabrutinib), or are forced to stop due to side effects (e.g., atrial fibrillation, bleeding). Pirtobrutinib, a non-covalent (reversible) BTK inhibitor, works even in the presence of resistance mutations such as C481S, offering an important new option especially for those that have also been treated with Venetoclax. For those few who are suitable for cellular therapies then Pirtobrutinib is a proven bridging treatment to obtain remission before SCT or CAR-T. For those unsuitable for cellular therapies then Pirtobrutinib offers an additional therapeutic option to try to obtain another response and extend their lives. All these groups of patients will hugely benefit from NICE approval of Pirtobrutinib.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A well tolerated new class of BTKi which overcomes the resistance to covalent BTKI's conferred by the most common mutations of BTK with the advantage that it is oral treatment that is taken at home, reducing hospital attendances. • Offers a valuable alternative BTKi for patients with cardiac co-morbidites, AF, hypertension, unable to take other BTKi"s • Offers a valuable and much needed treatment option for the small group of 'double refractory' patients for whom cellular therapies are not an option due to age or comorbidities • Offers a valuable and non chemo option for patients needing bridging treatment to obtain remission before allo SCT or CAR-T • Demonstrates strong efficacy, including in high-risk groups (e.g. with TP53 mutations or prior BCL2 inhibitor exposure), as shown in the BRUIN trial.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Friday 31 October.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating chronic lymphocytic leukaemia

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Catherine Parbutt
2. Name of organisation	1. The Leeds Teaching Hospitals NHS Trust 2. British Oncology Pharmacy Association (BOPA)
3. Job title or position	1. Consultant Pharmacist for Cancer Services 2. Member of BOPA Education and Training Committee
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic lymphocytic leukaemia? ☐ A specialist in the clinical evidence base for chronic lymphocytic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for chronic lymphocytic leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Control the disease, achieve remission, relief from symptoms to improve quality of life, extend life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in lymphocyte count (if elevated at start of treatment), reduction in size of lymph nodes +/- spleen (if enlarged at start of treatment), improvement in symptoms such as fatigue, night sweats, weight loss etc, improvement in blood count parameters that might have been affected by lymphocytosis e.g. Haemoglobin (Anaemia) or Platelets (Thrombocytopenia)
10. In your view, is there an unmet need for patients and healthcare professionals in chronic lymphocytic leukaemia?	Yes - for older, frailer patients who progress on front line covalent BTKi (Bruton's Tyrosine Kinase inhibitor) therapy - there are often no suitable options available for 2nd line treatment. Many of these patients would not be fit enough to receive Venetoclax based therapy (often due to poor renal function), and idelalisib is rarely used due to significant toxicity profile. Equally, third line options are lacking for patients who have had a covalent BTKi up-front and then Venetoclax-Rituximab in the first relapse setting. Clinical trials are the mainstay for this group of patients but there are not always suitable trials open / slots available - and variable accessibility depending on location.
11. How is chronic lymphocytic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	British Society for Haematology Guideline for the treatment of CLL 2025 2025 British Society for Haematology Guideline for the treatment of chronic lymphocytic leukaemia The pathway of care for CLL patients is reasonably well defined - diagnosis/mutational analysis, active monitoring, treatment when indicated by iwCLL criteria, further treatment following disease progression.

• Does the treatment pathway figure in appendix A accurately reflect treatments in NHS clinical practice? • What impact would the technology have on the current pathway of care?	Where there are differences of opinion is in the choice of first line treatment - fixed vs continuous therapy options. The BSH guidelines support clinicians and patients with a decision tool (Table 1) that gives consideration to CLL-related factors, patient vulnerabilities and patient priorities and preferences. The treatment pathway in Appendix A does broadly reflect NHS clinical practice, although the important role played by clinical trials in this field should be acknowledged and a "Clinical Trial" option should be included on both first line and relapsed treatment algorithms. The NHS funded option that is missing is Venetoclax monotherapy TA796 which can be used at progression for certain groups of patients. 1 Recommendations | Venetoclax for treating chronic lymphocytic leukaemia | Guidance | NICE This technology would offer an additional option in the "after progression" algorithm - particularly for patients who have had previous covalent BTKi therapy and unsuitable for existing commissioned options (Venetoclax-Rituximab or Idelalisib). It would also offer a commissioned third (or subsequent) line option for those who have had both a covalent BTKi and Venetoclax based regimen.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Yes - this medication will be used in the same way as the covalent BTKis are currently. In many centres, this is an MDT approach with Consultant initiation/early review and then follow up/on-going monitoring in Pharmacist or Nurse-led clinics. No resource differences - initial frequent (e.g. 4 weekly) review until stable, and then 3 monthly review (e.g. can be conducted by telephone, with annual face to face review)

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Clinical setting - Secondary care / Specialist Haematology clinic only. No specific investment
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes - for patients with relapsed CLL (previously treated with a covalent BTKi) who are unsuitable for venetoclax-rituximab or idelalisib and have no opportunity for entry into a clinical trial, the only option is best supportive care. Pirtobrutinib would bring an additional option for these patients - and it is an oral therapy, taken at home - with no additional hospital visits (other than clinic/monitoring) or procedures (e.g. cannulation etc). Pirtobrutinib would likely increase quality and duration of life for these patients versus best supportive care. The case would be similar in the 3rd line setting for patients who have progressed on both a covalent BTKi and a venetoclax based regimen - unless they have a clinical trial option, best supportive care is the only option here too. Pirtobrutinib would bring an additional option that would likely increase both quality and duration of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No - the data from the BRUIN CLL 321 study showed that pirtobrutinib had benefit across clinically relevant sub-groups including those with high risk features such as del(17p)/TP53 mutations, complex karyotype and unmutated IGHV. It also showed benefit in both venetoclax-naïve and ventoclax pre-treated patients (although there was a difference in time to next treatment between the two groups).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	This technology will likely be the same to use as covalent BTKis with initial regular monitoring, increasing to 3 monthly review as patients become stable.

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Concomitant medications will likely be aciclovir for herpes/varicella prophylaxis and co-trimoxazole for PJP (Pneumocystis jirovecii pneumonia) which are standard with covalent BTKis. Pirtobrutinib will be easier to use than Venetoclax as it doesn't have an escalation phase and so doesn't require weekly appointments and extensive tumour lysis syndrome monitoring.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Pirtobrutinib will be started when the patient's disease progresses (symptomatic, blood parameters deteriorating etc) and they meet the NICE/Blueteq commissioned criteria (if supported). It is recommended to repeat TP53 mutation/deletion at disease progression, but this is standard practice. Treatment will be stopped if the patient experiences unacceptable toxicity, disease progresses or patient sadly passes away.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Pirtobrutinib is an oral treatment that can be monitored remotely (via local bloods and telephone/video consultation) once patient is stable, usually after first few cycles.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Not innovative but addresses an unmet need as described above - provides an alternative for patients whose only option currently is a clinical trial or best supportive care.

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the BRUIN-CLL-321 study, the most frequent adverse event in patients receiving pirtobrutinib was pneumonia. This is a composite of immune-compromise - by the underlying CLL and the treatment. It must also be remembered that these patients were often heavily pre-treated and so may also have had long-standing immune suppression / hypogammaglobulinaemia. Other key adverse events were anaemia and neutropenia (the latter also potentially being linked to the incidence of infection). These adverse events could be linked to the CLL, and the impact of disease on the bone marrow - as well as drug related effects. Otherwise, pirtobrutinib appeared to be largely well tolerated with bleeding adverse events primarily low grade. 17% of patients in the BRUIN-CLL-321 study discontinued pirtobrutinib due to an adverse event, but only 5% were considered treatment-related. Measures can be taken to reduce specific types of infection (aciclovir and co-trimoxazole as described above), and GCSF support can be used where appropriate to support neutropenia. Standard supportive medications such as loperamide and anti-emetics can be provided in case of diarrhoea or nausea/vomiting respectively. None of these medications have significant cost implications.
20. Do the clinical trials on the technology reflect current UK clinical practice?	No. The BRUIN-CLL-321 study compared Pirtobrutinib to either IdelaR (Idelalisib+Rituximab) or BR (Benadmustine+Rituximab). Neither of these are considered to be current standard of care after relapse. IdelaR has a significant

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	toxicity profile and chemo/immunotherapy (e.g. BR) is no longer part of UK guidelines/algorithm. However, in the current relapse algorithm, patients who have received a covalent BTKi and are unsuitable for Venetoclax-Rituximab or Idelalisib, have only a clinical trial or best supportive care as their options. Therefore, a median time to next treatment (TNTT) of 24 months with pirtobrutinib is likely to offer more than could be achieved with best supportive care. TNTT is a key outcome measure - and often provides a more accurate reflection than Progression Free Survival (PFS). This is particularly pertinent with clinical trials where patients receive imaging e.g. CT scans much more regularly than in standard practice. Therefore, a "relapse" can often be detected by enlargement of a lymph node on a scan, earlier than a patient is symptomatic and/or blood counts start to deteriorate. In the BRUIN-CLL-312 study, patients were allowed to continue pirtobrutinib beyond IRC (Investigator Review Committee)-assessed PD (Progressive Disease) if the investigator determined continued clinical benefit. 38.6% of patients in the pirtobrutinib group who had IRC-assessed PD continued treatment, and many did not require a new line of therapy for considerable time. Of note, median PFS was 14 months for pirtobrutinib, median TNTT was 24 months.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA931?	No
23. How do data on real-world experience compare with the trial data?	No real world experience as yet - use confined to clinical trial setting.

24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

CLL is a chronic blood cancer, often with an initial period of active surveillance before commencing treatment.
Treatment for CLL aims to control the disease, provide relief from symptoms and improve quality and duration of life.
There is an unmet need for an additional therapeutic option in the first relapse setting for patients who have had front line treatment with a covalent BTKi, and who are unsuitable for Venetoclax-Rituximab or Idealisib therapy. For these patients, the options are entry into a clinical trial (depending on availability) or best supportive care. Pirtobrutinib would provide an oral option for these patients.
There is also an unmet need in the second (or subsequent) relapse setting for patients who have received both a covalent BTKi and Venetoclax-based regimen. Again, these patients only have the options of idelalisib, clinical trial or best supportive care. Pirtobrutinib would provide an oral option for these patients too.
Pirtobrutinib appeared to be relatively well tolerated in clinical trials with a predictable side effect profile, and no serious safety flags.

Thank you for your time.

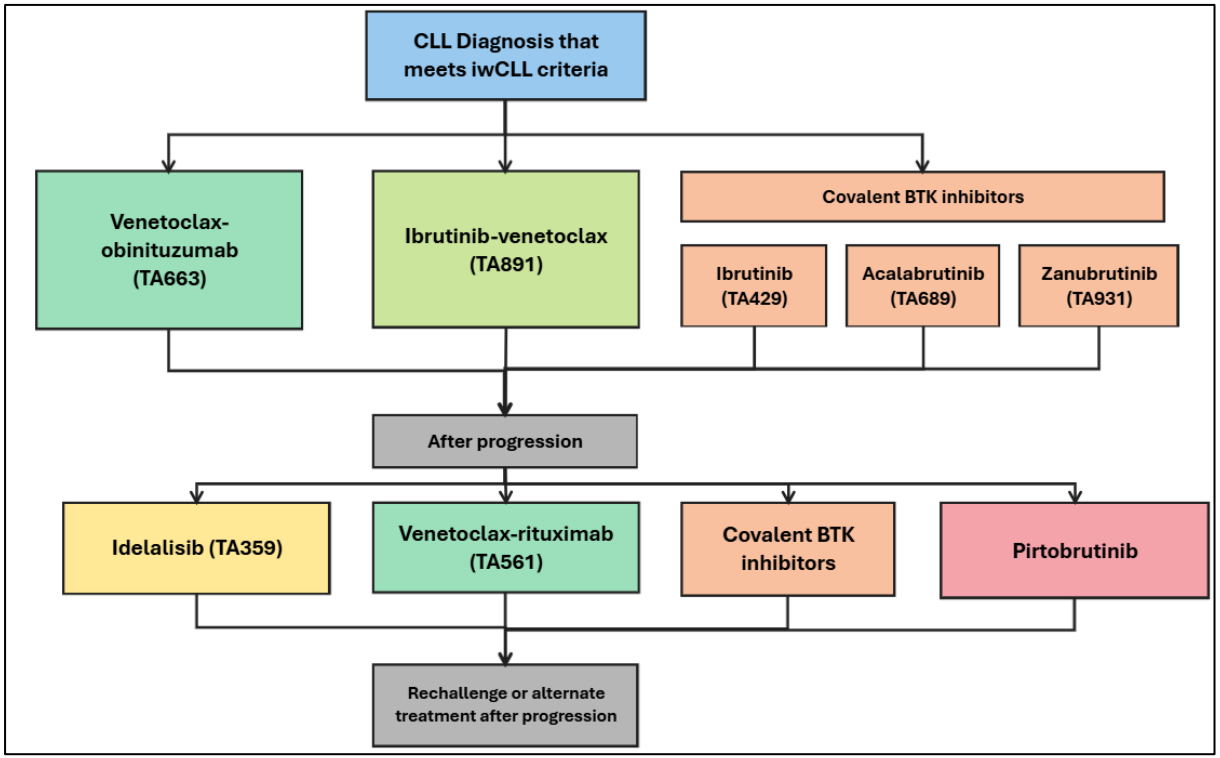
Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

Appendix A:



NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with chronic lymphocytic leukaemia or caring for a patient with chronic lymphocytic leukaemia. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 31 October.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with chronic lymphocytic leukaemia

Table 1 About you, chronic lymphocytic leukaemia, current treatments and equality

1. Your name	Dorothy Chivers (Dot)
2. Are you (please tick all that apply)	☒ A patient with chronic lymphocytic leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with chronic lymphocytic leukaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	CLL Support Charity
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: CLL Forums ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with chronic lymphocytic leukaemia? **If you are a carer (for someone with chronic lymphocytic leukaemia), please share your experience of caring for them**	Living with CLL is a rollercoaster. I was diagnosed with CLL at 62. Depression and anxiety set in, and the reassurances that more people die with the disease than because of it just didn't register. Extreme concern that my husband won't cope on his own if I die. Watch and wait – just 12 months for me, was torture. Life revolved around blood tests, increasing fatigue, repeated infections that never really go, continual worry and anxiety, fear of chemotherapy, knowing how it had affected my mother. Living in a state of permanent anxiety pretty much sums up the emotional feelings in the early stages. But then there's the physical side – perpetual tiredness, and the frustration at not being able to do the things that you love doing, purely because of this wretched illness – gardening, sewing, making cakes for people, travelling. And then treatment comes along and that brings more worries – will it work, what side effects will it have, and that eternal feeling of will I ever feel normal again, will I ever get my life back again and what happens if it doesn't work? The feeling of relief when the treatment kicks in and actually does its job, is amazing. To be able to do the things I love again, to actually be able to walk into town and back without having to get a taxi, is amazing! But back again to tremendous anxiety when the side effects become intolerable and treatment has to stop. And so the rollercoaster starts all over again. How long will I stay fairly well? And feeling relatively well, and being able to see the effect that the whole thing is having on the rest of the family, guilt really, seriously kicks in. Guilt that my husband spends his days worrying about me, guilt that he isn't sleeping properly because of his anxiety, guilt and worry that his BP medication has had to be increased – in my mind because of his worry about me. Instead of being able to shrug off the latest virus/bug that's doing the rounds, the terror that this could be the one that 'gets' you is a very, very real concern for both of us. And as for having a

	social life – basically off the cards simply to reduce the risk of infections. CLL rules, not just my life, not only my husbands life, but that of the whole family.
7a. What do you think of the current treatments and care available for chronic lymphocytic leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a. Pleased that there are newer, kinder treatments available, but side effects and the impact they can have is a constant concern. I've been very thankful that even though I have had to stop both my first line of treatment and the 2nd because of side effects, both gave me some time in remission – not as long as would have been expected had I completed the courses, but nonetheless, periods of time when I could lead something resembling a normal life. But it's concerns about, the length of remission that treatment will give, the side effects I'll have and what else is there that will suit me and be effective, if my body rejects this one, that is concerning. And this raises the question of: is this the end of the line, of has something else now available that hopefully will not be rejected by my awkward body. b. People on the CLL forums seem to have virtually identical opinions to me - appreciative of home based pill regimes whilst at the same time worrying about side effects, and how to cope with them.
8. If there are disadvantages for patients of current NHS treatments for chronic lymphocytic leukaemia (for example, how they are given or taken, side effects of treatment, and any others), please describe these	It would seem from comments that most current treatments come with disadvantages – frequent hospitals visits can place a financial burden on people. People comment on having to reduce their work hours, or even give up work completely, due to side effects, such as heart issues, with a resulting shortfall in income. And with the increasing retirement age, this is an issue that may well affect more patients in the future.
9a. If there are advantages of pirtobrutinib for treating chronic lymphocytic leukaemia over current treatments on the NHS, please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	a. For me – Pirtobrutinib is a wonder drug, with measurable results within weeks. As an example, my spleen which the surgeon who repaired my hernia, 2 months prior to starting treatment told me 'you need to get that enormous spleen sorted, and quickly' – was down to only 12cms withing 12 weeks and back to normal by 6 months, where it has stayed ever since. No side effects! Not even a headache. In the 5+ years since taking Pirtobrutinib, we have travelled the world, including visiting our son in Australia twice, and our daughter and family (who now live in America)

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does pirtobrutinib for treating chronic lymphocytic leukaemia help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	multiple times. That is quite apart from all the places we have visited on cruises. I truly have my life back. So easy to take – just 2 pills once a day. Huge reduction in the number of infections that I have picked up. b. The lack of side effects/my tolerance of the drug is number 1 for me, as it really does mean that I have stopped worrying about whether is it going to suit me. Not only am I still tolerating the drug 5+ years down the line, I am in complete and continuing remission. c. Being a simple once a day pill regime, it avoids frequent hospital visits. Also the lack of side effects, means that should I need to work, I could do so without worry
10. If there are disadvantages of pirtobrutinib for treating chronic lymphocytic leukaemia over current treatments on the NHS, please describe these. For example, are there any risks with chronic lymphocytic leukaemia? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No.
11. Are there any groups of patients who might benefit more from pirtobrutinib for treating chronic lymphocytic leukaemia or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	People who have difficulty tolerating the existing treatments
12. Are there any potential equality issues that should be taken into account when considering chronic lymphocytic leukaemia? Please explain if you think	No

any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Very well tolerated
- Lack of side effects
- It works quickly
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175978

Completed 28 August 2025

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

External Assessment Group (EAG) Report

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Rebecca Bresnahan, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Vincy Huang, Economic Modeller, LRiG, University of Liverpool

Marty Chaplin, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Ruaraidh Hill, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Stella Williams, Consultant in Haemato-Oncology, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool

Correspondence to: Rebecca Bresnahan, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 28 August 2025

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme as project number 175978.

Declared competing interests of the authors: Dr Stella Williams received reimbursement from Abbvie, AstraZeneca and Takeda for attending symposiums and for speaking and from Roche for speaking andhas received Beigene meeting hospitality. Dr Jeff Smith received reimbursement from Abbvie and Roche for attending symposiums, from Abbvie, AstraZeneca and Roche for speaking, from Hartley Taylor and various UK North Lymphoma forum sponsors for organising education and has received hospitality from Hartley Taylor.

Acknowledgements: The authors would like to thank: Dr Jeff Smith (Consultant Haematologist, The Clatterbridge Cancer Centre NHS Foundation Trust) who provided feedback on a draft version of the report, Sophie Beale who reviewed and provided feedback on draft versions of the clinical and statistical sections of the report, Sam Bryning who quality checked cost-effectiveness results and Angela Stainthorpe who reviewed and provided feedback on a draft version of the report and contributed to finalising the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Bresnahan R, Mahon J, Huang V, Chaplin M, Hill R, Dundar Y, McEntee J, Williams S. Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]: A Single Technology Appraisal. Liverpool Reviews and Implementation Group, 2025.

Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic evidence
Vincy Huang	Critical appraisal of the economic model
Marty Chaplin	Critical appraisal of the statistical evidence
Ruaraidh Hill	Critical appraisal of the clinical evidence
Yenal Dundar	Critical appraisal of the search strategies
Joanne McEntee	Critical appraisal of the company submission
Stella Williams	Clinical advice and critical appraisal of the clinical evidence

Table of contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AIC	Akaike information criterion
AFT	accelerated failure time
BCL2i	B-cell lymphoma 2 inhibitor
BCRi	B-cell receptor inhibitor
BIC	Bayesian information criterion
BR	bendamustine with rituximab
BSC	best supportive care
BTKi	Bruton's tyrosine kinase inhibitor
cBTKi	covalent Bruton's tyrosine kinase inhibitor
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CS	company submission
CSR	clinical study report
DCO	data cut-off
EAG	Evidence Assessment Group
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
GHS/QoL	global health score/quality of life
HCRU	healthcare resource use
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IdelaR	idelalisib with rituximab
IL58	five-item EORTC Item Library 58
IPCW	inverse probability censoring weighting
IRC	independent review committee
ITC	indirect treatment comparison
ITT	intention-to-treat
IwCLL	International Workshop on Chronic Lymphocytic Leukaemia
K-M	Kaplan-Meier
MAIC	matching-adjusted indirect comparison
MIMS	Monthly Index of Medical Specialties
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PD	progressed disease

PF	progression-free
PFS	progression-free survival
PH	proportional hazards
PRO	patient-reported outcome
QALY	quality adjusted life year
PI3Ki	phosphoinositide 3-kinase inhibitor
RCT	randomised controlled trial
RoB2	Cochrane Risk of Bias Assessment for Randomised Trials Tool v2.0
RPSFTM	Rank Preserving Structural Failure Time Model
R/R	relapsed or refractory
SCT	stem cell transplant
SLL	small lymphocytic lymphoma
SLR	systematic literature review
TEAE	treatment-emergent adverse event
TSAP	trial statistical analysis plan
TTD	time to treatment discontinuation
TTNT	time to next treatment
TTW	time to worsening
VenI	ibrutinib with venetoclax
Ven-mono	venetoclax monotherapy
VenR	venetoclax with rituximab

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs):

- Section 1.1 provides an overview of the key issues
- Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER
- Section 1.3 presents the key issues identified by the EAG in more detail
- Section 1.4 and Section 1.5 provide the secondary issues and modelling errors identified by the EAG.

Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

Table A Summary of the EAG's key issues

ID6269	Summary of issue	Impact on results	Report sections
Issue 1	No clinical effectiveness evidence for the most relevant comparators	Unknown	2.3, 3.4, 3.5, 3.7, 4.2.4.1
Issue 2	No cost-effectiveness results for the comparisons of pirtobrutinib versus cBTKi or versus BSC	Unknown	2.3, 4.2, 4.2.3, 4.2.4, 5.1.1, 5.2.2, 5.5

BSC=best supportive care; cBTKi=covalent Bruton's tyrosine kinase inhibitor

The key difference between the company's preferred assumptions and the EAG's preferred assumptions is the comparators that the EAG considers need to be included for a meaningful cost-effectiveness analysis of pirtobrutinib versus current standard of care in NHS clinical practice.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- increasing overall survival
- increasing time in a progression-free state.

Overall, the technology is modelled to affect costs by:

- having a lower unit price than current treatments (after the company proposed Patient Access Scheme [PAS] discount)
- being given as an oral tablet, rather than intravenously at hospital (i.e., rituximab).

The modelling assumptions that have the greatest effect on the ICER are:

- the HR used to adjust the OS curve for investigator's choice
- post-progression costs for the post-cBTKi group
- the distribution chosen to model TTD for the dual-exposed population.

1.3 EAG's key issues

Issue 1 No clinical effectiveness evidence for the most relevant comparators

Report section	Section 2.3, Section 3.4, Section 3.5, Section 3.7, Section 4.2.4.1
Description of issue and why the EAG has identified it as important	The company has only presented clinical effectiveness evidence for the comparison of pirtobrutinib versus investigator's choice (IdelaR or BR). The company has provided no clinical effectiveness evidence for the comparisons of pirtobrutinib versus a cBTKi, VenR or BSC (which the EAG considers are the most relevant comparators). The company considered that cBTKis were not relevant comparators as only a small proportion of patients discontinue prior cBTKis due to intolerance or AEs and only these patients would be eligible for rechallenge with cBTKis. The EAG considers that cBTKis are relevant comparators for: • patients with R/R CLL who have previously been treated with a cBTKi and who discontinue prior treatment with a cBTKi due to intolerance • patients with R/R CLL who have previously been treated with VenI (i.e., a combined BTKi and BCL2i therapy) in the first-line setting and who relapse after completing treatment with VenI, but who are not refractory to ibrutinib. Clinical advice to the EAG is that patients who relapse after completing treatment with VenI in the first-line setting but who are not refractory, would be eligible for, and likely rechallenged with, either a cBTKi or a BCL2i.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
Could any additional evidence or analyses be provided to resolve this key issue?	In the absence of direct clinical effectiveness evidence for the comparison of pirtobrutinib versus cBTKis, VenR or BSC, the company completed a feasibility assessment to determine whether it was appropriate to perform ITCs. The company concluded, and the EAG agrees, that it was not appropriate to conduct ITCs. The EAG considers that clinical advice on the relative effectiveness of pirtobrutinib vs the most relevant comparators could be informative

BCL2i=B-cell lymphoma 2 inhibitor; BR=bendamustine with rituximab; BSC=best supportive care; cBTKi=covalent Bruton's tyrosine kinase inhibitor IdelaR=idelalisib with rituximab; ITC=indirect treatment comparison; VenI=ibrutinib with venetoclax; VenR=venetoclax with rituximab

Issue 2 No cost-effectiveness results for the comparisons of pirtobrutinib versus cBTKi or versus BSC

Report section	Section 2.3, Section 4.2, Section 4.2.3, Section 4.2.4, Section 5.1.1, Section 5.2.2, Section 5.5
Description of issue and why the EAG has identified it as important	The company provided cost comparison evidence for the comparison of pirtobrutinib versus VenR. The company provided no cost effectiveness evidence for the comparisons of pirtobrutinib versus a cBTKi or BSC
What alternative approach has the EAG suggested?	The EAG has assumed equal OS, PFS and TTD and AEs for pirtobrutinib and cBTKis to allow cost comparisons to be performed for patients with R/R CLL **suitable** for treatment with a cBTKi. The EAG has assumed equal OS, PFS and TTD and AEs for IdelaR and BSC to allow a cost utility analysis of pirtobrutinib versus BSC for patients with R/R CLL **unsuitable** for treatment with a cBTKi or BCL2i.
What is the expected effect on the cost-effectiveness estimates?	Using the proposed PAS for pirtobrutinib and list prices for all other treatments (including subsequent therapies), pirtobrutinib would be less expensive than a cBTKi. The cost-effectiveness of pirtobrutinib versus BSC is unclear.
Could any additional evidence or analyses be provided to resolve this key issue?	Clinical advice on the plausibility of similarity of effectiveness and time on treatment for pirtobrutinib versus cBTKis or VenR and IdelaR versus BSC

BR=bendamustine with rituximab; BSC=best supportive care; cBTKi=covalent Bruton's tyrosine kinase inhibitor IdelaR=idelalisib with rituximab; ITC=indirect treatment comparison; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation; VenI=ibrutinib with venetoclax; VenR=venetoclax with rituximab

1.4 Secondary issues identified by the EAG

The EAG has identified the following secondary issues which the EAG considers have a less significant impact on cost-effectiveness results than the key issues presented in Section 1.3:

- the post-progression utility values chosen by the company do not align with trial evidence from the BRUIN CLL-321 trial (Section 4.3.2.2)
- the company has incorrectly calculated the cost for stem cell transplant (Section 4.3.3.7).

1.5 Company's modelling errors identified by the EAG

The company incorrectly applied a severity modifier to pirtobrutinib QALYs rather than to incremental QALYs (see Section 5.1.1).

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table B Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company base case			
Post-cBTKi population	[redacted]	0.568	[redacted]
Dual-exposed population	[redacted]	[redacted][a]	[redacted]
EAG's corrected company base case			
Dual-exposed population	[redacted]	[redacted][a]	[redacted]
Key issue 2: Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi is suitable: pirtobrutinib versus a cBTKi (ibrutinib, zanubrutinib or acalabrutinib) (EAG's preferred base case)	Pirtobrutinib vs ibrutinib: [redacted] Pirtobrutinib vs zanubrutinib: [redacted] Pirtobrutinib vs acalabrutinib: [redacted]	-	-
Key issue 2: Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a BCL2i is suitable: pirtobrutinib versus VenR (EAG's preferred base case)	Pirtobrutinib vs VenR: [redacted]	-	-
Key issue 2: Patients with R/R CLL who have previously been treated with a cBTKi who are unsuitable for treatment with a cBTKi or a BCL2i: versus BSC	Pirtobrutinib vs BSC: [redacted]	Pirtobrutinib vs BSC: 0.666	Pirtobrutinib vs BSC: [redacted] per QALY gained[a]
Additional EAG preferred assumption: Utility value in progressed state based on baseline utility value from dual-exposed population of BRUIN CLL-321 trial ([redacted])	Pirtobrutinib vs IdelaR: Post cBTKi population: [redacted] Dual-exposed population: [redacted]	Pirtobrutinib vs IdelaR: Post cBTKi population: 0.565 Dual-exposed population: 0.446	Pirtobrutinib vs IdelaR: Post cBTKi population: [redacted] per QALY gained Dual-exposed population: [redacted] per QALY gained[a]
Additional EAG preferred assumption: Costs of SCT correctly calculated	Pirtobrutinib vs IdelaR: Post cBTKi population: [redacted] Dual-exposed population: [redacted]	Pirtobrutinib vs IdelaR: Post cBTKi population: 0.568 Dual-exposed population: 0.485	Pirtobrutinib vs IdelaR: Post cBTKi population: [redacted] per QALY gained Dual-exposed population: [redacted] per QALY gained[a]

EAG's preferred base-case deterministic (Patients with R/R CLL who have previously been treated with a cBTKi who are unsuitable for treatment with a cBTKi or a BCL2i)	Pirtobrutinib vs IdelaR: [redacted] Pirtobrutinib vs BSC: [redacted]	Pirtobrutinib vs IdelaR: 0.446 Pirtobrutinib vs BSC: 0.498	Pirtobrutinib vs IdelaR: [redacted] per QALY gained Pirtobrutinib vs BSC: [redacted][a] per QALY gained
EAG's preferred base-case probabilistic (Patients with R/R CLL who have previously been treated with a cBTKi who are unsuitable for treatment with a cBTKi or a BCL2i)	Pirtobrutinib vs IdelaR: [redacted] Pirtobrutinib vs BSC: [redacted]	Pirtobrutinib vs IdelaR: 0.341 Pirtobrutinib vs BSC: 0.382	Pirtobrutinib vs IdelaR: [redacted] per QALY gained Pirtobrutinib vs BSC: [redacted][a] per QALY gained

[a] 1.2 severity weighting applied to incremental QALYs
BCL2i=B-cell lymphoma 2 inhibitor; BSC=best supportive care; cBTKi=covalent Bruton's tyrosine kinase inhibitor; ICER=incremental cost-effectiveness ratio; IdelaR=idelalisib with rituximab; QALYs=quality adjusted life year; SCT=stem cell transplant; VenR=venetoclax with rituximab

1.7 Outline of confidential comparator or subsequent treatment prices

The EAG has produced a confidential appendix with confidential prices for comparators and subsequent treatments (see Section 5.4).

2 BACKGROUND

In this External Assessment Group (EAG) report, the EAG critiques the company submission (CS) for pirtobrutinib as a treatment for chronic lymphocytic leukaemia (CLL) after 1 or more Bruton's tyrosine kinase inhibitors (BTKis).

The primary source of direct clinical effectiveness evidence presented by the company for the comparison of pirtobrutinib versus investigator's choice (idelalisib with rituximab [IdelaR] or bendamustine with rituximab [BR]) is the BRUIN CLL-321 trial.[1] This trial enrolled 217/238 (91.2%) patients with CLL and 21/238 (8.8%) patients with small lymphocytic lymphoma (SLL).

The population specified in the final scope[2] issued by NICE includes patients with CLL and patients with SLL; however, the company is only seeking a NICE recommendation for pirtobrutinib as a treatment for patients with CLL (see Table 1). This is in line with the UK licensed indication for pirtobrutinib which is for "...the treatment of adults with relapsed or refractory [R/R] CLL who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)." Medicines and Healthcare products Regulatory Agency (MHRA) approval was granted on the 13 August 2025.[3]

In this report, references to the CS are to the company's full evidence submission. Additional evidence was provided by the company in response to the NICE clarification letter.

2.1 Critique of the company's description of underlying health problem

The company has presented a description of CLL in the CS (CS, Section 1.3.1 and Section 1.3.2); clinical advice to the EAG is that the company's description is accurate. A summary of the company's description is presented in Box 1.

Box 1 Summary of company's description of CLL

In summary:

- CLL is the most common type of leukaemia and is characterised by the overproduction of cluster of differentiation 5+ (CD5+) B lymphocytes, a type of white blood cell[4]
- people are diagnosed with CLL if they have ≥5×10^9/L monoclonal CD5+ B lymphocytes in the peripheral blood for ≥3 months[5]
- in the UK, approximately 4,000 people are diagnosed with CLL each year[6]
- approximately 63% of people with CLL are male, and men have a worse disease prognosis than women[6]
- CLL is commonly diagnosed in people aged 85 to 89 years[6]

- in England, reported 5-year survival rates are approximately 95% for people with CLL who are aged <60 years and approximately 70% for people with CLL who are aged ≥80 years[7]

2.2 Critique of the company's overview of current service provision

2.2.1 CLL staging

The company stated that the Binet[8] and Rai[9] staging systems (CS, Section 1.3.1.1) and the International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) 2018 criteria[5] (CS, Section 1.3.3.1) are used to stage CLL at diagnosis and this information is used to inform treatment decisions. Clinical advice to the EAG is that the iwCLL 2018 criteria[5] are used in National Health Service (NHS) practice to identify patients with CLL who require active therapy. Clinical advice to the EAG supports the company position (CS, p29 and p33) that a 'watch and wait' approach is used when patients are asymptomatic and considered to have low risk CLL.

2.2.2 NHS patient pathway

The company has presented the current NHS treatment pathway for patients with CLL (CS, Figure 2) and the positioning of pirtobrutinib, should pirtobrutinib be recommended by the National Institute of Health and Care Excellence (NICE) for routine commissioning (CS, Figure 3). The treatment pathway presented by the company was informed by NICE guidance,[10-20] BSH treatment guidelines[21] and by clinical advice to the company.[22]

For patients with R/R CLL who have previously been treated with one or more covalent BTKis (cBTKis), the company has positioned pirtobrutinib as an alternative treatment to a:

- cBTKi
    - acalabrutinib
    - zanubrutinib
    - ibrutinib
- BCL2i
    - venetoclax with rituximab (VenR)
    - venetoclax monotherapy (Ven-mono)
- PI3Ki
    - IdelaR.

The company's positioning of pirtobrutinib is in line with its UK licensed indication which is for pirtobrutinib for "...the treatment of adults with relapsed or refractory [R/R] CLL who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)." Clinical advice to the EAG is that patients who have received one or more previous active therapies would be considered

to have R/R CLL. Relapsed CLL is defined as disease progression after achieving partial or complete response to treatment for ≥6 months and refractory CLL is defined as either non-response to therapy, progression while on treatment, or progression <6 months of completing a fixed duration treatment.[23]

The company considered (CS, p38 and p41) cBTKis and B-cell lymphoma 2 inhibitor (BCL2is) to be standard of care (SoC) for patients with R/R CLL who have previously been treated with one or more cBTKis. Clinical advice to the EAG agrees that cBTKis and BCL2is are standard of care for patients with R/R CLL who have previously been treated with one or more cBTKis in NHS clinical practice.

Clinical advice to the EAG is that:

- patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is **suitable** are treated with VenR or another cBTKi (if they had previously discontinued treatment with a cBTKi due to intolerance)
- patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is **unsuitable** are treated with IdelaR, conventional chemotherapy or best supportive care (BSC)
- patients with R/R CLL who have previously been treated with a cBTKi and a BCL2i, i.e., the dual-exposed population, if eligible, are rechallenged with a BCL2i and are treated with VenR (rechallenge is permitted for patients who relapse after completing treatment with venetoclax);[20] patients who are not eligible for rechallenge with a BCL2i are treated with IdelaR, another cBTKi (if they had previously discontinued treatment with a cBTKi due to intolerance or if they have relapsed but are not refractory to a cBTKi), conventional chemotherapy or BSC.

Clinical advice to the EAG is that:

- treatment with a BCL2i is suitable for most NHS patients and would only be unsuitable for a small proportion of NHS patients with poor renal function
- VenR is more effective than Ven-mono and therefore patients for whom BCL2i is suitable would be treated with VenR
- patients who have previously been treated with ibrutinib with venetoclax (VenI) in the first-line setting (i.e., a combined BTKi and BCL2i therapy), who relapse after completing treatment with VenI, but who are not refractory, would be eligible for, and likely rechallenged with, either a cBTKi or a BCL2i
- IdelaR is rarely used in NHS clinical practice due to toxicity concerns and patient intolerability
- conventional chemotherapy (e.g., BR) is very rarely used in NHS clinical practice but may be considered before BSC
- only patients who have exhausted all active treatment options would receive BSC.

In response to clarification question A2, the company described (and clinical advice to the EAG agrees) that:

- there is no standard definition of BSC
- the aim of BSC is to manage CLL symptoms and improve health-related quality of life (HRQoL); BSC does not prevent disease progression
- BSC may include treatments for infections, treatments to manage anaemia or thrombocytopenia, pain medications and/or treatments for autoimmune conditions.

2.3 Critique of the company's definition of decision problem

A summary of the final scope[2] issued by NICE and the decision problem addressed by the company is presented in Table 1.

2.3.1 Evidence sources

The primary source of direct clinical effectiveness evidence presented by the company for the comparison of pirtobrutinib versus investigator's choice (IdelaR or BR) is the BRUIN CLL-321 trial.[24]

Table 1 Summary of decision problem

	Final scope[2] issued by NICE	Decision problem addressed in the company submission and rational if different from the final scope[2] issued by NICE	EAG comment
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. The population addressed by the company does not include patients with SLL and is in line with the UK licensed indication for pirtobrutinib.	Although the population specified in the final scope[2] issued by NICE includes patients with CLL and patients with SLL, the company is only seeking a NICE recommendation for patients with CLL. The EAG considers that this is appropriate as the UK licensed indication for pirtobrutinib is for "...the treatment of adults with **relapsed or refractory [R/R] CLL** who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)" and 91.2% of BRUIN CLL-321 trial patients had CLL. In addition, the EAG considers that BRUIN CLL-321 data can be used to reflect the clinical effectiveness of patients with CLL. Clinical advice to the EAG is that all patients who have received ≥1 prior treatments would be considered to have R/R CLL.
Intervention	Pirtobrutinib	As per NICE scope.	As per NICE scope.
Comparator(s)	• Zanubrutinib • Acalabrutinib • Ibrutinib • Venetoclax (if disease has progressed after a B-cell receptor pathway inhibitor) • Venetoclax with rituximab • Idelalisib with rituximab • Best supportive care	The company only presented evidence for the comparison of pirtobrutinib versus IdelaR for patients with R/R CLL who have previously been treated with one or more cBTKis. The company considered that VenR was a relevant comparator for patients for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable and for patients who are dual-exposed. However, the company considered that it was unfeasible to conduct ITCs for the comparison of pirtobrutinib vs VenR.	The company considered (CS, p38 and p41) and clinical advice to the EAG agrees that SoC refers to the suitability of a BCL2i and/or a cBTKi for patients with R/R CLL. The EAG considers that the relevant comparators for the three subpopulations identified by the company (see Subgroups) are: **1. Patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable** • VenR

		The company considered that zanubrutinib, acalabrutinib and ibrutinib were not relevant comparators for this appraisal as only a small proportion of patients discontinue prior cBTKis due to intolerance or AEs and only these patients would be eligible for rechallenge with cBTKis. The company also considered that it was unfeasible to conduct ITCs for the comparison of pirtobrutinib vs zanubrutinib, acalabrutinib or ibrutinib. The company considered that Ven-mono was not a relevant comparator. Clinical advice to the company was that Ven-mono is not considered SoC in NHS clinical practice. The company considered (company response to clarification question A2 and clarification question A3) that BSC is difficult to define and that patients with R/R CLL would not receive BSC if they were eligible for active treatments and therefore BSC is not a relevant comparator. The company identified no trials that compared pirtobrutinib or any other relevant comparators vs BSC or vs placebo (as a proxy for BSC) and therefore indirect comparisons were not feasible.	• cBTKi (for patients who discontinue prior treatment with a cBTKi due to intolerance) Clinical advice to the EAG is that: • treatment with a BCL2i is suitable for most patients and would only be unsuitable for patients with poor renal function • Ven-mono is rarely used in NHS clinical practice and is not a relevant comparator (in agreement with the company) • VenR is commonly used in NHS clinical practice and is the most relevant comparator for people who have previously been treated with a cBTKi and for whom SoC is suitable. **2. Patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is unsuitable** • IdelaR • BSC Clinical advice to the EAG is that a BCL2i is only unsuitable for a small proportion of patients with poor renal function. Clinical advice to the EAG is that IdelaR is rarely used to treat NHS patients with R/R CLL due to toxicity. The EAG considers that, in the absence of any other active treatments, IdelaR and BSC are the most relevant comparators for patients who have previously been treated with a cBTKi and for whom SoC is unsuitable. **3. Patients with R/R CLL who have previously been treated with a cBTKi and a BCL2i (either sequentially or in combination), i.e., the dual-exposed population**

			• VenR (for patients who relapse after completing treatment with venetoclax) • cBTKi (for patients who discontinue prior treatment with a cBTKi due to intolerance and for patients who relapse after completing treatment with VenI but who are not refractory to ibrutinib) • IdelaR • BSC In NHS clinical practice, rechallenge with venetoclax is permitted for patients who achieve a response to a fixed-duration venetoclax-based regimen and then experience disease progression after completing venetoclax treatment.[20] Clinical advice to the EAG is that NHS patients who relapse ≥6 months after completing venetoclax treatment can be rechallenged with venetoclax. Clinical advice to the EAG is that patients who relapse after completing treatment with VenI in the first-line setting (i.e., a combined BTKi and BCL2i therapy) but who are not refractory, would be eligible for, and likely rechallenged with, either a cBTKi or a BCL2i. For TA891,[16] clinical advice to the AC was that the fixed duration of VenI reduced the likelihood that patients treated with VenI would become resistant to either venetoclax or ibrutinib; an NHS England representative advised that rechallenge with a cBTKi or a BCL2i should be allowed for patients who had responded well to VenI in the first-line setting. Clinical advice to the EAG is that Ven-mono is rarely used in NHS clinical practice because it is less effective than VenR and agreed that Ven-mono is not a relevant comparator. The

			EAG therefore considers that VenR is the most relevant comparator for patients who are dual-exposed and who are not refractory to BCL2is. Clinical advice to the EAG is that IdelaR is rarely used to treat NHS patients with R/R CLL due to toxicity. Clinical advice to the company and to the EAG is that BSC is difficult to define and that BSC is only a relevant comparator for a very small proportion of patients who have previously been treated with a cBTKi and a BCL2i and who are dual-refractory. In the absence of direct clinical effectiveness evidence for the comparison of pirtobrutinib versus acalabrutinib, zanubrutinib, ibrutinib, VenR or BSC, the company completed a feasibility assessment to determine whether it was appropriate to perform ITCs. The company concluded (CS, Section 2.10.1.3), and the EAG agrees, that it was not appropriate to conduct ITCs (see Section 3.5).
Outcomes	The outcome measures to be considered include: • OS • PFS • response rate • TTNT • AEs of treatment • HRQoL	• OS • PFS • response rate • TTNT • TTW • AEs of treatment • HRQoL The company provided patient-reported TTW because the outcome was assessed in the BRUIN CLL-321 trial.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed	As per the NICE reference case.	As per the NICE reference case.

	in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of biosimilar and generic products should be taken into account.		
Subgroups	Adults with CLL or SLL who have had at least two prior lines of therapy including a BTKi and BCL2i.	The company identified the following three subpopulations as relevant to this appraisal: • patients with CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable • patients with CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is unsuitable • patients with CLL who have previously been treated with a cBTKi and a BCL2i (either sequentially or in combination); referred to as the dual-exposed population	The company identified three subpopulations but has only presented clinical and cost effectiveness evidence for the dual-exposed subpopulation. The company was not able to identify BRUIN CLL-321 trial patients for whom SoC was suitable or BRUIN CLL-321 trial patients for whom SoC was unsuitable and was therefore unable to present evidence separately for these subpopulations.
Special considerations	Guidance will only be issued in accordance with the marketing	N/A; the decision problem addressed in the CS is in line with the NICE scope.	The company is only seeking a NICE recommendation for pirtobrutinib as a

including issues related to equity or equality	authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		treatment for patients with R/R CLL, in line with the UK licensed indication for pirtobrutinib.

AEs=adverse events; BCL2i=B-cell lymphoma 2 inhibitor; BSC=best supportive care; BTKi=Bruton's tyrosine kinase inhibitor; cBTKi=covalent Bruton's tyrosine kinase inhibitor; CLL=chronic lymphocytic leukaemia; EAG=external assessment group; HRQoL=health-related quality of life; ITC=indirect treatment comparator; NHS=National Health Service; NICE=National Institute of Health and Care Excellence; OS=overall survival; PFS=progression-free survival; R/R=relapsed or refractory; SoC=standard of care; SLL=small lymphocytic lymphoma; TTNT=time to next treatment; TTW=time to worsening; Ven-mono=venetoclax monotherapy; VenI=ibrutinib with venetoclax; VenR=venetoclax with rituximab

Source: CS, Table 1 and CS, Section 1.3.3.3

3 CLINICAL EFFECTIVENESS

This section includes a summary and critique of the clinical effectiveness evidence included in the CS:

- Section 3.1 includes the EAG's critique of the company's review of clinical and safety evidence
- Section 3.2 and Section 3.3 includes the EAG's critique of the included studies and clinical effectiveness analyses
- Section 3.4 to Section 3.5 includes the EAG's summary and critique of the company feasibility assessment for indirect treatment comparisons.

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify and select clinical effectiveness evidence for pirtobrutinib and other relevant treatments for patients with R/R CLL. The company's SLR was broader than was required to address the final scope[2] issued by NICE; the company did not restrict the eligibility criteria to patients with R/R CLL who had previously been treated with a cBTKi due to the limited evidence available for this population. The company's literature searches were comprehensive and were updated <6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 2. The EAG considers that the company's systematic review methods were appropriate.

Table 2 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Partly	See CS, Appendix B.1.3, Table 12 Objective stated as identifying "published randomised control[led] trials" but in CS, Section B.1.3 and CS, Table 12 a broader range of study designs were listed
Were appropriate sources searched?	Yes	See CS, Appendix B.1.1.1 and Appendix B.1.1.2 for the sources searched for the original SLR and updated SLR
Was the timespan of the searches appropriate?	No	See CS, Appendix B.1.2.1, Table 6 to Table 8 for the timespans for the original SLR. See Appendix B.1.2.2, Table 9 to Table 11 and the company response to clarification question C3 and clarification question C4, Table 6 to Table 8 for the timespans for updated SLR searches. In response to clarification question C4, the company clarified that the updated SLR was "executed in two parts". The original SLR searches were performed 26 September 2023 and the updated SLR searches were performed 21 May 2024 and 19 February 2025
Were appropriate search terms used?	Yes	See CS, Appendix B.1.2.1, Table 6 to Table 8 for the original SLR search strategies and CS, Appendix B.1.2.2, Table 9 to Table 11 for the updated SLR search strategies
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix B.1.3, Table 12 The SLR eligibility criteria included studies of patients with R/R CLL or patients with CLL who have received ≥1 prior treatments. The company SLR population was broader than was required to address the final scope[2] issued by NICE
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix B.1.3
Were data extracted by two or more reviewers independently?	Yes	See Clinical SLR report,[25] Section 2.5.2. One reviewer extracted data and these data were independently checked by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	See CS, Section 2.5. The company used the Cochrane Risk of Bias Assessment for Randomised Trials Tool v2.0[26] (RoB2) to assess the risk of bias of the BRUIN CLL-321 trial
Was the quality assessment conducted by two or more reviewers independently?	Yes	See Clinical SLR report,[25] Section 3.6 One reviewer quality assessed the included trials and quality assessments were independently checked by a second reviewer
Were attempts to synthesise evidence appropriate?	Yes	See CS, Section 2.10 The company completed a feasibility assessment to assess whether ITCs would generate reliable clinical effectiveness estimates for the comparisons of pirtobrutinib vs the comparators listed in CS, Table 37. The company considered (and the EAG agrees) that ITCs were not feasible for the comparisons of pirtobrutinib vs the relevant comparators (see Section 3.4 to Section 3.5 for the EAG's summary and critique of the company's feasibility assessment)

ITC=indirect treatment comparison; SLR=systematic literature review
Source: LR*i*G in-house checklist

3.2 Critique of the methods of the trials of the technology of interest

The company's SLR identified one randomised controlled trial (RCT), the BRUIN CLL-321 trial, that provided clinical effectiveness evidence for the comparison of pirtobrutinib versus IdelaR for patients with R/R CLL who had previously been treated with a cBTKi. This trial was identified in the updated SLR.

3.2.1 Characteristics of the BRUIN CLL-321 trial

The key characteristics of the BRUIN CLL-321 trial are presented in Table 3.

Patients were randomised 1:1 to either treatment with pirtobrutinib or investigator's choice (IdelaR or BR). In the investigator's choice arm, 82/119 (68.9%) patients received IdelaR and 37/119 (31.1%) patients received BR. Patients were pre-assigned to receive either IdelaR or BR as investigator's choice therapy prior to randomisation.[27] The company reported that the investigator's choice was largely dependent on the region of enrolment, due to local marketing authorisations (CS, p48 and p55).

Clinical advice to the EAG is that:

- IdelaR is only a treatment option for NHS patients with R/R CLL:
    - for whom treatment with a BCL2i is unsuitable and whose disease is refractory to cBTKis
    - who are dual-exposed and whose disease is refractory to cBTKis and BCL2is.
- BR is very rarely used in NHS clinical practice for patients with R/R CLL.

The EAG considers that IdelaR is only a relevant comparator for:

- patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is **unsuitable**
- patients with R/R CLL who have previously been treated with a cBTKi and a BCL2i (i.e., the dual-exposed population) who are not eligible for rechallenge with a BCL2i.

Clinical advice to the EAG is that IdelaR is slightly more effective than BR for patients with R/R CLL. The EAG identified a network meta-analysis (NMA) by Kim 2025[28] that estimated the relative efficacy of systemic treatments in patients with R/R CLL. The NMA[28] results showed that treatment with IdelaR numerically improved progression-free survival (PFS) compared to treatment with BR. However, the patients included in the NMA[28] had not previously been treated with a cBTKi and therefore a broader population than the BRUIN CLL-321 trial population. The EAG therefore considers that if the investigator's choice arm data are used as a proxy for the effectiveness of IdelaR, then the relative efficacy of pirtobrutinib versus IdelaR may be overestimated.

Investigator's choice arm patients were permitted to crossover to the pirtobrutinib arm on independent review committee (IRC)-confirmed progressive disease (PD), according to iwCLL 2018[5] criteria.

Table 3 Clinical effectiveness studies of technology of interest

	BRUIN CLL-321 trial
Role in this evaluation	Primary source of direct clinical effectiveness evidence for the comparison of pirtobrutinib versus investigator's choice (IdelaR or BR)
Study type	Ongoing, phase III, open label, multicentre, international, randomised (1:1) controlled trial
Patient group	Adult patients with confirmed diagnosis of CLL/SLL with R/R disease previously treated with a covalent BTKi (patients who had also previously been treated with venetoclax [a BCL2 inhibitor] were eligible for inclusion)
Subgroups	• age at study entry • sex • race • ethnicity • geographical region • histology (CLL versus SLL) • Rai stage (0-II versus III-IV) • ECOG PS • prior lines of systemic therapies • prior BCL2 treatment • prior venetoclax treatment • most recent prior anticancer therapy including cBTKi • reason for discontinuation from the most recent prior cBTKi • bulky disease • β2 microglobulin group at baseline • cytogenetic features • high risk features
Exclusion criteria	See CS, Table 14. Exclusion criteria included prior exposure to noncovalent (reversible) BTKi or a major bleeding event on a prior BTKi
Intervention	200mg QD oral pirtobrutinib in continuous 28-day cycles
Comparator	Investigators preselected whether patients would be treated with IdelaR or BR: • 150mg BID oral idelalisib in continuous 28-day cycles with 375mg/m^2 IV rituximab on Day 1 of Cycle 1, then 500mg/m^2 Q2W for four infusions and Q4W for three infusions • 70mg/m^2 IV bendamustine on Day 1 and Day 2 of each 28-day cycle for Cycle 1 to Cycle 6 with 375mg/m^2 IV rituximab Day 1 of Cycle 1 and then 500mg/m^2 on Day 1 of each 28-day cycle for Cycles 2 to Cycle 6
Primary outcome	IRC-assessed PFS
Secondary outcomes	OS, investigator-assessed PFS, ORR, BOR, DoR, EFS, TTNT, TTW of CLL/SLL-related symptoms, TTW of physical function and safety
Exploratory outcomes	EORTIC QLQ-C30 and EQ-5D-5L
Location	232 centres across Australia, Austria, Belgium, Canada, China, Croatia, Czechia, France, Germany, Hungary, Ireland, Israel, Italy, Japan, the Republic of Korea, Poland, Russian Federation, Singapore, Spain, Switzerland, Taiwan, Turkey, UK (13 sites) and USA

BID=twice daily; CLL=chronic lymphocytic leukaemia; DoR=duration of response; EFS=event-free survival; IdelaR=idelalisib plus rituximab; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L=EuroQol-5 Dimensions-5 Levels; IRC=independent review committee; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; QD=once daily; Q2W=every 2 weeks; Q4W=every 4 weeks; TTNT=time to next treatment; TTW=time to worsening.
Source: CS, Table 14 and Table 20

3.2.2 Characteristics of the BRUIN CLL-321 trial patients

The company identified three subpopulations as relevant to the appraisal (see Table 1) but only presented evidence from the BRUIN CLL-321 trial for the ITT population and the dual-exposed subpopulation (i.e., patients who have previously been treated with a cBTKi and a BCL2i).

The baseline characteristics of the BRUIN CLL-321 trial ITT population are presented in Table 4 and Table 5. Clinical advice to the EAG is that, overall, the baseline characteristics of the BRUIN CLL-321 trial ITT population are representative of NHS patients with R/R CLL who have previously been treated with one or more cBTKis, with the exceptions that, compared to NHS patients the BRUIN CLL-321 trial patients were:

- younger
- more heavily pretreated; a smaller proportion of NHS patients are dual-exposed and very few NHS patients have received prior chemotherapy.

The baseline characteristics of the BRUIN CLL-321 trial dual-exposed subpopulation are presented in CS, Section 2.3.2.2.

Table 4 Baseline characteristics of the BRUIN CLL-321 trial ITT population

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)
Race, n (%)		
Asian	14 (11.8)	15 (12.6)
Black or African American	1 (0.8)	5 (4.2)
White	98 (82.4)	95 (79.8)
Not reported	5 (4.2)	4 (3.4)
Duration of disease (months), median (range)	118.70 (16.76 to 300.22)	120.87 (8.05 to 323.52)
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)
Bulky disease, n (%)		
<5cm	67 (56.3)	54 (45.4)
≥5cm	48 (40.3)	58 (48.7)
No measurable target lesion at baseline	4 (3.4)	7 (5.9)
ß$_2$ microglobulin (mg/L), n (%)		
≤3.5	27 (22.7)	39 (32.8)
>3.5	89 (74.8)	77 (64.7)
Missing/Unknown	3 (2.5)	3 (2.5)
High-risk features, n (%)		
TP53 mutation [a]	33 (27.7)	26 (21.8)
Del(17p)[b]	39 (32.8)	43 (36.1)
TP53 mutation and/or del(17p)[c]	50 (42.0)	51 (42.9)
IGHV unmutated[d]	90 (75.6)	74 (62.2)
Complex karyotype[e]	53 (44.5)	44 (37.0)
11q deletion[f]	19 (16.0)	25 (21.0)

[a] Data were missing/unknown for 31/119 (26.1%) pirtobrutinib arm patients and 38/119 (31.9%) investigator's choice arm patients
[b] Data were missing/unknown for 8/119 (6.7%) pirtobrutinib arm patients and 7/119 (5.9%) investigator's choice arm patients
[c] Data were missing/unknown for 31/119 (26.1%) pirtobrutinib arm patients and 31/119 (26.1%) investigator's choice arm patients
[d] Data were missing/unknown for 22/119 (18.5%) pirtobrutinib arm patients and 26/119 (21.8%) investigator's choice arm patients
[e] Data were missing/unknown for 45/119 (37.8%) pirtobrutinib arm patients and 44/119 (37.0%) investigator's choice arm patients
[f] Data were missing/unknown for 18/119 (15.1%) pirtobrutinib arm patients and 20/119 (16.8%) investigator's choice arm patients
ECOG PS=Eastern Cooperative Oncology Group performance status; TP53=tumour protein 53; del(17p)=deletion of the short arm of chromosome 17; IGHV=immunoglobulin heavy-chain variable region gene
Source: CS, Table 15 and Table 16

Table 5 Prior systemic therapies of the BRUIN CLL-321 trial ITT population

Prior systemic therapy	Pirtobrutinib (n=119)	IdelaR or BR (n=119)
Number of lines of prior systemic therapy, median (range)	3 (1 to 13)	3 (1 to 11)
cBTKi		
Acalabrutinib	17 (14.3)	20 (16.8)
Ibrutinib	100 (84.0)	106 (89.1)
Zanubrutinib	9 (7.6)	7 (5.9)
Other	5 (4.2)	3 (2.5)
Venetoclax	60 (50.4)	60 (50.4)
BCL2i	60 (50.4)	62 (52.1)
Chemotherapy	81 (68.1)	83 (69.7)
Anti-CD20 antibody	86 (72.3)	83 (69.7)
PI3K agent	11 (9.2)	11 (9.2)
IMID/immunomodulator	2 (1.7)	3 (2.5)
Prior stem cell transplant therapy	3 (2.5)	1 (0.8)
Other systemic therapy	6 (5.0)	9 (7.6)

BCL2i=B-cell lymphoma 2 inhibitor; cBTKi=covalent Bruton's tyrosine kinase inhibitor; IMID=immunomodulatory drug; PI3K=phosphoinositide 3-kinase
Source: CS, Table 17

3.2.3 Quality assessment of the BRUIN CLL-321 trial

The company conducted a quality assessment of the BRUIN CLL-321 trial (CS, Section 2.5 and company response to clarification question C5, Table 11) using the Cochrane Risk of Bias Assessment for Randomised Trials Tool v2.0[26] (RoB2). However, in the RoB2 tool guidance, it is recommended that each outcome of interest should be assessed separately using the RoB2 tool.[26] The EAG has therefore completed RoB2[26] quality assessments for the primary outcome, IRC-assessed PFS, and the key secondary outcome, overall survival (OS). The company's assessments and EAG comments are presented in Table 6 and Table 7. The EAG's assessment is that the BRUIN CLL-321 trial is of good methodological quality.

Table 6 Quality assessment of the BRUIN CLL-321 trial: IRC-assessed PFS (primary outcome)

Bias domain and signalling question	Company assessment	EAG assessment	EAG comment
Bias arising from the randomisation process			
1.1 Was the allocation sequence random?	Y; Low risk of bias	Y; Low risk of bias	Randomization was performed using an IXRS and stratified by del(17p) status using fluorescence in situ hybridization from either local or central testing during screening (yes or no) and previous treatment with venetoclax (yes or no)
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y; Low risk of bias	Y; Low risk of bias	
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N; Low risk of bias	N; Low risk of bias	Baseline patient characteristics were generally balanced between treatment arms
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-
Bias due to deviations from intended interventions			
2.1 Were participants aware of their assigned intervention during the trial?	Y; High risk of bias	Y; Low risk of bias	The BRUIN CLL-321 trial was an open-label trial, however, the EAG considers that IRC-assessed PFS results would not be impacted by patients, carers and site personnel being aware of the patient's treatment allocation
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y; High risk of bias	Y; Low risk of bias	
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Y; High risk of bias	Y; High risk of bias	Patients randomised to investigator's choice were permitted to switch to treatment with pirtobrutinib following disease progression
2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	PN; Low risk of bias	N; Low risk of bias	IRC-assessed PFS results (primary outcome) were not confounded by patient crossover
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA; Other	-	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y; Low risk of bias	Y; Low risk of bias	Intention-to-treat analysis

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA; Other	-	-
Risk of bias judgment (low/high/some concerns)	**Some concerns**	**Low risk**	-
Bias due to missing outcome data			
3.1 Were data for this outcome available for all or nearly all participants randomised?	Y; Low risk of bias	Y; Low risk of bias	Yes, data reported for ITT population, with results presented in accordance with the CONSORT guidelines
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA; Other	-	-
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA; Other	-	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI; Other	-	-
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-
Bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	N; Low risk of bias	N; Low risk of bias	Disease progression was assessed according to standard iwCLL 2018 criteria
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N; Low risk of bias	N; Low risk of bias	PFS assessed by blinded IRC
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N; Low risk of bias	N; Low risk of bias	
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA; Other	-	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA; Other	-	-
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-

Bias in selection of the reported result			
5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?	Y; Low risk of bias	Y; Low risk of bias	Yes, the analyses followed the study protocol; with all revisions fully documented.
Is the numerical result being assessed likely to have been selected on the basis of the results from:			
5.2... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N; Low risk of bias	N; Low risk of bias	All IRC-assessed PFS results reported for all planned analyses.
5.3... multiple eligible analyses of the data?	N; Low risk of bias	N; Low risk of bias	
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-
Overall bias			
Risk of bias judgment (low/high/some concerns)	**Some concerns**	**Low risk**	-

CONSORT=Consolidated Standards of Reporting Trials; del(17p)=deletion of the short arm of chromosome 17; IRC=independent review committee; ITT=intention-to-treat; iwCLL=International Workshop on Chronic Lymphocytic Leukemia; IXRS=interactive voice/web response system; N=no; NA=not applicable; PFS=progression-free survival; PN=probably no; PY=probably yes; Y=yes
Source: company response to clarification question C5, Table 11

Table 7 Quality assessment of the BRUIN CLL-321 trial: OS (key secondary outcome)

Bias domain and signalling question	Company assessment	EAG assessment	EAG comment
Bias arising from the randomisation process			
1.1 Was the allocation sequence random?	Y; Low risk of bias	Y; Low risk of bias	Randomization was performed using an IXRS and stratified by del(17p) status using fluorescence in situ hybridization from either local or central testing during screening (yes or no) and previous treatment with venetoclax (yes or no)
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y; Low risk of bias	Y; Low risk of bias	
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N; Low risk of bias	N; Low risk of bias	Baseline patient characteristics were generally balanced between treatment arms
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-
Bias due to deviations from intended interventions			
2.1 Were participants aware of their assigned intervention during the trial?	Y; High risk of bias	Y; Low risk of bias	The BRUIN CLL-321 trial was an open-label trial, however, the EAG considers that OS results would not be impacted by patients, carers and site personnel being aware of the patient's treatment allocation
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y; High risk of bias	Y; Low risk of bias	
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Y; High risk of bias	Y; High risk of bias	Patients randomised to investigator's choice were permitted to switch to treatment with pirtobrutinib following disease progression
2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	PN; Low risk of bias	Y; High risk of bias	OS results were confounded by patient crossover
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA; Other	N; High risk of bias	Crossover only applied to the investigator's choice arm
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y; Low risk of bias	PY; Low risk of bias	The EAG considers that the two-stage AFT method is an appropriate method of crossover adjustment, however, additional sensitivity analyses would have provided greater clarity around the residual uncertainty relating to the true OS treatment effect

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA; Other	-	-
Risk of bias judgment (low/high/some concerns)	**Some concerns**	**High risk**	-
Bias due to missing outcome data			
3.1 Were data for this outcome available for all or nearly all participants randomised?	Y; Low risk of bias	Y; Low risk of bias	Yes, data reported for ITT population, with results presented in accordance with the CONSORT guidelines
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA; Other	-	-
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA; Other	-	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI; Other	-	-
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-
Bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	N; Low risk of bias	N; Low risk of bias	OS was defined as the time from randomization until death from any cause
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N; Low risk of bias	N; Low risk of bias	-
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N; Low risk of bias	Y; High risk of bias	The EAG considers that OS is an objective outcome that would not be influenced by outcome assessors' awareness of the intervention received
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA; Other	N; Low risk of bias	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA; Other	-	-
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-

Bias in selection of the reported result			
5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?	Y; Low risk of bias	Y; Low risk of bias	Yes, the analyses followed the study protocol; with all revisions fully documented.
Is the numerical result being assessed likely to have been selected on the basis of the results from:			
5.2... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N; Low risk of bias	N; Low risk of bias	All OS results reported for all planned analyses.
5.3... multiple eligible analyses of the data?	N; Low risk of bias	N; Low risk of bias	
Risk of bias judgment (low/high/some concerns)	**Low risk**	**Low risk**	-
Overall bias			
Risk of bias judgment (low/high/some concerns)	**Some concerns**	**High risk**	-

AFT=accelerated failure time; CONSORT=Consolidated Standards of Reporting Trials; del(17p)=deletion of the short arm of chromosome 17; ITT=intention-to-treat; IXRS=interactive voice/web response system; N=no; NA=not applicable; OS=overall survival; OS=overall survival; PN=probably no; PY=probably yes; Y=yes
Source: company response to clarification question C5, Table 11

3.2.4 Statistical approach adopted for the analysis of results from the BRUIN CLL-321 trial

Generally, the EAG considers that the company used appropriate statistical methods to analyse BRUIN CLL-321 trial data. However, the EAG notes that the censoring rules described in CS, Table 20 are inappropriate; for example, for OS analyses, it is stated that patients who experienced a death on or before the data cut-off (DCO) date would be censored at the date of death. The EAG considers that the inappropriate censoring rules described in the CS are most likely due to a transcription error as the censoring methods described in the Trial Statistical Analysis Plan (TSAP)[29] are appropriate.

The company appropriately applied a sequential hypothesis testing procedure to control the overall type 1 error rate for the study at 0.05. This testing procedure allowed formal testing of IRC-assessed PFS at the time of the primary PFS analysis; if the result from this test was statistically significant (2-sided $p<0.05$), then formal testing of OS at the final OS analysis would be conducted (with a one-sided $p<0.02499$ indicating a statistically significant difference). For the sequential hypothesis testing procedure, the company pre-specified that an arbitrary one-sided alpha of 0.00001 would account for a descriptive interim OS analysis at the time of the primary PFS analysis (29 August 2023 DCO). The EAG highlights that only the p-values from the primary PFS analysis (i.e., IRC-assessed PFS) and the final OS analysis in the BRUIN CLL-321 trial ITT population are from formal statistical tests; all other BRUIN CLL-321 trial p-values presented in the CS and in this EAG report are nominal.

A key feature of the BRUIN CLL-321 trial is that patients who were randomised to the investigator's choice arm could crossover to the pirtobrutinib arm upon IRC-confirmed PD. To assess the impact of this treatment switching, the company pre-specified (TSAP, p18) a sensitivity analysis for OS. In this analysis, patients who crossed over from the investigator's choice arm to the pirtobrutinib arm were censored at the time of crossover. The EAG highlights that this sensitivity analysis is at risk of selection bias as switching is highly likely to be related to prognosis. However, the company also appropriately explored more complex methods to account for treatment switching, including the Rank Preserving Structural Failure Time Model (RPSFTM), the inverse probability censoring weighting (IPCW) method and the two-stage accelerated failure time (AFT) method. These methods were not pre-specified in the TSAP. Further discussion of these complex methods is provided in Section 3.3.1.1.

As Cox proportional hazard (PH) models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for time-to-event outcomes, the company assessed the validity of the PH assumption. The Cox PH model is only an appropriate method if the PH assumption

holds, i.e., if the event hazards associated with the intervention and comparator data are proportional over time. The company considered log-cumulative hazard plots, Schoenfeld residual plots and a statistical test of proportional hazards to assess the PH assumption. These plots and test results were provided in the CS reference pack. The statistical test method was not provided in the CS; the EAG has assumed that the company appropriately used the Schoenfeld residuals test (Grambsch-Therneau test). The company assessed the validity of the PH assumption for investigator-assessed PFS, IRC-assessed PFS, and time to treatment discontinuation (TTD), a post-hoc endpoint used in the company's economic model. No assessment of PH was provided for OS or time to next treatment (TTNT).

3.3 Critique of the results of the trials of the technology of interest

The company has presented BRUIN CLL-321 trial results from the primary analysis (DCO 29 August 2023) and the most recent analysis (DCO 29 August 2024 DCO[30]) in CS, Section 2.6.

Key BRUIN CLL-321 trial results from the most recent DCO (29 August 2024 DCO[30]) for the ITT population and for the dual-exposed population are presented in Section 3.3.1 and Section 3.3.2, respectively.

3.3.1 BRUIN CLL-321 trial key efficacy results

ITT population OS, independent review committee IRC-assessed PFS, investigator-assessed PFS and TTNT results are presented in Table 8. Objective response rate (ORR) results are presented in Table 9.

These results show that the BRUIN CLL-321 trial IRC-assessed PFS, investigator-assessed PFS and TTNT hazard ratios (HRs) were nominally statistically significant and favoured pirtobrutinib over investigator's choice. The BRUIN CLL-321 trial OS HR numerically favoured investigator's choice over pirtobrutinib; however:

- the OS results were confounded by crossover (see Section 3.3.1.1)
- the CIs were wide and crossed 1
- the differences in OS event rates were modest.

Furthermore, regarding the assessment of PH for IRC-assessed PFS and investigator-assessed PFS, the company states, and the EAG agrees, that the plots and tests were "...inconsistent in assessing proportional hazards with plots tending to show nonproportionality and statistical tests unable to reject the null hypothesis of proportionality due to nonsignificant results". In light of the company's assessment, the EAG considers that a single, constant hazard ratio from a Cox PH model may not accurately represent the treatment effect over the

entire follow-up period for these endpoints. The validity of the PH assumption for OS and TTNT remains unknown.

Table 8 BRUIN CLL-321 trial key efficacy results: ITT population

	Pirtobrutinib (n=119)	IdelaR or BR (n=119)
IRC-assessed PFS		
Median follow-up, months (95% CI)	19.35 (16.66 to 22.14)	17.74 (13.93 to 22.90)
Number of events, n (%)	74 (62.2)	79 (66.4)
Median PFS, months (95% CI)	13.96 (11.24 to 16.56)	8.74 (8.08 to 10.38)
HR (95% CI); p-value	0.536 (0.385 to 0.746); p=0.0002[a]	
Investigator-assessed PFS		
Median follow-up, months (95% CI)	19.38 (16.72 to 21.98)	17.54 (13.93 to 22.90)
Number of events, n (%)	69 (58.0)	77 (64.7)
Median PFS, months (95% CI)	15.28 (12.81 to 19.94)	9.20 (7.33 to 10.64)
HR (95% CI); p-value	0.475 (0.338 to 0.669); p<0.0001[a]	
OS		
Median follow-up, months (95% CI)	20.37 (18.23 to 21.88)	19.22 (18.10 to 21.06)
Number of events, n (%)	38 (31.9)	32 (26.9)
Median OS, months (95% CI)	29.67 (27.10 to NE)	NE (28.88 to NE)
HR (95% CI); p-value	1.090 (0.679 to 1.749); p=0.7202	
3-month OS rate, % (95% CI)	[redacted]	[redacted]
6-month OS rate, % (95% CI)	[redacted]	[redacted]
9-month OS rate, % (95% CI)	[redacted]	[redacted]
12-month OS rate, % (95% CI)	[redacted]	[redacted]
15-month OS rate, % (95% CI)	[redacted]	[redacted]
18-month OS rate, % (95% CI)	[redacted]	[redacted]
21-month OS rate, % (95% CI)	[redacted]	[redacted]
24-month OS rate, % (95% CI)	[redacted]	[redacted]
TTNT		
Median follow-up, months (range)	[redacted]	[redacted]
Number of events, n (%)	54 (45.4)	82 (68.9)
Median TTNT, months (95% CI)	24.0 (17.8 to 29.7)	10.9 (8.7 to 12.5)
HR (95% CI); p-value	0.37 (0.25 to 0.52); p<0.0001[a]	

[a] Nominal p-value
CI=confidence interval; HR=hazard ratio; IRC=independent review committee; ITT=intention-to-treat; PFS=progression-free survival; OS=overall survival; TTNT=time to next treatment
Source: CS, Table 25, Table 27, Table 30 and Table 33; CSR Addendum 2, Table 15

Table 9 BRUIN CLL-321 trial IRC-assessed ORR results: ITT population

	Pirtobrutinib (n=119)	IdelaR or BR (n=119)
Median follow-up, months (95% CI)	19.35 (16.66 to 22.14)	17.74 (13.93 to 22.90)
ORR, n (%)	58 (48.7)	46 (38.7)
p-value	p=0.1100[a]	
BOR		
CR, n (%)	[redacted]	[redacted]
PR, n (%)	[redacted]	[redacted]
SD, n (%)	[redacted]	[redacted]
PD, n (%)	[redacted]	[redacted]

[a] Nominal p-value
BOR=best overall response; CI=confidence interval; CR=complete response; IRC=independent review committee; ITT=intention-to-treat; ORR=overall response rate; PD=progressed disease; PR=partial response; SD=stable disease
Source: CS, Table 29

3.3.1.1 OS sensitivity analyses

The company considered (CS, p78) that the BRUIN CLL-321 trial OS results were confounded by crossover. In the BRUIN CLL-321 trial, 50/66 (75.8%) investigator's choice arm patients who were eligible for crossover switched to pirtobrutinib following IRC-confirmed PD (CS, Section 2.3.3). The company performed OS sensitivity analyses to assess the impact of patient crossover on OS results (CS, Section 2.4.2.3 and p80), including one pre-specified OS sensitivity analysis (TSAP, p18) and three additional methodologically complex exploratory OS sensitivity analyses, namely: the RPSFTM, the IPCW method and the two-stage AFT method (CS, Section 2.4.2.3). The company did not provide RPSFTM OS sensitivity analysis results as the company considered the method to be inappropriate (see Section 3.3.1.2).

OS sensitivity analysis results from the most recent DCO (29 August 2024 DCO[30]) are presented in Table 10. The BRUIN CLL-321 trial OS sensitivity analysis HRs numerically favoured pirtobrutinib over investigator's choice, however, CIs were wide and crossed 1 and the EAG considers that there are limitations to the OS sensitivity analyses used (see Section 3.3.1.2).

Table 10 BRUIN CLL-321 trial OS sensitivity analysis results

OS analysis	Pirtobrutinib versus investigator's choice, HR (95% CI)
Unadjusted	1.090 (0.679 to 1.749)
Pre-specified sensitivity analysis	
Patients censored at the time of crossover	0.986 (0.570 to 1.706)
Post-hoc sensitivity analyses	
IPCW method	0.872 (0.507 to 1.500)
Two-stage AFT method	0.776 (0.479 to 1.258)

AFT=accelerated failure time; CI=confidence interval; HR=hazard ratio; IPCW=inverse probability censoring weighting; OS=overall survival
Source: CS, Table 30 and Table 31

3.3.1.2 Critique of OS sensitivity analyses

In the pre-specified sensitivity analysis, patients who crossed over from the investigator's choice arm to the pirtobrutinib arm were censored at the time of crossover. The EAG highlights that this sensitivity analysis is at risk of selection bias as switching is highly likely to be related to prognosis.

The EAG highlights that the RPSFTM relies critically on the assumption that the treatment effect for patients who switch to the experimental treatment is the same as the treatment effect for patients initially randomised to the experimental group. This "common treatment effect" assumption may not be valid for BRUIN CLL-321 trial investigator's choice arm patients who only switch to pirtobrutinib after disease progression. Clinical advice to the EAG is that patients who are treated with pirtobrutinib from randomisation are likely to experience greater treatment benefit than patients who switch to pirtobrutinib after initially being randomised to investigator's choice. The EAG therefore agrees with the company's judgement that it is inappropriate to use this method to adjust for treatment switching in the BRUIN CLL-321 trial (CS, p69).

The IPCW method relies on the "no unmeasured confounders" assumption, i.e., all variables that influence both i) the decision to switch treatments and ii) patient mortality, which must be measured and included in the weighting model. The company included various covariates measured at baseline (for all investigator's choice arm patients) and various covariates measured at the time of disease progression (for patients in the investigator's choice arm who experienced disease progression) in their IPCW model (see CS, p69). The company did not include del(17p) and/or TP53 mutation in their IPCW model; clinical advice to the EAG is that these covariates may influence both the decision to switch treatments and patient mortality.

An important limitation of the IPCW method is that when switching proportions are high, IPCW results can be prone to substantial bias due to extreme weights. At the time of the BRUIN CLL-321 final OS analysis, 75.8% of patients eligible to switch had done so (50/66 patients

with disease progression). The company's IPCW model is therefore likely to have produced extreme weights as the model reweights the small number of non-switchers (n=16) to represent the much larger proportion of patients who did switch.

The two-stage AFT model is likely to be a more robust method than the IPCW method when switching rates are high. The two-stage AFT method does not rely on reweighting non-switchers and is therefore inherently not prone to bias due to extreme weights. Similar to the IPCW method, the AFT method requires the "no unmeasured confounders" assumption. For the two stage AFT model, the assumption requires that all variables that influence both i) the decision to switch treatments for patients with PD and ii) post-progression patient mortality, must be included in the AFT model. The company included various covariates measured at the time of disease progression in the AFT model (see CS, p70) but did not include del(17p) and/or TP53 mutation. Clinical advice to the EAG is that these covariates may influence both the decision to switch treatments and post-progression mortality.

Considering the methods explored by the company, the EAG considers that the two-stage AFT method is the most appropriate approach to use to account for treatment switching. However, the company did not provide certain important details regarding the methods used to implement the two-stage AFT model including:

- the methods used to select covariates; the EAG does not know if it would have been feasible for the company to include del(17p) and/or TP53 mutation status in the model
- whether any bootstrapping or re-censoring was performed; the company discussed bootstrapping (CS, Section 3.3.2.2) but it is not clear whether this method was applied. The NICE Decision Support Unit (DSU)[31] recommends that, for submissions to NICE, the two-stage estimation methods should be applied with and without re-censoring. Applying bootstrapping methods would also ensure that uncertainty around the reported effect estimates was correctly estimated
- the methods used to generate a HR. The company has not demonstrated that the PH assumption holds, nor has the company stated that the HR should be interpreted as an average treatment effect over the trial follow-up period; it is not clear how the reported HR should be interpreted.

The EAG considers that more comprehensive exploration of crossover methods would have been informative. For example, the company could have explored recent developments to the RPSFTM that allow for relaxation of the common treatment effect assumption, and/or examined the distribution of weights applied in the IPCW model, potentially implementing weight truncation, if necessary, to investigate the impact of any extreme weights on reported effect estimates.

3.3.2 BRUIN CLL-321 trial subgroup analyses

Subgroup analysis stratified by prior treatment with a BCL2i (i.e., the dual-exposed population) was a pre-specified subgroup analysis in BRUIN CLL-321 trial (see Table 3). The company provided IRC-assessed PFS from the most recent DCO (29 August 2024 DCO) and OS, investigator-assessed PFS and TTNT from the primary analysis (DCO 29 August 2023) for the dual-exposed subpopulation (i.e., patients who have previously been treated with a cBTKi and a BCL2i).

OS, IRC-assessed PFS and TTNT for the dual-exposed subpopulation are presented in Table 11. These data show that the BRUIN CLL-321 trial IRC-assessed PFS, investigator-assessed PFS and TTNT hazard ratios (HRs) were [redacted] in the dual-exposed subpopulation. However, the BRUIN CLL-321 trial OS HR [redacted] in the dual-exposed subpopulation. The company did not perform OS sensitivity analyses for the dual-exposed subpopulation and therefore the OS results presented are not adjusted for patient crossover.

Table 11 BRUIN CLL-321 trial key efficacy results: dual-exposed subpopulation

	Pirtobrutinib (n=60)	IdelaR or BR (n=62)
IRC-assessed PFS (29 August 2024 DCO)		
Number of events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	0.539 (0.349 to 0.831); NR	
Investigator-assessed PFS (29 August 2024 DCO)[a]		
Number of events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
OS (29 August 2024 DCO)[b]		
Number of events, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
TTNT (29 August 2024 DCO)[c,d]		
HR (95% CI); p-value	0.37 (0.23 to 0.62); p<0.0001[e]	

[a] Data extracted from CS, Table 28; investigator-assessed PFS was reported as HR 0.460 (95% CIs 0.294 to 0.719) in CS, Figure 17
[b] Data extracted from CS, Table 32 which was incorrectly titled "PFC based on investigator assessment"; OS was reported as HR 1.458 (95% CIs 0.803 to 2.647) in CS, Figure 18
[c] Data extracted from CS, Table 34; TTNT was reported as HR 0.409 (95% CIs 0.255 to 0.654) in Sharman 2025,[1] Figure A2
[d] In CS, Table 34, the number of patients in the IdelaR or BR arm was reported as n=60
[e] Nominal p-value

CI=confidence interval; DCO=data cut-off; HR=hazard ratio; IRC=independent review committee; ITT=intention-to-treat; NE=not estimable; NR=not reported; OS=overall survival; PFS=progression-free survival; TTNT=time to next treatment
Source: CS, Table 26, Table 28, Table 32 and Table 34 and Figure 16 to Figure 18; CSR Addendum 2, Figure 3

3.3.3 BRUIN CLL-321 trial patient reported outcomes

In the BRUIN CLL-321 trial, HRQoL data were collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the five-item EORTC Item Library 58 (IL58) and the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L). HRQoL data were collected at Week 5, Week 9, Week 13, Week 17, Week 21 and Week 25.

The company provided EORTC QLQ-C30 data from the 9 February 2024 DCO in the BRUIN-CLL-321 trial patient reported outcomes (PRO) report.[32] The company stated (BRUIN-CLL-321 trial PRO report,[32] p48) "that none of the PRO endpoints in this trial were alpha-controlled and the sample size was not planned to detect clinically meaningful differences with sufficient power; therefore, these results should be considered as descriptive and hypothesis generating". The company did not provide BRUIN-CLL-321 trial EQ-5D-5L results for the ITT population because "[EQ-5D-5L] analyses were to be conducted at the country level with appropriate weights assigned by region for health technology assessment (HTA) purposes".[32]

Time to worsening (TTW) of PROs are presented in Table 12 and the proportion of BRUIN CLL-321 trial patients with improved, stable or worse PROs during the period from baseline to Week 25 are presented in Table 13.

Table 12 BRUIN CLL-321 trial TTW in PROs: ITT population

	Pirtobrutinib (n=[redacted])	IdelaR or BR (n=[redacted])
TTW in CLL/SLL-related symptoms		
Number of events, n (%)	[redacted]	[redacted]
Median TTW, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
TTW in physical function		
Number of events, n (%)	[redacted]	[redacted]
Median TTW, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
TTW in expanded fatigue		
Number of events, n (%)	[redacted]	[redacted]
Median TTW, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
TTW in EORTC QLQ-C30 GHS/QoL		
Number of events, n (%)	[redacted]	[redacted]
Median TTW, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	

[a] Nominal p-value
CI=confidence interval; EORTC=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS=global health score; HR=hazard ratio; ITT=intention to treat; NE=not estimable; PRO=patient reported outcomes; QoL=quality of life; TTW=time to worsening
Source: BRUIN CLL-321 trial PRO report,[1] Table 10 to Table 13

Table 13 Proportion of BRUIN CLL-321 trial patients with improved, stable or worse PROs between baseline and Week 25: ITT population

	Pirtobrutinib (n=[redacted])	IdelaR or BR (n=[redacted])
CLL/SLL-related symptoms		
Worse, n (%)	[redacted]	[redacted]
Stable, n (%)	[redacted]	[redacted]
Improved, n (%)	[redacted]	[redacted]
Not reported, n (%)	[redacted]	[redacted]
EORTC QLQ-C30 physical function		
Worse, n (%)	[redacted]	[redacted]
Stable, n (%)	[redacted]	[redacted]
Improved, n (%)	[redacted]	[redacted]
Not reported, n (%)	[redacted]	[redacted]
Expanded fatigue		
Worse, n (%)	[redacted]	[redacted]
Stable, n (%)	[redacted]	[redacted]
Improved, n (%)	[redacted]	[redacted]
Not reported, n (%)	[redacted]	[redacted]

EORTC=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ITT=intention to treat; PRO=patient reported outcomes
Source: BRUIN CLL-321 trial PRO report,[1] Figure 3, Figure 6 and Figure 9

3.3.3.1 Time to worsening in CLL/SLL-related symptoms

In the BRUIN CLL-321 trial, CLL/SLL-related symptoms were assessed using eight EORTC QLQ-C30 items and the IL58.

[redacted] clinically meaningful change (i.e., <15.38 point decrease or <10.25 increase) in CLL/SLL-related symptoms from baseline to Week 25. CLL/SLL-related symptom scores were [redacted] in the pirtobrutinib arm than in the investigator's choice arm at [redacted]. TTW in CLL/SLL-related symptoms [redacted].

3.3.3.2 EORTC QLQ-C30 physical function

[redacted] clinically meaningful change (i.e., <13.3 point increase or decrease) in EORTC physical function from baseline to Week 25. TTW for EORTC physical function [redacted].

3.3.3.3 Expanded fatigue

Expanded fatigue was measured using three items from the EORTC QLQ-C30 fatigue subscale and three items from the IL58.

[redacted] clinically meaningful change (i.e., <16.66 point decrease or <11.11 increase) in expanded fatigue from baseline to Week 25. TTW of expanded fatigue [redacted].

3.3.3.4 EORTC QLQ-C30 GHS/QoL

TTW of EORTC QLQ-C30 GHS/QoL [redacted]. [redacted] EORTC QLQ-C30 GHS/QoL from baseline to Week 25.

3.3.4 BRUIN CLL-321 trial safety and tolerability results

The company presented BRUIN CLL-321 trial safety and tolerability data in CS, Section 2.11. BRUIN CLL-321 trial safety results from the most recent DCO (29 August 2024 DCO) are summarised in Section 3.3.4.1 to Section 3.3.4.3. Pirtobrutinib and idelalisib are continuous treatments, whereas bendamustine and rituximab have a fixed duration of approximately 6 months (see Table 3). Median duration of pirtobrutinib treatment was longer (15.05 months, range: [redacted] months to [redacted] months) than the median duration of idelalisib treatment (7.08 months, range: [redacted] months to [redacted] months). At the time of the most recent DCO (29 August 2024 DCO), a higher proportion of patients in the pirtobrutinib arm (46/119, 38.7%) were still receiving their randomised treatment than in the investigator's choice arm (5/119, 4.2%) and 29/50 (58%) investigator's choice arm patients who switched to pirtobrutinib following disease progression were still receiving pirtobrutinib treatment (CS, Section 2.3.3).

3.3.4.1 Treatment-emergent adverse events

Nearly all patients in the pirtobrutinib arm (108/116, 93.1%) and in the investigator's choice arm (107/109, 98.2%) experienced ≥1 treatment-emergent adverse event (TEAE).

The most common any grade AE (Sharman 2025,[1] Table A3 and CSR Addendum 2,[30] Table 30) was infections (pirtobrutinib: 74/116, 63.8%; investigator's choice: 54/109, 49.5%), including pneumonia (pirtobrutinib: 26/116, 22.4%; investigator's choice: 13/109, 11.9%) and COVID-19 (pirtobrutinib: 15/116, 12.9%; investigator's choice: 20/109, 18.3%). Blood and lymphatic system disorders were also common (pirtobrutinib: [redacted], [redacted]; investigator's choice: [redacted], [redacted]) including anaemia (pirtobrutinib: 23/116, 19.8%; investigator's choice: 19/109, 17.4%) and neutropenia (pirtobrutinib: 21/116, 18.1%; investigator's choice: 17/109, 15.6%).

3.3.4.2 Adverse events of special interest

The adverse events of special interest (AESIs) were infections, bleeding, cytopenia, and atrial fibrillation and atrial flutter (CS, Table 50):

- a higher proportion of patients in the pirtobrutinib arm (74/116, 63.8%) experienced infection-related AESIs than in the investigator's choice arm (54/119, 49.5%)
- a higher proportion of patients in the pirtobrutinib arm (25/116, 21.6%) experienced bleeding-related AESIs, including bruising and haemorrhaging, than in the investigator's choice arm (11/119, 10.1%)
- a lower proportion of patients in the pirtobrutinib arm ([redacted], [redacted]) experienced neutropenia than in the investigator's choice arm ([redacted], [redacted])
- only a very small proportion of patients in either treatment arm experienced atrial fibrillation and atrial flutter (3/116 [2.6%] pirtobrutinib arm patients and 1/119 [0.9%] investigator's choice arm patients).

3.3.4.3 Deaths

No patients in either treatment arm died due to AEs whilst receiving treatment. The proportion of patients who died due to AEs within 30 days of their last dose of study drug ([redacted] [redacted] pirtobrutinib arm patients and [redacted] [redacted] investigator's choice arm patients) and the proportion of patients who died due to AEs >30 days after their last dose of study drug ([redacted] [redacted] pirtobrutinib arm patients and [redacted] [redacted] investigator's choice arm patients) [redacted] (CS, Table 51). [redacted] was assessed to be related to the study drug.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The company's SLR did not identify any head-to-head trials investigating the efficacy of pirtobrutinib versus cBTKis, VenR or IdelaR and therefore, the company assessed the feasibility of conducting indirect comparisons (CS, Section 2.10.1).

As noted in Section 3.4, the company's SLR included studies that recruited R/R CLL patients who had received any previous treatment. This broad approach was necessary due to the limited evidence available for patients with CLL who had previously been treated with a cBTKi. The company's original SLR identified 25 relevant RCTs[33-57] and the updated SLR identified one additional RCT (the BRUIN CLL-321 trial).

The company assessed whether there was sufficient evidence from the 26 included RCTs[1,33-57] to perform indirect comparisons for the following populations:

- **patients with R/R CLL who had previously been treated with a cBTKi:** aside from the BRUIN CLL-321 trial, only one other RCT, the UNITY-CLL trial,[56] reported outcome data for patients who had previously been treated with a cBTKi. However, the UNITY-CLL trial assessed an irrelevant comparator (umbralisib). Another RCT, the MURANO trial,[36] included a small proportion of patients (<3%) who had previously been treated with a B-cell receptor inhibitor (BCRi) which refers to both BTKi and phosphoinositide 3-kinase inhibitor (PI3Ki) treatments.
- **patients with R/R CLL who had previously been treated with a BTKi and a BCL2i:** aside from the BRUIN CLL-321 trial, only one RCT, the UNITY-CLL trial,[56] included patients who had previously been treated with a BTKi and a BCL2i. However, the UNITY-CLL trial[56] did not report subgroup data for the very small proportion of dual-exposed patients (<1%) and assessed an irrelevant comparator (umbralisib).

The company determined that the evidence base was insufficient to perform indirect comparisons for either of these populations. The EAG agrees with the company's judgements. The company therefore conducted their feasibility assessment for the broader population of R/R CLL patients who had received any previous treatment.

3.4.1 Indirect treatment comparison feasibility assessment

The company identified that 6/26 RCTs[1,33-37] compared relevant treatments; these were automatically included in the company's feasibility assessment. The remaining 20 RCTs did not make comparisons between relevant treatments, i.e. the trials included only one or no treatment(s) of interest. However, the company included two of these RCTs[38,39] in the company's feasibility assessment, as these trials could potentially be used to link relevant treatments in the network of evidence. The other 18 RCTs[40-57] were excluded from the company's feasibility assessment (CS, Table 38). The EAG considers the exclusion of these trials to be appropriate. In total, the company's feasibility assessment included eight RCTs.[1,33-39]

The company conducted a thorough examination of clinical and methodological heterogeneity of the eight RCTs[1,33-39] included in the feasibility assessment (CS, Section 2.10.1.2). The company highlighted that limited data were available for various potential effect modifiers, including ethnicity/race (two RCTs[33,39]), CLL-IPI (one RCT[39]) and C481 mutation status (no RCTs). A summary of other potential effect modifiers across the eight RCTs was presented in CS, Table 40 to Table 42 and CS, Figure 19 to Figure 26. The company identified major heterogeneity for the following potential effect modifiers: disease stage, Eastern Cooperative Oncology Group performance status (ECOG PS), mutation status (tumour protein 53 [TP53], deletion of the long arm of chromosome 11 [del11q], deletion of the short arm of chromosome 17 [del17p]), number of prior treatments, and prior treatment types. The EAG agrees with the

company that there are considerable differences between the eight RCTs[1,33-39] included in the feasibility assessment.

In particular, the EAG highlights that differences between the eight RCTs[1,33-39] in types of prior treatment is an important source of heterogeneity. While all patients in the BRUIN CLL-321 trial had received prior treatment with a BTKi, and a small proportion (<3%) of MURANO trial[36] patients had received prior treatment with a BCRi (encompassing both BTKi and PI3Ki treatments), the remaining six RCTs[33-35,37-39] included only BTKi-naïve patients (prior BTKi therapy was specified as an exclusion criterion). Clinical advice to the EAG is that prior BTKi use is likely to have an impact on the relative efficacy of pirtobrutinib versus relevant comparators. The EAG considers that it would be inappropriate to perform indirect comparisons without accounting for these important differences.

The EAG highlights that it is not possible to adjust for the potential effect modification resulting from prior BTKi use using methods such as network meta-regression or population-adjusted indirect comparisons, as no studies reported subgroup data for BTKi-experienced and BTKi-naïve patients. It is therefore not possible to estimate the extent of effect modification by prior BTKi use. The EAG therefore considers that it would be inappropriate to perform indirect comparisons including data from the BRUIN CLL-321 trial and any of the seven other RCTs[33-39] included in the feasibility assessment.

An additional issue is that, to form a connected network of evidence including the BRUIN CLL-321 trial and trials of the covalent BTKis, the company would need to have assumed that the efficacy of BRUIN CLL-321 trial investigator's choice was of equivalent to the efficacy of ASCEND trial[34] investigator's choice. However, the treatments within these "investigator's choice" arms varied: 77% of ASCEND trial[34] patients received IdelaR and 23% received BR whereas 69% of BRUIN CLL-321 trial patients received IdelaR and 31% received BR. Therefore, to assume that the two investigator's choice arms were equivalent requires the assumption of equivalent efficacy between IdelaR and BR. Similarly, to form a connection between pirtobrutinib and VenR, the company would need to assume that the efficacy of the MURANO trial[36] BR arm was equivalent to the efficacy of the BRUIN CLL-321 trial investigator's choice arm. Again, this requires the assumption of equivalent efficacy between IdelaR and BR.

Clinical advice to the EAG is that treatment with IdelaR is slightly more effective than treatment with BR for patients with CLL who have previously received targeted therapy. In an NMA[28] comparing treatments for patients with R/R CLL, the reported PFS result numerically favoured IdelaR over BR (HR=0.67, 95% CI: 0.39 to 1.17). The EAG therefore considers that an

assumption that the efficacy of IdelaR and BR are equivalent may introduce bias into the results of indirect comparisons. The EAG is unaware of any methods that could be used to reliably adjust for differences in efficacy between IdelaR and BR and generate reliable effectiveness estimates for treatment with IdelaR (rather than investigator's choice) versus the covalent BTKis and VenR.

3.5 Critique of the indirect comparison or multiple treatment comparison

The company concluded from the feasibility assessment that it was not feasible to conduct indirect comparisons for comparisons of pirtobrutinib versus VenR or pirtobrutinib versus cBTKis. The company therefore did not present any indirect treatment comparison results in the CS. Overall, the EAG considers that the company's decision not to perform any indirect comparisons was appropriate.

3.5.1 Additional indirect evidence

In response to clarification question B1, the company referenced a published unanchored matching-adjusted indirect comparison (MAIC),[58] which aimed to estimate the treatment effect of pirtobrutinib versus Ven-mono in patients with R/R CLL who had been previously treated with a cBTKi. The MAIC included data from two single-arm trials: the BRUIN trial[59] for pirtobrutinib (146 patients who had previously been treated with a cBTKi and were venetoclax-naive) and the Jones trial[60] for Ven-mono (91 patients who had previously been treated with a cBTKi and were venetoclax-naive). After adjusting for differences in key prognostic factors and effect modifiers between the trials, the point estimate of the weighted PFS HR indicated similar efficacy for pirtobrutinib and Ven-mono (HR=1.01; 95% CI: 0.58 to 1.73), while the OS HR numerically favoured pirtobrutinib over Ven-mono (HR=0.64; 95% CI: 0.25 to 1.67). Patients treated with pirtobrutinib had a higher objective response rate (80.2%) than patients treated with Ven-mono (64.8%). Weighted odds ratios (ORs) favoured pirtobrutinib over Ven-mono for all grade ≥3 TEAEs that were reported for both trials. The company considered Ven-mono was not a relevant comparator to pirtobrutinib (see Table 1). Clinical advice to the EAG is that Ven-mono is rarely used in NHS clinical practice.

3.6 Additional work on clinical effectiveness done by the EAG

The EAG did not conduct any additional clinical effectiveness analyses.

3.7 Conclusions of the clinical-effectiveness section

The company provided clinical effectiveness evidence for the comparison of pirtobrutinib versus investigator's choice (IdelaR or BR) from the BRUIN CLL-321 trial (an ongoing phase

III RCT) for the ITT population and for the dual-exposed population. The EAG considers that the BRUIN CLL-321 trial is a well-conducted trial of good methodological quality.

The BRUIN CLL-321 trial results for the ITT population showed that compared to investigator's choice, pirtobrutinib nominally statistically significantly improved IRC-assessed PFS, investigator-assessed PFS and TTNT, and numerically **improved** OS. However, the OS results were confounded by crossover and CIs were wide and crossed 1. Overall, HRQoL outcomes were [redacted] between treatment arms and [redacted].

The company explored one pre-specified OS sensitivity analysis and three additional methodologically complex exploratory OS sensitivity analyses to adjust for crossover in the ITT population. The EAG considers that the two-stage AFT method is an appropriate method of crossover adjustment for the BRUIN CLL-321 trial, however, additional sensitivity analyses would have provided greater clarity around the residual uncertainty relating to the true OS treatment effect.

The BRUIN CLL-321 trial results showed that, for the dual-exposed population, compared to investigator's choice, pirtobrutinib [redacted]. The company did not perform OS sensitivity analyses to adjust for crossover for the dual-exposed subpopulation.

The company provided no clinical effectiveness evidence:

- for the comparisons of pirtobrutinib versus a cBTKi, a BCL2i or BSC (which the EAG considers are relevant comparators)
- separately for the two other subpopulations identified by the company, namely:
    - patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable
    - patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is unsuitable.

The company conducted a feasibility assessment and concluded that it was not feasible to conduct indirect comparisons of pirtobrutinib versus VenR or pirtobrutinib versus cBTKis. Overall, the EAG agrees that the company's decision not to perform any indirect comparisons was appropriate.

3.7.1 Safety conclusions

Clinical advice to the EAG is that pirtobrutinib is tolerable and that the AEs associated with pirtobrutinib are manageable in NHS clinical practice.

4 COST EFFECTIVENESS

This section includes a summary and critique of the cost-effectiveness evidence included in CS:

- Section 4.1 includes the EAG's critique of the company's review of the cost-effectiveness evidence
- Section 4.2 includes the EAG's summary and critique of the company's economic evaluation.

The two key components of the cost-effectiveness evidence presented in the CS are (i) a SLR of the cost effectiveness literature and (ii) a report of the company economic evaluation. The company has provided an electronic copy of their economic model, developed in Microsoft® Excel.

4.1 Critique of the review of cost-effectiveness evidence

The company conducted an SLR to identify and appraise literatures on i) cost effectiveness evaluations, ii) HRQoL and PRO data, and iii) healthcare resource use (HCRU) and cost data relevant to the decision problem.

The population considered in the SLR was defined as patients with R/R CLL. The population term used in the economic SLR aligned with the clinical SLR. No restrictions relating to language or geographical location were applied in any of the SLRs.

The company initially conducted the SLR search in February 2022. The search was updated in April 2022 (SLR update 1), October 2023 (SLR update 2) and most recently in September 2024 (SLR update 3).

Full details of the company's SLR methods and results are presented in the CS (Appendix E [cost effectiveness], Appendix F [HRQoL] and Appendix G [cost and health care resource use]).

The company identified a total of 41 studies, of which, 36 reported cost and HCRU data, seven reported utility data, and 22 reported HRQoL or PRO data (CS, Appendix E, Table 42). The company presented details of 35/41 included studies (identified from the original SLR, SLR 1 and SLR 2) that provided economic evaluation evidence in CS, Appendix E, Table 43. The company used the Drummond quality checklist to quality assess the 35 included studies (CS, Appendix E, Table 44). The company provided a summary of the remaining six studies in the economic systematic literature review of R/R CLL or SLL final report[61] (Table 14); the EAG is not aware of any quality assessments having been conducted for these studies.

The company's SLR was broader than was required to address the final scope[2] issued by NICE; the company did not restrict the eligibility criteria to patients with R/R CLL who had previously been treated with a cBTKi. Therefore, the company did not utilise any data from the SLR identified studies in the company model.

An assessment of the extent to which the company's systematic reviews were conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 14. The EAG considers the methods used to conduct the company's systematic reviews of cost effectiveness evidence, HRQoL and HCRU studies were of a good standard.

Table 14 EAG appraisal of systematic review methods

Review process	EAG response	
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix E.1.2, Appendix F.1.2 and Appendix G.1.2.
Were appropriate sources searched?	Yes	See CS, Appendix E.1.1, Appendix F.1.1 and Appendix G.1.1.
Was the timespan of the searches appropriate?	Yes	See CS, Appendix E.1.1, Appendix F.1.1 and Appendix G.1.1.
Were appropriate search terms used?	Yes	See CS, Appendix E.1.1.1, Table 20 to Table 34.
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix E.1.2, Appendix F.1.2 and Appendix G.1.2.
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix E.1.2
Was data extracted by two or more reviewers independently?		One reviewer extracted data and these data were independently checked by a second reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Partly	See CS, Appendix E.2.5, Table 44 The company used the Drummond quality checklist to quality assess the 35 included studies that provided economic evaluation evidence. However, quality assessments were not provided for the identified HRQoL and HCRU studies.
Was the quality assessment conducted by two or more reviewers independently?	Yes	See economic SLR report,[61] Section 2.5.4 One reviewer quality assessed the included trials and quality assessments were independently checked by a second reviewer.
Were attempts to synthesise evidence appropriate?	N/A	-

HRQoL=health-related quality of life; HCRU= healthcare resource use; N/A=not applicable; SLR=systematic literature review
Source: LR*i*G in-house checklist

4.2 Critique of the submitted economic evaluation

The company conducted a cost-utility analysis of pirtobrutinib versus IdelaR for patients with R/R CLL previously treated with one or more cBTKi; the company referred to this population as the "post-cBTKi population" (CS, Section 1.1). Clinical efficacy inputs from the BRUIN CLL-321 trial investigator's choice arm were used in the model; the company stated (CS, p135) that this was appropriate as it maintained trial randomisation and ensured sufficient power for PFS analyses. Most investigator's choice arm patients (70.6%) received IdelaR, and clinical advice to the company was that the data were generalisable to patients treated with IdelaR in UK clinical practice.

4.2.1 In clarification questions B1 and B2, the EAG requested that the company conduct cost-effectiveness analyses for pirtobrutinib versus the other relevant comparators (i.e., VenR, a cBTKi and BSC) using the survival data from the BRUIN CLL-321 trial as a proxy in the absence of direct or indirect comparative clinical effectiveness data. In response to clarification questions B1 and B2, the company submitted a cost-comparison analysis of pirtobrutinib versus VenR for the post-cBTKi population and the dual-exposed population using the survival KM data from the BRUIN CLL-321 trial pirtobrutinib arm as a proxy for the effectiveness of VenR (i.e., assuming that pirtobrutinib and VenR had comparable efficacy in the target indication), and considering the differences in safety. The company acknowledged the inherent uncertainty of these cost effectiveness estimates. NICE reference case checklist

The EAG appraisal of the company's economic analyses using the NICE Reference Case checklist is shown in Table 15.

Table 15 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	QALYs were appropriately used to reflect patient health benefits.
Perspective on costs	NHS and Personal Social Services	The analysis adopted the NHS and PSS perspective, which is appropriate for the decision problem.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company used cost-utility analysis with fully incremental analysis for the comparison of pirtobrutinib vs IdelaR, which aligns with the NICE reference case checklist. Additionally, in response to clarification, the company conducted a cost-comparison analysis for the comparator of pirtobrutinib vs VenR.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime horizon is considered long enough to capture all relevant costs and outcomes for the population included in this decision problem.
Synthesis of evidence on health effects	Based on systematic review	The company's economic SLR identified Holzner 2004[62] which reported a post-progression utility value of 0.60. The company referenced TA561[20] to inform adverse event disutility values.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	In the BRUIN CLL-321 trial, HRQoL data were collected using EQ-5D-5L. This is in line with the NHS reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	HRQoL was reported directly by patients in the BRUIN CLL-321 trial, which is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The EQ-5D-5L data from the BRUIN CLL-321 trial were mapped to the UK EQ-5D-3L using the Hernandez-Alava 2022.[63] crosswalk value set. This method is deemed appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	National Cost Collection 2023/24[64] were used to inform HCRU and cost. End-of-life costs were sourced from Round 2015[65] and inflated to 2022/23 prices. It is in alignment with the checklist.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	A discount rate of 3.5% was applied to both costs and outcomes.

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimensions; HCRU=healthcare resource use; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSS=Personal Social Services; QALY=quality adjusted life
Source: EAG assessment of NICE Reference Case

4.2.2 Model structure

The company developed a partitioned survival model to assess the cost-effectiveness of pirtobrutinib as a treatment for patients with R/R CLL who have previously been treated with a cBTKi. The structure of the company model is shown in Figure 1.

The model comprises three mutually exclusive health states: progressed disease (PD), progression-free (PF), and dead. The PF health state is split into two mutually exclusive sub-states: on-treatment and off-treatment to reflect maximum duration of treatment (Figure 2). Once the maximum duration of treatment is reached, patients transition to the off-treatment PF state, which incurs no further costs associated with drug or drug administration.

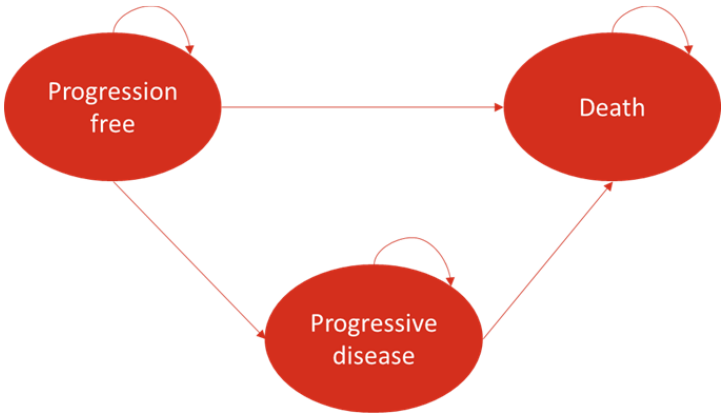


Figure 1 Structure of the company model

Source: CS, Figure 27

Patients in the PF health state have stable disease and do not have actively progressing disease according to iwCLL 2018[5] criteria and in line with the BRUIN CLL-321 trial PFS outcome definitions. Patients in the PD health state have experienced disease progression, discontinue their current treatment, and switch to BSC.

Patients with R/R CLL enter the model in the PF health state. After each model cycle, patients can remain in the PF health state or transition to the PD health state or the dead health state, dependent on whether their disease remains stable or progresses and the time spent on treatment. The distribution of patients across these states over time is based on cumulative survival probabilities derived from curves fitted to PFS, OS and TTD K-M data from the BRUIN CLL-321 trial (details provided in the CS, Section 3.3.2).

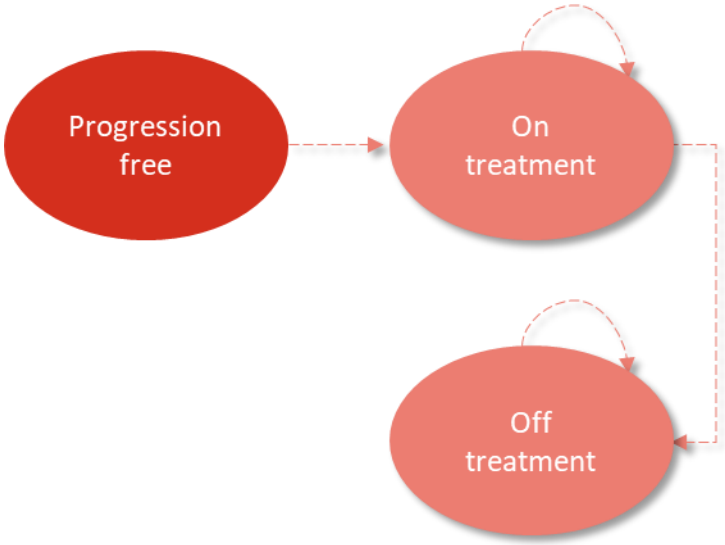


Figure 2 Progression-free health state

Source: CS, Figure 28

The model operates on a 28-day cycle, consistent with the BRUIN CLL-321 trial dosing schedule. It models patients over a lifetime horizon (76 years in the model although less than [redacted] of patients are alive in either model arm by 20 years).

4.2.2.1 EAG Critique of model structure

The EAG considers that the model structure employed by the company is suitable for the decision problem.

4.2.3 Population

The cost-utility model provided by the company at submission simulates two populations of adult patients with R/R CLL who have previously been treated with a cBTKi:

- post-cBTKi population (i.e., R/R CLL patients who have been previously treated with a cBTKi)
- dual-exposed population (i.e., R/R CLL patients who have been previously treated with both a cBTKi and a BCL2i, either sequentially or in combination).

The company did not conduct cost-utility analyses for the post-cBTKi population for whom SoC is suitable due to insufficient robust comparative evidence for VenR. Instead, the company provided a cost-comparison model in response to EAG clarification questions.

The baseline characteristics of the modelled population are shown in Table 16.

Table 16 Modelled baseline patient characteristics

Model parameter	Post-cBTKi population	Dual-exposed population	Source
Mean age (years)	67.0	66.8	BRUIN CLL-321[66]
Female (%)	30.3%	40.0%	
Mean patient BSA, m^2 (SD)	1.92 (0.24)	1.93 (0.26)	

BSA=body surface area; SD=standard deviation
Source: CS, Table 54

4.2.3.1 EAG Critique of population

The EAG considers that the populations modelled should be defined by the relevant comparators and not only by prior treatment. The EAG considers that the populations modelled should have been patients with R/R CLL who have previously been treated with a cBTKi (see Section 4.2.4.1 for discussion):

- for whom treatment with a cBTKi is suitable
- for whom treatment with a BCL2i is suitable
- for whom treatment with a cBTKi or a BCL2i is unsuitable.

4.2.4 Interventions and comparators

The economic model compares the costs and benefits of pirtobrutinib versus IdelaR in the post-cBTKi and dual-exposed populations.

Pirtobrutinib dosing in the model reflects the BRUIN CLL-321 trial, in which patients received 200mg orally once daily (QD) in 28-day cycles until disease progression, unacceptable toxicity, or treatment discontinuation for other reasons.[67] IdelaR comprises idelalisib 150mg orally twice daily (BID) in 28-day continuous cycles,[68] plus rituximab 375mg/m² IV on Cycle 1 Day 1, then 500mg/m² IV every 2 weeks for four infusions and every 4 weeks for three infusions.[69]

4.2.4.1 EAG Critique of interventions and comparators

The EAG considers that IdelaR is not a suitable comparator for decision making for most patients in either population considered by the company.

Clinical advice to the EAG is that IdelaR is rarely used in NHS clinical practice due to toxicity concerns and patient intolerability, and therefore nearly all patients with R/R CLL who have previously been treated with a cBTKi for whom SoC (i.e., treatment with a BCL2i and/or cBTKi) is **unsuitable** and who have sufficient performance status are ca into clinical trials, where possible.

This aligns with clinical advice to the TA931[15] appraisal committee (Zanubrutinib for treating chronic lymphocytic leukaemia) that 'idelalisib plus rituximab is rarely used in clinical practice because it has an intensive dosing regimen and is associated with an increased infection risk'.

Clinical advice to the EAG is that NHS patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or cBTKi) is **suitable** are not treated with IdelaR; they are treated with VenR or another cBTKi (if they had previously discontinued treatment with a cBTKi due to intolerance).

Clinical advice to the EAG is that, for the dual-exposed population:

- patients who discontinue prior treatment with a cBTKi due to intolerance can be rechallenged with a cBTKi
- patients who achieve a response to a fixed-duration venetoclax-based regimen and then experience disease progression after completing venetoclax treatment can be rechallenged with venetoclax (i.e., VenR); for patients who have been treated with ibrutinib with venetoclax (VenI) first-line (i.e., a combined BTKi and BCL2i treatment), rechallenge with VenR or a cBTKi is likely.

The CAPTIVATE trial[70] further supports rechallenge with a cBTKi or a BCL2i in a dual-exposed population. In the CAPTIVATE trial,[70] VenI was given as a fixed duration treatment for 15 months. The CAPTIVATE trial[71] results showed that only 1/40 patients with disease progression following treatment with VenI had developed an acquired resistance-associated mutation in BCL2(A113G) and that 19/22 patients retreated with ibrutinib on disease progression responded to treatment (i.e., achieved a complete or partial response). For TA891[16] (ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia), clinical advice to the AC was that the fixed duration of VenI reduced the likelihood that patents treated first-line with VenI would become resistant to either venetoclax or ibrutinib; an NHS England representative advised that rechallenge with a cBTKi or a BCL2i should be allowed for patients who had responded well to VenI in the first-line setting.

In summary, the EAG considers that the company cost-effectiveness analysis of pirtobrutinib compared to IdelaR is of limited use to decision makers for the two populations modelled. The EAG considers that the company should have provided cost effectiveness evidence for the populations identified by the EAG (see Section 4.2.3.1) for the following comparisons:

- patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi is suitable: pirtobrutinib versus a cBTKi (ibrutinib, zanubrutinib or acalabrutinib)
- patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a BCL2i is suitable: pirtobrutinib versus a BCL2i (VenR)
- patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi or a BCL2i is unsuitable: pirtobrutinib versus IdelaR or BSC.

In clarification question B1 and clarification question B2, the EAG requested that the company provide analyses for the comparison of pirtobrutinib versus three additional comparators for the post-cBTKi, BL2Ci-naïve population (i.e., patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a BCL2i is suitable) and the dual-exposed

population (pirtobrutinib versus VenR and versus a cBTKi for both populations; BSC for the dual-exposed population only). These analyses were to be carried out using the assumption that comparator PFS, OS and TTD are equal to those modelled by the company for pirtobrutinib for each population. In the absence of comparative evidence of pirtobrutinib and these comparators, the EAG considered that it may be informative to explore the likely cost-differences between treatments if efficacy was similar.

The company presented cost-effectiveness results for the comparison of pirtobrutinib versus VenR for the post-cBTKi, BL2Ci-naïve population and the dual-exposed population. Whilst not a formal cost-comparison analysis, differences in quality adjusted life years (QALYs) for this comparison were small as they only related to disutilities from adverse events. The company referred to this model as a cost-comparison analysis.

The company did not present the requested analyses for the comparison of:

- pirtobrutinib versus a cBTKi for the post-cBTKi, BL2Ci-naïve population (clarification question B1) and the dual-exposed population (clarification question B2)
- pirtobrutinib versus BSC for the dual-exposed population (clarification question B2).

The company considered that cBTKis and BSC are not relevant comparators for pirtobrutinib, as patients who have previously been treated with a cBTKi and who progressed during treatment with a cBTKi should be considered refractory to cBTKis as they will likely have developed resistance to cBTKis, and patients with R/R CLL should not be offered BSC when IdelaR is available.

The cost-effectiveness modelling provided by the company at the time of submission and the cost-comparison analysis provided at clarification allows the comparison of:

- patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi is suitable: pirtobrutinib versus VenR.
- patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi or a BCL2i is unsuitable: pirtobrutinib versus IdelaR.

The cost-comparison analysis for the comparison of pirtobrutinib versus VenR in the population suitable for treatment with a BCL2i is dependent on the assumption that pirtobrutinib is equally as effective as VenR. In response to clarification question B1, the company referenced a published unanchored MAIC,[58] which estimates the treatment effect of pirtobrutinib versus Ven-mono in patients with R/R CLL who had been previously treated with a cBTKi (see Section 3.5.1). The MAIC results suggest that pirtobrutinib and Ven-mono may have comparable effectiveness with the point estimates from the MAIC favouring pirtobrutinib. The company considered that the study “raises important questions regarding the optimal treatment sequencing of pirtobrutinib and venetoclax in cBTKi-treated CLL” (company

response to clarification question B1). Clinical advice to the EAG is that VenR is more effective than Ven-mono. The EAG therefore considers the assumption that pirtobrutinib is equally as effective as VenR to be highly uncertain.

Further, the unanchored MAIC[58] only addressed grade ≥3 TEAEs that were reported for both included trials. As not all AE differences could be included in the cost-comparison analysis the EAG considers that differences should not have been modelled and so has undertaken an analysis removing differences in AEs between pirtobrutinib and VenR, noting that the inclusion or exclusion of AEs makes minimal difference to conclusions drawn from the cost-comparison analysis.

The most suitable cost-utility analysis of pirtobrutinib versus IdelaR in the population unsuitable for treatment with a cBTKi is the dual-exposed population analysis performed by the company as these patients are more likely to be unsuitable for treatment with a cBTKi or a BCL2i having been exposed to both treatments (as opposed to the post-cBTKi population where a proportion have not previously been treated with a BCL2i). However, in the BRUIN CLL-321 trial, [redacted] of dual-exposed pirtobrutinib arm patients and [redacted] of dual-exposed investigator's choice arm patients received a cBTKi at progression (CS, Table 82). This suggests that the dual-exposed population modelled by the company uses data that includes patients who would be suitable for rechallenge with a cBTKi. It is unclear how this affects the results of the cost-effectiveness analysis.

To generate results for the remaining population comparisons, the EAG has adopted the following approaches:

- **Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi is suitable: pirtobrutinib versus ibrutinib, zanubrutinib or acalabrutinib**

  The EAG has used the company cost-comparison model for the comparison of pirtobrutinib versus VenR as the base model and set adverse events to be equal for all treatments. Costs (list price) and dosing schedules were then adjusted to represent each of the individual cBTKi treatments. The EAG considers this approach to be justified as available evidence[72] suggests that cBTKi regimens are at least as efficacious as BCL2i regimens in the first-line setting and if it is reasonable to assume similar efficacy for pirtobrutinib and VenR for patients with CLL in the first-line setting, then it is also reasonable to assume similar efficacy of pirtobrutinib versus cBTKi treatment in patients with R/R CLL who have received one or more prior treatments.

The post-cBTKi population in the model was used as the basis of the cost-comparison analyses.

- **Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi or a BCL2i is unsuitable: pirtobrutinib versus BSC**
  The EAG has used the company cost-utility model for dual-exposed patients but set PFS and TTD for the IdelaR arm of the model to be zero – effectively assuming that all patients on BSC have the costs and utilities of people with progressed disease and removing the costs, PFS benefits and adverse events of IdelaR from the model. As cBTKis were included as subsequent therapies for dual-exposed patients treated with IdelaR, the costs of these treatments have been removed from the model for this analysis with all other subsequent therapies reweighted to account for this. As IdelaR may have some survival benefit over BSC, this may underestimate the QALY gain of pirtobrutinib compared to BSC and so may overestimate the ICER per QALY gained of pirtobrutinib versus BSC.

4.3 Treatment effectiveness and extrapolation

The company conducted survival extrapolation for pirtobrutinib and investigator's choice of IdelaR or BR for OS, TTD, Investigator-assessed PFS, and IRC-assessed PFS using BRUIN CLL-321 trial data (29 August 2024 DCO). Cox models and a range of parametric survival models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, generalised gamma, and flexible-spline–based Weibull with one, two, or three knots) were explored. The model used in the analysis was selected based on long-term plausibility, statistical fit (Akaike information criterion [AIC], Bayesian information criterion [BIC]), visual fit to KM data, and clinical plausibility. Models predicting survival exceeding age-matched general population estimates or inconsistent with comparable long-term studies were excluded.

4.3.1.1 Progression-free survival

Investigator-assessed PFS was used in the base case for both post-cBTKi and dual-exposed populations, as the company considered it more reflective of clinical practice. The company explored IRC-assessed PFS in a scenario analysis (CS, Table 98).

For the post-cBTKi population, due to poor plausibility of all other distributions, the gamma distribution was used in the base case and the Weibull distribution was used in a scenario analysis. Clinical expert opinion to the company supported the gamma distribution as the most appropriate choice, which also had low AIC/BIC values and maintained a realistic long-term PFS benefit for pirtobrutinib.

For the dual-exposed population, Log-logistic and log-normal distributions were excluded due to limited clinical plausibility. Clinical expert opinion supported the selection of gamma (with low AIC and BIC values) for the base case and Weibull assessed in a scenario analysis.

4.3.1.2 Overall survival

The company extrapolated the BRUIN CLL-321 trial OS results and adjusted for bias introduced by patient crossover using three adjustment methods (details available in Section 3.3.1.1), namely two-stage AFT, IPCW and RPSFTM. The company considered (and the EAG agrees) that the two-stage AFT method is the most appropriate approach to use in the base case to account for treatment switching; the company also provided sensitivity analyses results using the IPCW method (CS, Table 98).

In the base case, OS was modelled by applying the HR from the two-stage crossover Cox model to the unbiased pirtobrutinib OS curve. For the post-cBTKi population, seven of the nine modelled distributions were excluded due to implausible survival projections or crossing curves, leaving gamma and Weibull for consideration. Clinical expert opinion supported gamma, which had low AIC/BIC values and avoided comparator OS overestimation and pirtobrutinib OS underestimation seen with Weibull. Gamma was selected for the base case, with Weibull examined in a scenario analysis.

For the dual-exposed population, seven of the nine modelled distributions were excluded due to unrealistic long-term projections or curve crossing. Gamma, supported by clinical expert opinion and low AIC/BIC values, was preferred over Weibull, which tended to overestimate comparator OS. Gamma was used in the base case, while Weibull was assessed in a scenario analysis.

4.3.1.3 Time to treatment discontinuation

Time to treatment discontinuation (TTD) was defined as the time from first exposure to treatment to discontinuation. For crossover patients, discontinuation was the earlier of pre-crossover discontinuation or first exposure in the crossover period. Ongoing treatment was censored at last exposure. In the base case, TTD was modelled from TTD curves to align with data from the BRUIN CLL-321 trial and clinical practice, where treatment beyond progression is allowed. The model permitted TTD to exceed PFS, consistent with the trial protocol. In a scenario analysis, TTD was modelled using PFS curves, time on treatment was assumed equivalent to PFS except for treatments with maximum treatment cycles.

For the post-cBTKi population, log-logistic and log-normal distributions were excluded due to concerns over clinical plausibility. Gompertz had the lowest AIC and BIC values, while Weibull

overestimated TTD for pirtobrutinib. Visual inspection showed Gompertz aligned more closely with trial KM data at the tail of the curve. Gompertz was used in the base case, with Weibull included in a scenario analysis.

For the dual-exposed population, log-logistic and log-normal were excluded due to the lack of clinical plausibility. Gompertz offered both the lowest AIC and BIC and a clinically credible fit, whereas Weibull appeared to project longer TTD than observed in the trial. The base case applied Gompertz, and a scenario analysis explored the Weibull alternative.

4.3.1.4 EAG Critique of treatment effectiveness

The EAG considers the approach to extrapolating curves adopted by the company to be acceptable. The EAG highlights that the curve selection makes limited difference to the cost-comparison analyses which is the preferred approach of the EAG for decision making for two of the three populations the EAG considers should be assessed as part of this appraisal.

4.3.2 Health-related quality of life

The company collected EQ-5D-5L data from BRUIN CLL-321 trial participants and mapped these to EQ-5D-3L values using the algorithm by Hernandez-Alava 2022.[63] PF utility was estimated from pre-progression responses. Due to limited utility data for the PD state from the trial participants, a value of 0.60 cited from Holzner 2004[62] was applied to both post-cBTKi and dual-exposed groups. The PF utility estimate of 0.814 was used for both populations.

Table 17 Base case health state utility values used in the company model

Model health state	Utility value (SE)
Progression-free	0.814 (0.018)[32]
Progressed disease	0.600 (0.060)[15]

SE=standard error
Source: CS, Table 73

4.3.2.1 Adverse event utility decrements

The company's model included grade 3/4 AEs observed in the BRUIN CLL-321 trial. For each AE, total disutility was calculated by multiplying the AE disutility value (CS, Table 72) by the event duration (CS, Table 88), with both sourced from previous NICE TAs (TA561,[20] TA689[13] and T931[15]). In the base case, AE-related QALY loss was applied as a one-off decrement in the first model cycle.

4.3.2.2 EAG Critique of health related quality of life

The EAG requested evidence from the company at clarification to support the utility value in the PFS state being close to the population norm. The company explained that in the BRUIN CLL-321 trial, baseline utility values were below population norms but as patients responded

to treatment this resulted in increases in utility values seen in the PFS state. The EAG is satisfied that the PFS utility value used in the model is fair for pirtobrutinib and for IdelaR or BSC for the population unsuitable for treatment with a cBTKi or BCL2i.

The progressed disease utility value used by the company does not have face validity. The baseline utility value in the BRUIN CLL-321 trial for the dual-exposed population was [redacted] (company response to clarification question B4) which represents a population who are in a progressed state from at least two prior treatments before commencing a new treatment. The baseline utility value for the ITT population from the BRUIN CLL-321 trial was almost identical at [redacted] (company response to clarification question B4) which suggests that there is very little difference in utility at progression by line of treatment. The EAG has therefore used the utility value at baseline for the dual-exposed population from the BRUIN CLL-321 trial ([redacted]) for progressed disease.

Table 18 Health state utility values used in the company model: EAG and company

Model health state	Company utility value	EAG utility value
Progression-free	0.814	0.814
Progressed disease	0.600	[redacted]

Source: Company response to clarification question B4

In addition, the EAG noted a reporting error in the CS Table 88. The disutility of hyperkalaemia was reported incorrectly, where it was assumed to be the same as hypertension. The correct value was applied in the company model.

4.3.3 Resources and costs

4.3.3.1 Drug acquisition costs

Drug acquisition costs are presented in Table 19. Costs were sourced from Drugs and pharmaceutical electronic market information tool (eMIT; preferred) or Monthly Index of Medical Specialties (MIMS) when eMIT data were unavailable. Idelalisib and rituximab are available to the NHS at confidential discounted Patient Access Scheme (PAS) prices.

Drug acquisition costs were calculated at the individual drug level, with per-cycle costs accounting for available vial sizes, vial permutations, patient body surface area (BSA; maximum 5 m^2), and vial wastage.

Table 19 Drug acquisition costs

Drug	Form	Strength	Pack size	Cost per pack
Pirtobrutinib	Oral	50 mg	28 tablets	[redacted]
	Oral	100 mg	56 tablets	[redacted]
Idelalisib	Oral	100 mg	60 tablets	£3,114.75[73]
	Oral	150 mg	60 tablets	£3,114.75[73]
Rituximab	IV	100 mg/10 mL	2 vials	£314.33[73]
	SC	500 mg/50 mL	1 vial	£785.84[73]

IV=intravenous; SC=subcutaneous
Source: CS, Table 74

4.3.3.2 Drug administration costs

An administration cost was applied only for intravenous (IV) rituximab (Table 20), with a maximum treatment duration of six cycles assumed. No administration costs were applied for pirtobrutinib or idelalisib, as both are orally administered.

Table 20 Drug administration costs

Resource	Unit cost	Use per cycle			Source
		Pirtobrutinib	IdelaR		
			Cycles 1-2	Cycles 3-6	
Deliver simple parenteral chemotherapy at first attendance	£203.98	0	1	1	2023/24 National Cost Collection[64]
Deliver subsequent elements of a chemotherapy cycle	£295.13	0	1	0	
Deliver complex chemo, including prolonged treatment at 1st attendance	£501.32	0	0	0	
Per cycle administration cost, mean (SE)		£0 (0)	£499.10 (99.82)	£203.98 (40.80)	

IdelaR=idelalisib plus rituximab; SE=standard error
Source: CS, Table 76

In the cost comparison analysis provided in the clarification letter, rituximab administration costs for VenR were included with reference to the dosing schedule used in the MURANO trial.[36]

4.3.3.3 Subsequent treatments costs

In the company model, patients received subsequent treatments on disease progression. Drug acquisition costs are reported in Table 19, Table 21 and CS, Table 78 to Table 80. The distribution and duration of subsequent treatments (Table 22) were informed by the BRUIN CLL-321 trial. The company defined three approaches for modelling post-progression costs. In the base case, post-progression costs were modelled under the "different in both regards" scenario, where both cost per cycle and total costs differed between pirtobrutinib and IdelaR, reflecting differences in post-progression treatment mix. The company conducted scenario analyses using an "equivalent in total" scenario where total costs were the same across regimens, and an "equivalent per cycle" scenario where per-cycle costs were the same across regimens.

The drug costs for the comparator treatments used in both the company's and the EAG's cost-comparison models are provided in Table 21.

Table 21 Drug acquisition costs (subsequent treatments and comparator treatments)

Drug	Form	Strength	Pack size	Cost per pack
Zanubrutinib	Oral	80 mg	120 tablets	£4,928.65
Venetoclax	Oral	10 mg	14 tablets	£59.87
	Oral	50 mg	7 tablets	£149.67
	Oral	100 mg	7 tablets	£299.34
	Oral	100 mg	112 tablets	£4,789.47
Acalabrutinib	Oral	100 mg	60 tablets	£5,059.00
Ibrutinib	Oral	140mg	28 tablets	£5723.20

Source: CS, Table 77

Table 22 Subsequent treatment distribution and treatment duration

Treatment	Post-cBTKi population			Dual-exposed population		
	Post-progression use		Mean 28-day cycles	Post-progression use		Mean 28-day cycles
	Pirtobrutinib	Inv. choice		Pirtobrutinib	Inv. choice	
Covalent BTK inhibitor						
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Noncovalent BTK inhibitor						
Pirtobrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCL2i						
Venetoclax						
Weeks 1 to 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 5+			[redacted]			[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy						
FCR						
Fludarabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide						
Rituximab						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles 2-6			[redacted]			[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 antibody						
Rituximab						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles 2-6			[redacted]			[redacted]
Obinutuzumab						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles 2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PI3K agent						
Idelalisib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IMID/immunomodulator						
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAR-T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stem cell transplant						
AlloSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic therapy						
Other systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other molecular pathways/small molecule inhibitors						
Other molecular pathways/small molecule inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AlloSCT=allogeneic stem cell transplant; BCL2i=B-cell lymphoma 2 inhibitor; BTK=Bruton tyrosine kinase; CAR-T=chimeric antigen receptor T-cell therapy; FCR=fludarabine, cyclophosphamide, and rituximab; IMID=immunomodulatory drug; Inv. choice=investigator's choice; PI3K=phosphoinositide 3-kinase
Source: Company response to clarification, Appendix 2, Table 18

4.3.3.4 Health state and resource use costs

Other medical costs and utilisation inputs were estimated separately for two groups. Patients in the on-treatment group, including those in the PF health state and those in the PD state receiving subsequent therapy, incurred an annual cost of £400.49. Patients in the off-treatment group, defined as those in the PD state receiving BSC, incurred an annual cost of £8,337.84. These costs were derived using unit costs (CS, Table 83) and resource use estimates (CS, Table 84). The approach followed the assumptions in NICE TA561,[20] which stated that on-treatment resource use was the same as in the PF health state and that PD costs were a weighted average of time on subsequent treatment and time on no treatment.

4.3.3.5 Adverse event and monitoring costs

Total AE management costs were estimated by multiplying the incidence of each AE (CS, Table 71) by its corresponding unit cost from the National Cost Collection (CS, Table 86), resulting in £492.97 for pirtobrutinib and £589.00 for IdelaR.

In the cost comparison analysis submitted in the clarification letter, the company included six Grade ≥3 AEs (fatigue, hyperuricaemia, hypocalcaemia, leukopenia, lower respiratory tract infection, and upper respiratory tract infection) from the MURANO trial[36] along with their associated management costs.

4.3.3.6 End of life costs

A single terminal care cost of £12,187.14 was applied when patients entered the death state. This cost was sourced from Round 2015[65,73] and inflated to 2022/2023 prices.

4.3.3.7 EAG Critique of resources and costs

The EAG considers the company's general approach to incorporating costs and resource use reasonable, although two issues were identified. Firstly, the company derived the weighted cost of stem cell harvesting incorrectly by using the number of submissions instead of the number of finished consultant episodes as weights from the National Cost Collection (CS, Table 78). The EAG recalculated the cost as £1,495 (compared to £5,992 in the company base case). Secondly, the reported cost of the allogenic stem cell transplant (SCT) procedure (CS, Table 79) did not fully align with the approach taken in a previous appraisal (TA975[74]). EAG included all items specified in TA975[74] (SA20–SA23, SA38, SA39) and produced a weighted cost of allogenic SCT procedure at £48,153 (compared to £61,328 in the company base case).

5 COST-EFFECTIVENESS RESULTS

Section 5.1 summarises the company's cost-effectiveness results, Section 5.2 presents the EAG's additional work and preferred assumptions, and Section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

The company base case in the CS included pirtobrutinib as a subsequent therapy for patients who were treated with IdelaR. At the clarification stage, the EAG asked these costs to be removed from the model as it was not appropriate to include a treatment not routinely used in the NHS as a subsequent therapy. The company agreed and removed the costs of pirtobrutinib as a subsequent therapy from their base case. In addition, the company removed CAR-T therapy from subsequent treatments as the company stated it was not routinely commissioned by the NHS for patients with R/R CLL who have previously been treated with a cBTKi.

Probabilistic base-case results (1,000 model iterations) from the post-clarification company economic model are presented in Table 23 and Table 24. A disease severity modifier of 1.2 was applied by the company for the dual-exposed population. The EAG notes that the company applied the 1.2 multiplier to the QALYs for people treated with pirtobrutinib rather than to incremental QALYs. The EAG has corrected this error in the company base case results.

All results are shown with list prices for all treatments.

Table 23 Company probabilistic pairwise post clarification base case results in patients with R/R CLL: post-cBTKi population (pirtobrutinib PAS price)

Technologies	Total		Incremental		ICER/QALY
	Costs	QALYs	Costs	QALYs	£/QALY
Pirtobrutinib	£169,483	2.574	£39,231	0.557	£70,377
IdelaR	£130,251	2.016			

cBTKi= covalent Bruton's tyrosine kinase inhibitor; ICER=incremental cost effectiveness ratio; IdelaR=idelalisib plus rituximab; PAS=patient access scheme; QALY=quality adjusted life years
Source: company response to clarification, Appendix 1, Table 13

Table 24 Company probabilistic pairwise post clarification base case results in patients with R/R CLL: dual-exposed population with severity weighting (x1.2) (pirtobrutinib PAS price)

Technologies	Total		Incremental		ICER/QALY
	Costs	QALYs	Costs	QALYs*1.2	£/QALY
Pirtobrutinib	[redacted]	1.726	[redacted]	0.470	[redacted]
IdelaR	[redacted]	1.334			

ICER=incremental cost effectiveness ratio; IdelaR=idelalisib plus rituximab; PAS=patient access scheme; QALY=quality adjusted life years
Source: company response to clarification, Appendix 1, Table 15 with EAG correction to incremental QALYs with severity weighting applied

At the request of the EAG, the company also produced cost effectiveness results for pirtobrutinib versus VenR for both populations, assuming the efficacy and time on treatment for VenR was equal to that for pirtobrutinib (Table 25 and Table 26). The company produced these analyses with the assumption that adverse events for patients receiving VenR or pirtobrutinib would be different, with adverse event rates for VenR estimated from the VenR arm of the MURANO trial.[36]

Table 25 Company post clarification base case cost comparison results in patients with R/R CLL: post-cBTKi population (pirtobrutinib PAS price)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	−£16,140
VenR	[redacted]	

cBTKi= covalent Bruton's tyrosine kinase inhibitor; PAS=patient access scheme; VenR=venetoclax and rituximab
Source: company response to clarification question B1, Table 2

Table 26 Company post clarification base case cost comparison results in patients with R/R CLL: dual-exposed population (pirtobrutinib PAS price)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	−£16,743
VenR	[redacted]	

PAS=patient access scheme; VenR=venetoclax and rituximab
Source: company response to clarification question B2, Table 4

5.1.2 Company's sensitivity and scenario analyses

5.1.2.1 Deterministic sensitivity analyses

In the deterministic sensitivity analyses (DSA), the company varied individual parameter inputs using upper and lower bounds of ±20% of the base-case values. For both the post-cBTKi and dual-exposed populations, the cost-effectiveness results were most sensitive to the HR used to adjust the OS curve for Investigator's choice.

5.1.2.2 Scenario analyses

The company conducted 11 scenario analyses (CS, Table 98) to explore alternative model assumptions and parameter values for the post-cBTKi and dual-exposed populations. For the post-cBTKi group, the most cost-effective results were observed when post-progression costs were assumed to be equivalent in total, while for the dual-exposed population, the most cost-effective results occurred when the Weibull distribution was used to model TTD.

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The EAG conducted model validation and verification in the following areas:

- cross-checking of parameter values against their original data sources, where data were available
- assessment of consistency between the executable model, the descriptions provided in the CS, and the company's clarification response
- cell-by-cell checks to ensure the accuracy and integrity of model programming.
- assessment of whether the model outputs were consistent with the model inputs and key outcomes from the trials and what clinical expert advice to the EAG would expect based upon outcomes from the BRUIN CLL-321 trial
- reproduction of the base-case results, PSA, DSAs, and scenario analyses presented in the CS using the company's executable model.

The EAG is satisfied following these checks that the model results accurately represent the assumptions and parameter values specified by the company in the CS and/or at clarification.

5.2.2 EAG's exploratory analyses using company's base case

The results of the EAG's individual revisions/scenarios using the company's base case are presented in Table 27.

Table 27 Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	Modelled post-cBTKi and dual-exposed populations (pirtobrutinib versus IdelaR) as a cost-utility analysis	Cost comparison analyses **Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi is suitable:** pirtobrutinib versus a cBTKi (ibrutinib, zanubrutinib or acalabrutinib) **Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a BCL2i is suitable:** pirtobrutinib versus VenR Cost-utility analyses **Patients with R/R CLL who have previously been treated with a cBTKi who are unsuitable for treatment with a cBTKi or a BCL2i:** pirtobrutinib versus BSC.	IdelaR is only a suitable comparator for patients who are unsuitable for treatment with a cBTKi or a BCL2i and clinical advice to the EAG is that IdelaR is rarely used in NHS clinical practice. A cBTKi or VenR are the most relevant comparators to pirtobrutinib for patients for whom a cBTKi or a BCL2i are suitable than these treatments. The available evidence from cost comparison analyses, although limited due to lack of comparative clinical effectiveness evidence, is more informative than cost-utility analyses.	4.2.4
2	Utility value in progressed state based on Holzner 2004[62] (0.60)	Utility value in progressed state based on baseline utility value from dual-exposed population of BRUIN CLL-321 trial	BRUIN CLL-321 baseline utility values of the ITT and dual-exposed populations were similar, suggesting that utility values before starting an active therapy (i.e., at progression) are similar regardless of previous lines of treatment. Further, clinical advice to the company was that the utility values in the dual-exposed population were representative of a heavily pretreated and clinically complex population	4.3.2
3	Costs of SCT incorrectly calculated	Costs of SCT correctly calculated	The company had estimated the cost of SCT incorrectly	4.3.3

BCL2i=B-cell lymphoma 2 inhibitor; BSC=best supportive care; cBTKi=covalent Bruton's tyrosine kinase inhibitor; IdelaR=idelalisib with rituximab; SCT=stem cell transplant; VenR=venetoclax with rituximab

All results are deterministic. The cost-comparison results would not meaningfully change with probabilistic analysis as the only variable that could change in PSA would be time on treatment which would change the magnitude of any differences in costs between treatment arms but not the direction of those differences. In addition, any difference in the magnitude would likely be small as mean time on treatment over the PSA runs would be similar to the mean time on treatment in the deterministic analysis. For the cost-utility analyses, the company PSA results were very similar to the deterministic analyses. PSA has been run for EAG preferred scenario for the cost utility analyses in 5.2.4.

All results have been generated using the proposed PAS price for pirtobrutinib and list prices for all other drugs.

Table 28 Results of EAG's exploratory analyses using company's base case

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs (x1.2 or 1.7 weighting)	ICER £/QALY (x1.2 or 1.7 weighting)
1a	Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi is suitable: pirtobrutinib versus a cBTKi (ibrutinib, zanubrutinib or acalabrutinib)	Pirtobrutinib vs ibrutinib: [redacted] Pirtobrutinib vs zanubrutinib: [redacted] Pirtobrutinib vs acalabrutinib: [redacted]	-	-
1b	Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a BCL2i is suitable: pirtobrutinib versus VenR	Pirtobrutinib vs VenR: [redacted]	-	-
1c	Patients with R/R CLL who have previously been treated with a cBTKi who are unsuitable for treatment with a cBTKi or a BCL2i: versus BSC.	Pirtobrutinib vs BSC: [redacted]	Pirtobrutinib vs BSC: 0.900 (1.2 weighting)	Pirtobrutinib vs BSC: [redacted] per QALY gained
2	Utility value in progressed state based on baseline utility value from dual-exposed population of BRUIN CLL-321 trial ([redacted])	Pirtobrutinib vs IdelaR: Post cBTKi population: [redacted] Dual-exposed population: [redacted]	Pirtobrutinib vs IdelaR: Post cBTKi population: 0.565 (1.0 weighting) Dual-exposed population: 0.446 (1.2 weighting)	Post cBTKi population: [redacted] per QALY gained Dual-exposed population: [redacted] per QALY gained
3	Costs of SCT correctly calculated	Pirtobrutinib vs IdelaR: Post cBTKi population: [redacted] Dual-exposed population: [redacted]	Pirtobrutinib vs IdelaR: Post cBTKi population: 0.568 (1.0 weighting) Dual-exposed population: 0.485 (1.2 weighting)	Post cBTKi population: [redacted] per QALY gained Dual-exposed population: [redacted] per QALY gained

BCL2i=B-cell lymphoma 2 inhibitor; BSC=best supportive care; cBTKi=covalent Bruton's tyrosine kinase inhibitor; IdelaR=idelalisib with rituximab; SCT=stem cell transplant; VenR=venetoclax with rituximab

The company considered that a severity modifier of 1.2 should be applied for the dual-exposed population.

For the cost comparison analyses undertaken by the EAG, a severity modifier is not applied as there is not QALY gain with pirtobrutinib. A severity modifier of 1.2 is applied by the EAG for the R/R CLL population unsuitable for cBTKi or BCL2i treatment in the scenario where the costs of SCT have been correctly calculated. In all other EAG scenarios, no severity modifier is applied as the absolute and proportional QALY shortfalls do not meet the threshold required.

5.2.3 EAG's preferred assumptions

The EAG preferred base case analyses are the cost comparison analyses for the comparisons of pirtobrutinib with a cBTKi or VenR (exploratory analyses 1a and 1b in Table 28) and the cost-utility analyses for the comparisons of pirtobrutinib with IdelaR or BSC with the EAG preferred utility values and costs of SCT (the company base case and exploratory analyses 1c in Table 28 with exploratory analyses 2 and 3 applied to both).

5.2.4 Scenario analyses using EAG's preferred assumptions

Results generated by the company model using the EAG preferred assumptions are shown in Table 29. The proposed PAS price for pirtobrutinib is used with the list price for all other drugs. The EAG notes that the company stated in their response to clarification that the analysis was over a lifetime horizon but the results presented were for a five-year time horizon. Results are therefore presented with a lifetime horizon and so differ from those reported by the company in the response to clarification.

Table 29 Cost comparison of pirtobrutinib versus VenR

Analysis	Pirtobrutinib		VenR		Incremental		Deterministic ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company analysis (patients with R/R CLL: post-cBTKi population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£1,569,701
Company analysis (patients with R/R CLL: dual-exposed population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£1,626,287
EAG preferred analysis (Patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a BCL2i is suitable)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BCL2i=B-cell lymphoma 2 inhibitor; cBTKi=covalent Bruton's tyrosine kinase inhibitor; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years; VenR=venetoclax with rituximab

Table 30 Cost comparison of pirtobrutinib versus a cBTKi (no company base case): patients with R/R CLL who have previously been treated with a cBTKi and for whom treatment with a cBTKi is suitable

Analysis	Pirtobrutinib		cBTKi		Incremental		Deterministic ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Pirtobrutinib versus ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pirtobrutinib versus zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pirtobrutinib versus acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

cBTKi=covalent Bruton's tyrosine kinase inhibitor; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years

Table 31 Probabilistic cost utility analysis results pirtobrutinib versus IdelaR

Analysis	Pirtobrutinib		IdelaR		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company analysis (patients with R/R CLL: dual-exposed population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred analysis: Patients with R/R CLL who have previously been treated with a cBTKi who are unsuitable for treatment with a cBTKi or a BCL2i	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]1.2 severity weighting applied to pirtobrutinib QALYs
BCL2i=B-cell lymphoma 2 inhibitor; cBTKi=covalent Bruton's tyrosine kinase inhibitor; ICER=incremental cost effectiveness ratio; IdelaR=idelalisib with rituximab; QALY=quality adjusted life years

Table 32 Probabilistic cost utility analysis results pirtobrutinib versus BSC (no company base)

Analysis	Pirtobrutinib		BSC		Incremental		ICER[a]
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
EAG preferred analysis: Patients with R/R CLL who have previously been treated with a cBTKi who are unsuitable for treatment with a cBTKi or a BCL2i	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]1.2 severity weighting applied to incremental QALYs
BCL2i=B-cell lymphoma 2 inhibitor; BSC=best supportive care; cBTKi=covalent Bruton's tyrosine kinase inhibitor; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years

5.3 Decision modifiers

5.3.1 QALY weighting for severity

In the company base case, a 1.2 severity modifier was applied to analyses of the dual-exposed population only. The company estimated that no severity modifier should be applied to the post-cBTKi population and the EAG agrees with this assessment. After application of the EAG's preferred progressed disease utility values, which the EAG calculated using the SCHARR/University of York/Luminity online severity modifier calculator, the EAG agreed that a 1.2 QALY shortfall should be applied to the company's dual-exposed population and the EAG's population of patients with R/R CLL for whom treatment with a cBTKi or a BCL2i is unsuitable. The company and EAG severity modifier calculations for these populations are shown in Table 33.

Table 33 Summary of company and EAG QALY shortfall analysis for the dual-exposed population

	General population QALYs	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Company	9.89	1.32	8.57	86.7%	1.2
EAG	10.21	1.51	8.70	85.2%	1.2

QALY=quality adjusted life years

5.3.2 Uncaptured benefits

The company have highlighted that the impact on caregiver quality of life has not been captured, although provided no qualitative detail on what the impact would be. It is therefore difficult to determine the magnitude of any benefit to the quality of life for carers from the introduction of pirtobrutinib.

The company also considered that the better AE profile for pirtobrutinib compared to other treatments and the benefits of pirtobrutinib is an oral treatment was not captured by the economic analysis – particularly VenR. However, the company did not consider any other treatments in the original submission and included adverse events in their cost-comparison analysis of pirtobrutinib versus VenR. Further, the cBTKis and venetoclax are all oral therapies and any utility benefit from oral therapy will have been captured as part of the EQ5D data collected in the BRUIN CLL-321 trial.

5.3.3 Health inequalities

The company considered that no information related to health inequalities was relevant to this appraisal.

5.4 Confidential comparator and subsequent treatment prices

Confidential prices are in place for the following comparators and subsequent treatments:

- idelalisib
- rituximab
- acalabrutinib
- ibrutinib
- cyclophosphamide
- fludarabine
- lenalidomide
- venetoclax
- zanubrutinib
- bendamustine

An appendix with the company base case and cost comparison analyses and the EAG cost comparison and cost-utility analyses using the confidential prices for the above drugs has been produced by the EAG.

5.5 Conclusions of the cost-effectiveness section

The analyses provided by the company in their submission and at clarification do not provide evidence of the cost-effectiveness of pirtobrutinib for the full population or against the full set of relevant comparators specified in the final scope[2] issued by NICE. Evidence was only provided by the company for pirtobrutinib versus IdelaR and versus VenR. The company provided no evidence for pirtobrutinib versus treatment with a cBTKi which the EAG considers is likely to be the most relevant comparators for patients who have been treated with VenI in the first-line setting. No evidence was provided by the company for pirtobrutinib versus BSC, which the EAG considers is a relevant comparator for patients who are unsuitable for a cBTKi or BL2Ci.

The absence of comparative efficacy evidence of pirtobrutinib versus any comparator except IdelaR makes undertaking robust cost-effectiveness analysis of pirtobrutinib versus the most relevant comparators unfeasible. Cost comparison analyses of pirtobrutinib versus the most relevant active treatment comparators was therefore undertaken by the company and the EAG, with a cost-utility analysis versus BSC. All these analyses are underpinned by an assumption of equal efficacy and equal time on treatment between pirtobrutinib and other active treatments and between IdelaR and BSC. These assumptions are essentially unsupported and therefore the analyses should be considered as exploratory only.

6 REFERENCES

1. Sharman JP, Munir T, Grosicki S, Roeker LE, Burke JM, Chen CI*, et al.* Phase III trial of pirtobrutinib versus idelalisib/rituximab or bendamustine/rituximab in covalent bruton tyrosine kinase inhibitor–pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma (BRUIN CLL-321). Journal of Clinical Oncology. 2025:JCO-25-00166.
2. National Institute for Care and Excellence. Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]. Final scope. Published 11 April 2025; Available from: https://www.nice.org.uk/guidance/gid-ta11298/documents/final-scope. Accessed 30 June 2025.
3. Medicines and Healthcare products Regulatory Agency. Public Assessment Report. National Procedure. Jaypirca 50 mg film-coated tablets. Jaypirca 100 mg film-coated tablets. Published September 2025; Available from: https://mhraproducts4853.blob.core.windows.net/docs/b608738be9c9b49c1845907db7e6fa417b3df79a. Accessed 15 September 2025.
4. Mukkamalla SKR, Taneja A, Malipeddi D, Master SR. Chronic lymphocytic leukemia. StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
5. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H*, et al.* iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018; 131:2745-60.
6. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) statistics. Published 3 June 2025; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll#heading-Zero Accessed 7 July 2025.
7. Haematological Malignancy Research Network. Survival statistics: Chronic lymphocytic leukaemia.; Available from: https://hmrn.org/statistics/survival. Accessed 6 August 2025.
8. Binet J, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J*, et al.* A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981; 48:198-206.
9. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975; 46:219-34.
10. National Institute for Care and Excellence. Rituximab for the first-line treatment of chronic lymphocytic leukaemia. Technology appraisal guidance [TA174] Published 22 July 2019; Available from: https://www.nice.org.uk/guidance/ta174/. Accessed 2 July 2025.
11. National Institute for Care and Excellence. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. Technology appraisal guidance [TA216]. Published 23 February 2011; Available from: https://www.nice.org.uk/guidance/ta216 Accessed 14 July 2025.
12. National Institute for Care and Excellence. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia. Technology appraisal guidance [TA343]. Published 2 June 2015; Available from: https://www.nice.org.uk/guidance/ta343. Accessed 14 July 2025.
13. National Institute for Health and Care Excellence. Acalabrutinib for treating chronic lymphocytic leukaemia. Technology appraisal guidance [TA689]. Published 21 April 2021; Available from: https://www.nice.org.uk/guidance/ta689. Accessed 14 July 2025.
14. National Institute for Health and Care Excellence. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. Technology appraisal guidance [TA663]. Published 9 December 2020; Available from: https://www.nice.org.uk/guidance/ta663. Accessed 14 July 2025.

15. National Institute for Health and Care Excellence. Zanubrutinib for treating chronic lymphocytic leukaemia. Technology appraisal guidance [TA931]. Published 22 November 2023; Available from: https://www.nice.org.uk/guidance/ta931. Accessed 14 July 2025.
16. National Institute for Health and Care Excellence. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia. Technology appraisal guidance [TA891]. Published 31 May 2023; Available from: https://www.nice.org.uk/guidance/ta891. Accessed 14 July 2025.
17. National Institute for Health and Care Excellence. Idelalisib for treating chronic lymphocytic leukaemia. Technology appraisal guidance [TA359]. Published 28 October 2015; Available from: https://www.nice.org.uk/guidance/ta359. Accessed 14 July 2025.
18. National Institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation. Technology appraisal guidance [TA429]. Published 25 January 2017; Available from: https://www.nice.org.uk/guidance/ta429. Accessed 14 July 2025.
19. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia. Technology appraisal guidance [TA796]. Published 15 June 2022; Available from: https://www.nice.org.uk/guidance/ta796. Accessed 14 July 2025.
20. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. Technology appraisal guidance [TA561]. Published 27 February 2019; Available from: https://www.nice.org.uk/guidance/ta561. Accessed 14 July 2025.
21. Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H*, et al.* Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology. 2022; 197:544-57.
22. Eli Lilly and Company. Data on File. Clinical validation meeting minutes.
23. Odetola O, Ma S. Relapsed/refractory chronic lymphocytic leukemia (CLL). Current Hematologic Malignancy Reports. 2023; 18:130-43.
24. Follows G, Burke JM, Grosicki S, Chen C, Sanna A, Roeker LE*, et al.* BRUIN CLL-321: A phase 3 open-label, randomized study of pirtobrutinib versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma. Journal of Clinical Oncology. 2023; 41:TPS7582-TPS.
25. Eli Lilly and Company. Data on File. Clinical SLR report (update SLR 1).
26. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I*, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. British Medical Journal. 2019; 366:l4898.
27. Eli Lilly and Company. Data on File. BRUIN CLL-321 protocol data.
28. Kim J, Cho J, Lim JH, Lee MH. Relative efficacy of systemic treatments for patients with relapsed/refractory chronic lymphocytic leukemia: a network meta-analysis according to 17p deletion/TP53 mutations. Blood research. 2025; 60:1.
29. Eli Lilly and Company. Data on File. Statistical analysis plan.
30. Eli Lilly and Company. Data on File. BRUIN CLL-321 CSR Addendum 2.
31. Gorrod H LN, Abrams K,. NICE DSU Technical Support Document 24: Adjusting survival time estimates in the presence of treatment switching: An update to TSD 16. Published April 2024; Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Accessed 22 July 2025.
32. Eli Lilly and Company. Data on File. BRUIN-CLL-321 (LOXO-BTK-20020) patient-reported outcome (PRO) report. 2025.
33. Brown JR, Eichhorst B, Hillmen P, Jurczak W, Kaźmierczak M, Lamanna N*, et al.* Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia (ALPINE). New England Journal of Medicine. 2023; 388:319-32.

34. Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M*, et al.* ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. Journal of Clinical Oncology. 2020; 38:2849-61.
35. Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR*, et al.* Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial (ELEVATE RR). Journal of clinical oncology. 2021; 39:3441-52.
36. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S*, et al.* Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia (MURANO). New England Journal of Medicine. 2018; 378:1107-20.
37. Burger JA, Sivina M, Jain N, Kim E, Kadia T, Estrov Z*, et al.* Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia (NCT02007044). Blood. 2019; 133:1011-9.
38. Flinn IW, Hillmen P, Montillo M, Nagy Z, Illés Á, Etienne G*, et al.* The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018; 132:2446-55.
39. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM*, et al.* Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. American Journal of Hematology. 2019; 94:1353-63.
40. Molica S, Shanafelt TD, Giannarelli D, Gentile M, Mirabelli R, Cutrona G*, et al.* The chronic lymphocytic leukemia international prognostic index predicts time to first treatment in early CLL: Independent validation in a prospective cohort of early stage patients. American Journal of Hematology. 2016; 91:1090-5.
41. Buzaglo JS, Miller MF, Zaleta AK, Johnson J, McManus S, Karten C*, et al.* Chronic lymphocytic leukemia patient reported outcomes and quality of life: findings from the cancer experience registry. Blood. 2017; 130:2122.
42. Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J*, et al.* Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. Journal of Clinical Oncology. 2010; 28:1756-65.
43. Awan FT, Hillmen P, Hellmann A, Robak T, Hughes SG, Trone D*, et al.* A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed chronic lymphocytic leukaemia. British Journal of Haematology. 2014; 167:466-77.
44. Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S*, et al.* Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): A randomised, double-blind, phase 3 study. The Lancet Oncology. 2016; 17:200-11.
45. Zelenetz AD, Barrientos JC, Brown JR, Coiffier B, Delgado J, Egyed M*, et al.* Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Oncology. 2017; 18:297-311.
46. Huang X, Qiu L, Jin J, Zhou D, Chen X, Hou M*, et al.* Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study. Cancer Medicine. 2018; 7:1043-55.
47. Michallet AS, Aktan M, Hiddemann W, Ilhan O, Johansson P, Laribi K*, et al.* Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: Primary analysis of the randomized, open-label mable study. Haematologica. 2018; 103:698-706.
48. Sharman JP, Brander DM, Mato AR, Ghosh N, Schuster SJ, Kambhampati S*, et al.* Ublituximab plus ibrutinib versus ibrutinib alone for patients with relapsed or refractory

high-risk chronic lymphocytic leukaemia (GENUINE): a phase 3, multicentre, open-label, randomised trial. The Lancet Haematology. 2021; 8:e254-e66.
49. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P*, et al.* Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. New England Journal of Medicine. 2014; 370:997-1007.
50. Sun C, Nierman P, Kendall EK, Cheung J, Gulrajani M, Herman SEM*, et al.* Clinical and biological implications of target occupancy in CLL treated with the BTK inhibitor acalabrutinib. Blood. 2020; 136:93-105.
51. Gritti G, Reda G, Maura F, Piciocchi A, Baldini L, Molica S*, et al.* Low dose alemtuzumab in patients with fludarabine-refractory chronic lymphocytic leukemia. Leukemia & Lymphoma. 2012; 53:424.
52. Hillmen P, Cohen DR, Cocks K, Pettitt A, Sayala HA, Rawstron AC*, et al.* A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated chronic lymphocytic leukaemia. British Journal of Haematology. 2011; 152:570-8.
53. Osterborg A, Udvardy M, Zaritskey A, Andersson PO, Grosicki S, Mazur G*, et al.* Phase III, randomized study of ofatumumab versus physicians' choice of therapy and standard versus extended-length ofatumumab in patients with bulky fludarabine-refractory chronic lymphocytic leukemia. Leukemia and Lymphoma. 2016; 57:2037-46.
54. Fowler NH, Samaniego F, Jurczak W, Ghosh N, Derenzini E, Reeves JA*, et al.* Umbralisib, a dual PI3Kdelta/CK1epsilon inhibitor in patients with relapsed or refractory indolent lymphoma. Journal of Clinical Oncology. 2021; 39:1609-18.
55. Spaner DE, McCaw L, Wang G, Tsui H, Shi Y. Persistent janus kinase-signaling in chronic lymphocytic leukemia patients on ibrutinib: Results of a phase I trial. Cancer Medicine. 2019; 8:1540-50.
56. Gribben JG, Jurczak W, Jacobs RW, Grosicki S, Giannopoulos K, Wrobel T*, et al.* Umbralisib plus ublituximab (U2) is superior to obinutuzumab plus chlorambucil (O+ Chl) in patients with treatment naïve (TN) and relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): results from the phase 3 Unity-CLL study. Blood. 2020; 136:37-9.
57. Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S*, et al.* Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. The Lancet Haematology. 2017; 4:e114-e26.
58. Al-Sawaf O, Jen MH, Hess LM, Zhang J, Goebel B, Pagel JM*, et al.* Pirtobrutinib versus venetoclax in covalent Bruton tyrosine kinase inhibitor-pretreated chronic lymphocytic leukemia: a matching-adjusted indirect comparison. Haematologica. 2024; 109:1866-73.
59. Mato AR, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA*, et al.* Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021; 397:892-901.
60. Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD*, et al.* Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. The Lancet Oncology. 2018; 19:65-75.
61. Eli Lilly and Company. Data on File. Economic SLR Report (original and update SLR 1).
62. Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. European journal of haematology. 2004; 72:381-9.
63. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. Pharmacoeconomics. 2023; 41:199-207.
64. NHS England. 2023/25 NHS Payment Scheme (amended). Annex B: Guidance on currencies. Published 27 March 2024; Available from:

https://www.england.nhs.uk/wp-content/uploads/2023/03/23-25NHSPS-amended_Annex-B-Guidance-on-currencies.pdf. Accessed 28 July 2025.
65. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. Palliative Medicine. 2015; 29:899-907.
66. Eli Lilly and Company. Data on File. BRUIN CLL-321 CSR.
67. European Medicines Agency. Jaypirca. Annex I. Summary of product characteristics. Published 25 April 2025; Available from: https://www.ema.europa.eu/en/documents/product-information/jaypirca-epar-product-information_en.pdf. Accessed 10 July 2025.
68. Electronic Medicines Consortium. Zydelig 100 mg film-coated tablets. Summary of product characteristics. Published 4 February 2025; Available from: https://www.medicines.org.uk/emc/product/3330/smpc. Accessed 11 July 2025.
69. Electronic Medicines Consortium. MabThera 100 mg concentrate for solution for infusion. Summary of product characteristics. Published 16 July 2024; Available from: https://www.medicines.org.uk/emc/product/3801/smpc. Accessed 11 July 2025.
70. Tam CS, Allan JN, Siddiqi T, Kipps TJ, Jacobs R, Opat S*, et al.* Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood. 2022; 139:3278-89.
71. Ghia P, Wierda WG, Barr PM, Kipps TJ, Siddiqi T, Allan JN*, et al.* Relapse after first-line fixed duration ibrutinib + venetoclax: high response rates to ibrutinib retreatment and absence of BTK mutations in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with up to 5 years of follow-up in the phase 2 CAPTIVATE study. Blood. 2023; 142:633.
72. Wen T, Sun G, Jiang W, Steiner K, Bridge S, Liu P. Comparing the efficacy and safety of first-line treatments for chronic lymphocytic leukemia: a network meta-analysis. Journal of the National Cancer Institute. 2025; 117:322-34.
73. Monthly Index of Medical Specialties. Tecartus. Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/tecartus. Accessed 28 July 2025.
74. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under. Technology appraisal guidance [TA975]. Published 15 May 2024; Available from: https://www.nice.org.uk/guidance/ta975 Accessed 14 July 2025.

Single Technology Appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

EAG report – factual accuracy check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 8 September 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Corrections and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 2.2.1, Page 14 states: "The company stated (CS, Section 1.3.1.1) that the Binet and Rai staging systems are used to stage CLL at diagnosis and this information is used to inform treatment decisions. However, clinical advice to the EAG is that the International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) 2018 criteria are used in National Health Service (NHS) practice to identify patients with CLL who require active therapy"	The text should be amended as follows: "The company stated (CS, Section 1.3.1.1) that the Binet and Rai staging systems are used to stage CLL at diagnosis and this information is used to inform treatment decisions. ~~However, clinical advice to the EAG is~~ **The company also stated** that the International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) 2018 criteria are used in National Health Service (NHS) practice to identify patients with CLL who require active therapy**; this was corroborated in clinical advice to the EAG**."	Lilly believes that this is not an accurate framing of the descriptions provided for staging and diagnosis in the CS. In the CS, the Binet and Rai systems are referred to in European and global contexts (i.e. not claiming that they represent typical NHS practice), respectively. Additionally, the CS notes that the 2018 iwCLL criteria inform treatment decisions in UK clinical practice, including "Watch and Wait".	The EAG has edited the text as follows: "The company stated that the Binet[7] and Rai[8] staging systems (CS, Section 1.3.1.1) and the International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) 2018 criteria[4] (CS, Section 1.3.3.1) are used to stage CLL at diagnosis and this information is used to inform treatment decisions. Clinical advice to the EAG is that the iwCLL 2018 criteria[5] are used in National Health Service (NHS) practice to identify patients with CLL who require active therapy."

Section 2.3.1, Page 18 states: "The company considered (company response to clarification question A2 and clarification question A3) that BSC is difficult to define and therefore is not a relevant comparator"	The text should be amended as follows: "The company considered (company response to clarification question A2 and clarification question A3) that BSC is difficult to define and ~~therefore is not a relevant comparator~~ **that patients with R/R CLL would not receive BSC when they would be eligible to receive an efficacious, active comparator in clinical practice. On this basis, the company argued that BSC would not constitute a relevant comparator to pirtobrutinib**"	Lilly suggests that wording here be amended to reflect the additional considerations discussed in the clarification response, on the relevance of BSC as a comparator to pirtobrutinib in the target indication. The current wording may be misconstrued; readers may assume that the difficulty to define BSC was the sole reason for dismissing BSC as a comparator to pirtobrutinib in this submission.	The EAG has amended the text as follows: "The company considered (company response to clarification question A2 and clarification question A3) that BSC is difficult to define and that patients with R/R CLL would not receive BSC if they were eligible for active treatments and therefore BSC is not a relevant comparator."
Section 2.3.1, Page 20 states: "The company identified three subpopulations but has only presented clinical and cost effectiveness evidence for the dual-exposed subpopulation. The company was not able to identify BRUIN CLL-321 trial patients for whom SoC	The text should be clarified as follows: **Section 2.3.1, Page 20:** "The company identified three subpopulations but has only presented clinical and cost effectiveness evidence for the dual-exposed subpopulation. The company was not able to identify BRUIN CLL-321 trial patients for whom SoC was suitable or BRUIN CLL-321 trial patients for whom SoC was unsuitable and was therefore unable to present evidence	Lilly acknowledges that separate subgroup analyses were not conducted for the subgroups of patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable or unsuitable.	The EAG has amended the text as follows: **Section 2.3.1, Page 21:** **"**The company… was therefore unable to present evidence separately for these subpopulations.**"**

was suitable or BRUIN CLL-321 trial patients for whom SoC was unsuitable and was therefore unable to present evidence for these subpopulations." **This is repeated in Section 3.2.2, Page 28:** "The company identified three subpopulations as relevant to the appraisal (see Table 1) but only presented evidence from the BRUIN CLL-321 trial for the ITT population and the dual-exposed subpopulation (i.e., patients who have previously been treated with a cBTKi and a BCL2i)" **And again in Section 3.6, Page 52:** "The company provided no clinical effectiveness evidence for: • the comparisons of pirtobrutinib versus a	**separately** for these subpopulations. **However, the ITT population of the BRUIN CLL-321 trial encompasses patients in both of these sub-populations, meaning that there are Phase III RCT data demonstrating the efficacy of pirtobrutinib versus an active comparator used in NHS practice covering both of these sub-populations.**" **Section 3.2.2, Page 28:** "The company identified three subpopulations as relevant to the appraisal (see Table 1) ~~but only~~ and presented evidence from the BRUIN CLL-321 trial for the ITT population and the dual-exposed subpopulation (i.e., patients who have previously been treated with a cBTKi and a BCL2i). **While data were not presented separately for the sub-populations of patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable or unsuitable", these patients were**	However, data on efficacy and safety for these patients were inherently captured in the ITT analyses discussed in the CS. Therefore, Lilly do not consider it fair to suggest that data for patients within these subgroups were not presented in the CS. The wording in the EAG report should therefore be amended as proposed.	**Section 3.2.2, Page 28:** This is not a factual inaccuracy. No amendments were made to the text. **Section 3.7, Page 52:** "…separately for the two other subpopulations identified by the company"

cBTKi, a BCL2i or BSC (which the EAG considers are relevant comparators) • the two other subpopulations identified by the company, namely: ○ patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable ○ patients with R/R CLL who have previously been treated with a cBTKi	**considered through the ITT analyses discussed in the CS.** **Section 3.6, Page 52:** "The company provided no clinical effectiveness evidence for: • the comparisons of pirtobrutinib versus a cBTKi, a BCL2i or BSC (which the EAG considers are relevant comparators) • **separately for** the two other subpopulations identified by the company, namely: ○ patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is suitable ○ patients with R/R CLL who have previously been treated with a cBTKi and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is unsuitable"		

and for whom SoC (i.e., treatment with a BCL2i and/or a cBTKi) is unsuitable"			
Section 3.3.1.2, Page 42 states: "Considering the methods explored by the company, the EAG considers that the two-stage AFT method is the most appropriate approach to use to account for treatment switching. However, the company did not provide certain important details regarding the methods used to implement the two-stage AFT model including: • … • whether any bootstrapping or re-censoring was performed. The	The text should be clarified as follows: "Considering the methods explored by the company, the EAG considers that the two-stage AFT method is the most appropriate approach to use to account for treatment switching. However, the company did not provide certain important details regarding the methods used to implement the two-stage AFT model including: • … • whether any bootstrapping or re-censoring was performed**, although the company discusses considerations for bootstrapping in Section 3.3.2.2**. The NICE Decision Support Unit (DSU) recommends that, for submissions to NICE, the two-stage estimation methods should be applied with and without re-censoring. Applying bootstrapping methods would	The text should be amended to note that bootstrapping is discussed.	The EAG has amended the text as follows: "whether any bootstrapping or re-censoring was performed; the company discussed bootstrapping (CS, Section 3.3.2.2) but it is not clear whether this method was applied."

NICE Decision Support Unit (DSU) recommends that, for submissions to NICE, the two-stage estimation methods should be applied with and without re-censoring. Applying bootstrapping methods would also ensure that uncertainty around the reported effect estimates was correctly estimated • …"	also ensure that uncertainty around the reported effect estimates was correctly estimated • …"		
Section 3.3.2, Pages 42–43 state: "The company provided IRC-assessed PFS from the most recent DCO (29 August 2024 DCO) and OS, investigator-assessed PFS and TTNT from the primary analysis (DCO 29 August 2023) for the dual-exposed subpopulation, as per the	The text should be amended as follows: "The company provided IRC-assessed PFS from the most recent DCO (29 August 2024 DCO) and OS, investigator-assessed PFS and TTNT from the primary analysis (DCO 29 August 2023) for the dual-exposed subpopulation, as per the final scope issued by NICE (i.e., patients who ~~had ≥2 prior lines of therapy including~~ **have received** a BTKi and BCL2i; see Table 1)"	The number of prior lines of therapy cited in the report for patients within the dual-exposed sub-population is incorrect, as this sub-population also includes patients who may have only received 1 prior line of therapy, e.g. through treatment with venetoclax in combination	The EAG has amended the text as follows: "The company provided IRC-assessed PFS from the most recent DCO (29 August 2024 DCO) and OS, investigator-assessed PFS and TTNT from the primary analysis

final scope issued by NICE (i.e., patients who had ≥2 prior lines of therapy including a BTKi and BCL2i; see Table 1)"		with ibrutinib (VenI). The text should be amended to remove the specification of the number of prior lines of therapy and should instead focus only on prior exposure to a BTKi and BCL2i.	(DCO 29 August 2023) for the dual-exposed subpopulation (i.e., patients who have previously been treated with a cBTKi and a BCL2i)."
Section 4.2, Page 56 states: "In response to clarification questions B1 and B2, the company submitted a cost-comparison analysis of pirtobrutinib versus VenR for the post-cBTKi population and the dual-exposed population. The company assumed that pirtobrutinib and VenR have comparable efficacy."	The text should be amended as follows: "In clarification questions B1 and B2, the EAG requested that the company conduct cost-effectiveness analyses for pirtobrutinib versus other relevant comparators, e.g., VenR, using the survival data from BRUIN CLL-321 as a proxy in the absence of direct or indirect comparative effectiveness data between pirtobrutinib and these comparators. In their responses to clarification questions B1 and B2, and in line with the EAG request, the company compared the cost-effectiveness of pirtobrutinib with VenR (in the post-cBTKi and dual-exposed populations respectively) using the survival KM data from the pirtobrutinib arm of BRUIN CLL-321 as a proxy for the effectiveness of VenR, essentially assuming that pirtobrutinib and VenR had comparable efficacy in the target indication. A cost-comparison analysis using these data was	Lilly request that greater clarity is provided surrounding the submission of the cost-comparison analysis.	The EAG amended the text as follows: "In clarification questions B1 and B2, the EAG requested that the company conduct cost-effectiveness analyses for pirtobrutinib versus the other relevant comparators (i.e., VenR, a cBTKi and BSC) using the survival data from the BRUIN CLL-321 trial as a proxy in the absence of direct or indirect comparative clinical effectiveness data. In response to clarification questions B1 and B2, the

	submitted by the company wherein the differences in safety expected between pirtobrutinib and VenR were considered. The company also acknowledged the inherent uncertainty with these comparisons in their response.		company submitted a cost-comparison analysis of pirtobrutinib versus VenR for the post-cBTKi population and the dual-exposed population using the survival KM data from the BRUIN CLL-321 trial pirtobrutinib arm as a proxy for the effectiveness of VenR (i.e., assuming that pirtobrutinib and VenR had comparable efficacy in the target indication), and considering the differences in safety. The company acknowledged the inherent uncertainty of these cost effectiveness estimates."
Section 4.2.4.1, Page 62 states: "The company considered that cBTKis and BSC are not relevant comparators	The text should be amended as follows: "The company considered that cBTKis and BSC are not relevant comparators for pirtobrutinib, as patients who ~~have previously been treated~~ **progressed during treatment**	The present wording in the EAG report is not an accurate reflection of the arguments reported by Lilly in the clarification	The EAG amended the text as follows: "The company considered that cBTKis and BSC are not relevant

for pirtobrutinib, as patients who have previously been treated with a cBTKi should be considered refractory to cBTKis, and patients with R/R CLL should not be offered BSC when IdelaR is available"	with a cBTKi should be considered refractory to cBTKis **as they were likely to have developed resistance to cBTKis**, and patients with R/R CLL should not be offered BSC when IdelaR is available"	response and should be amended as suggested.	comparators for pirtobrutinib, as patients who have previously been treated with a cBTKi and who progressed during treatment with a cBTKi should be considered refractory to cBTKis as they will likely have developed resistance to cBTKis, and patients with R/R CLL should not be offered BSC when IdelaR is available."
Section 4.2.4.1, Pages 62–63 state: "The cost-comparison analysis for the comparison of pirtobrutinib versus VenR in the population suitable for treatment with a BCL2i is dependent on the assumption that pirtobrutinib is equally as effective as VenR. In response to clarification	The text should be amended as follows: "The cost-comparison analysis for the comparison of pirtobrutinib versus VenR in the population suitable for treatment with a BCL2i is dependent on the assumption that pirtobrutinib is equally as effective as VenR. In response to clarification question B1, the company referenced a published unanchored MAIC, which estimates the treatment effect of pirtobrutinib versus Ven-mono in patients with R/R CLL who had been previously treated with a cBTKi (see Section 3.5.1). The MAIC	The present wording is not an accurate representation of the details discussed in the company response to clarification question B1 and B2, and have merged two unrelated points discussed separately within the responses. Notably, in the response to question B1, Lilly did not conclude that an	The EAG has amended the text as follows: "The company considered that the study "raises important questions regarding the optimal treatment sequencing of pirtobrutinib and venetoclax in cBTKi-treated CLL" (company response to clarification question

question B1, the company referenced a published unanchored MAIC, which estimates the treatment effect of pirtobrutinib versus Ven-mono in patients with R/R CLL who had been previously treated with a cBTKi (see Section 3.5.1). The MAIC results suggest that pirtobrutinib and Ven-mono may have comparable effectiveness with the point estimates from the MAIC favouring pirtobrutinib. The company therefore concluded that an assumption of equal efficacy of VenR and pirtobrutinib may be conservative towards the actual cost-effectiveness of pirtobrutinib. However, clinical advice to the EAG is that VenR is more effective than Ven-mono and therefore the EAG considers that it cannot be concluded that the analysis	results suggest that pirtobrutinib and Ven-mono may have comparable effectiveness with the point estimates from the MAIC favouring pirtobrutinib. The company ~~therefore concluded that an assumption of equal efficacy of VenR and pirtobrutinib may be conservative towards the actual cost-effectiveness of pirtobrutinib~~ **noted that the study raised important questions regarding the optimal treatment sequencing of pirtobrutinib and venetoclax in cBTKi-treated CLL, however did not conclusively consider pirtobrutinib to be better or equivalent than treatment with Ven-mono, and by extension VenR, in the absence of prospective direct comparisons and limited long-term follow-up data**. ~~However,~~ Clinical advice to the EAG is that VenR is more effective than Ven-mono. ~~and therefore the EAG considers that it cannot be concluded that the analysis performed by the company is conservative~~"	assumption of equal efficacy between pirtobrutinib and VenR would be conservative based on the results of the published MAIC of pirtobrutinib and Ven-mono. Rather, Lilly cautioned on drawing any conclusions of comparative efficacy between pirtobrutinib and venetoclax treatments based on this study due to the lack of any direct comparisons and limited follow-up data. Separately, Lilly then noted in response to clarification question B2 that using the Investigator's choice data to model the clinical efficacy of VenR, as requested by the EAG, would understate VenR's efficacy, given the availability of trial data confirming its superiority over IdelaR. Lilly therefore	B1). Clinical advice to the EAG is that VenR is more effective than Ven-mono. The EAG therefore considers the assumption that pirtobrutinib is equally as effective as VenR to be highly uncertain."

performed by the company is conservative”		chose the ‘conservative’ option of using pirtobrutinib data from the BRUIN CLL-321 trial as a proxy for the efficacy of VenR for the comparison in the dual-exposed population. Lilly therefore request that the wording in the EAG report be amended, as suggested, to more closely align with the real narrative discussed in the clarification responses.	
Section 5.3.3, Page 82 states: “The company presented no information related to health inequalities”	The text should be amended as follows: “The company ~~presented~~ **noted that** no information related to health inequalities **were identified as relevant**”	The text should be updated to reflect that this was considered by Lilly, but no relevant inequity implications were identified.	The EAG has amended the text as follows: “The company considered that no information related to health inequalities was relevant to this appraisal.”

Issue 2 Data and typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.3, Page 10 states: "…unsuitable for treatment with a cBTKi or BLC2i." **Section 5.2.2, Page 79 states:** "…unsuitable for cBTKi or BLC2i treatment…" **Section 5.3.1, Page 82 states:** "…treatment with a cBTKi or a BLC2i is unsuitable."	The word BLC2i should be amended to **BCL2i** in the noted sections.	Minor typographical error.	The EAG has amended the text as requested.
Section 1.6, Page 12 states:	The text should be amended as follows: "[a] 1.2 severity weighting applied to incremental QALYs ~~cBTKi~~"	Lilly believes that this is likely a typographical error.	The EAG has amended the text as requested.

"[a] 1.2 severity weighting applied to incremental QALYs cBTKi"			
Section 2, Page 13 states: "This is in line with the anticipated UK licensed indication for pirtobrutinib which is for "...the treatment of adults with relapsed or refractory [R/R] CLL who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)." Medicines and Healthcare products Regulatory Agency (MHRA) approval is expected in September 2025 (CS, Table 2). "	The text should be amended as follows: "This is in line with the ~~anticipated~~ UK licensed indication for pirtobrutinib which is for "...the treatment of **adult patients** with relapsed or refractory [R/R] CLL who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)." Medicines and Healthcare products Regulatory Agency (MHRA) approval **was received on the 13th of August 2025**" Mentions of the licensed indication being **anticipated** should be adjusted elsewhere in pages 14, 17, 22	The marketing authorisation for pirtobrutinib in relapsed or refractory CLL has now been granted by the MHRA, and the wording in the EAG report should be updated in line with the SmPC wording, as proposed.	The EAG has amended the text as follows: "Medicines and Healthcare products Regulatory Agency (MHRA) approval was granted on the 13 August 2025 (CS, Table 2).{Reference to MHRA PAR added}"
Section 3, Page 29 states: "[b] Data were missing/unknown for 39/119 (32.8%)	This footnote should be amended as follows: "[b] Data were missing/unknown for 8/119 (6.7%) pirtobrutinib arm patients and 7/119 (5.9%) investigator's choice arm patients"	The proportion of patients with missing/unknown data for del(17p) mutation status is incorrect for the	The EAG has amended the text as requested.

pirtobrutinib arm patients and 43/119 (36.1%) investigator's choice arm patients"		pirtobrutinib and Investigator's choice arms.	
Section 3.2.3, Pages 30, 33, and 36 cite the following as a source: "company response to clarification question C5, Table 9"	The reference should be amended as follows: "company response to clarification question C5, Table 11"	Reference is made to Table 9 for the quality assessment of the BRUIN CLL-321 trial, but this table contains EMBASE® search terms.	The EAG has amended the text as requested.
Section 3.3 Page 38 states: "The company has presented BRUIN CLL-321 trial results from the primary analysis (DCO 28 August 2023) and the most recent analysis (DCO 29 August 2024 DCO29) in CS, Section 2.6"	The text should be amended as follows: "The company has presented BRUIN CLL-321 trial results from the primary analysis (DCO ~~28~~ **29** August 2023) and the most recent analysis (DCO 29 August 2024 DCO29) in CS, Section 2.6"	The date of the primary analysis is 29th August 2023.	The EAG has amended the text as requested.
Section 3.3.2, Page 43 states the following as a source for Investigator-assessed PFS, OS and TTNT:	The text should be amended as follows: "29th August **2024** DCO"	The data presented in Table 11 are all derived from the 29th August 2024 DCO, not the 29th August 2023 DCO.	The EAG has amended the text as requested.

"29th August 2023 DCO"			
Section 3.3.2, Page 43 states: "[c] Data extracted from CS, Table 34; TTNT was reported as HR 0.409 (95% CIs 0.255 to 0.654) in Sharman 2025,1 Figure A2"	The footnote should be amended as follows: "[c] Data extracted from CS, Table 34; TTNT was reported as HR 0.405 (95% CIs **0.252** to **0.649**) in Sharman 2025,1 Figure A2"	The data should be corrected to align with those presented in the Sharman *et al.* (2025) publication.	This is not a factual inaccuracy. The EAG has presented the TNTT results for the "receipt of previous BCL2 inhibitors" subgroup, not the "receipt of previous venetoclax treatment" subgroup
Section 3.7.1, Page 52 states: "Clinical advice to the EAG is that pirtobrutinib is tolerable and that the AEs associated with ribociclib+AI are manageable in NHS clinical practice"	The text should be amended as follows: "Clinical advice to the EAG is that pirtobrutinib is tolerable and that the AEs associated with ~~ribociclib+AI~~ **pirtobrutinib** are manageable in NHS clinical practice"	Ribociclib+AI is not addressed in Lilly's submission.	The EAG has amended the text as requested.
Section 4.1, Page 53 states: "The company initially conducted the SLR search in February 2020. The search was	The text should be amended as follows: "The company initially conducted the SLR search in February ~~2020~~ **2022**. The search was updated in April 2022 (SLR update 1), October 2023 (SLR update 2) and most recently in September 2024 (SLR update 3)."	The original date of the SLR search was February 2022.	The EAG has amended the text as requested.

updated in April 2022 (SLR update 1), October 2023 (SLR update 2) and most recently in September 2024 (SLR update 3)"	The date of the original search is incorrectly presented as February 2020		
Section 4.1, Page 55 cites the following as a source for the question "Were appropriate search terms used?": "See CS, Appendix E.1.1.1, Table 18 to Table 34"	The text should be amended as follows: "See CS, Appendix E.1.1.1, Table 20 to Table 34"	Tables 18 and 19 do not contain search terms.	The EAG has amended the text as requested.
Section 4.2.1, Page 57 states: "In the BRUIN CLL-321 trial, HRQoL data were collected using EQ-5D-5L. This is in line with the NHS reference checklist"	The text should be amended as follows: "In the BRUIN CLL-321 trial, HRQoL data were collected using EQ-5D-5L. This is in line with the ~~NHS reference checklist~~ **NICE Reference Case**"	Lilly believes that this is likely a typographical error.	The EAG has amended the text as requested.
Section 4.2.3, Page 60 cites the following as a source:	The text should be amended as follows: "CS, Table 54"	The reference should be amended to Table 54 of the CS	The EAG has amended the text as requested.

"CS, Table 36"			
Section 4.2.4.1, Page 63 states: "However, in the BRUIN CLL-321 trial, 8.3% of dual-exposed pirtobrutinib arm patients and 16.7% of dual-exposed investigator's choice arm patients received a cBTKi at progression (CS, Table 35)"	The text should be amended as follows: "However, in the BRUIN CLL-321 trial, 8.3% of dual-exposed pirtobrutinib arm patients and 16.7% of dual-exposed investigator's choice arm patients received a cBTKi at progression (CS, Table ~~35~~ **82**)"	The reference should be amended to Table 82 of the CS	The EAG has amended the text as requested.

The EAG has also made the following changes to the EAG report to reflect feedback received from Dr Stella Williams post-submission to NICE:

- the EAG has added additional conflict of interest disclosures from Dr Stella Williams (EAG report, p3)
    - "Dr Stella Williams received reimbursement from Abbvie, AstraZeneca and Takeda for attending symposiums and for speaking and from Roche for speaking andhas received Beigene meeting hospitality."
- the EAG has amended the text in EAG report, Table 1:

- “Clinical advice to the EAG is that NHS patients who relapse ≥6 months after completing venetoclax treatment can be rechallenged with venetoclax.”

- the EAG has amended the text in EAG report, Section 4.2.4.1:
  - “Clinical advice to the EAG is that IdelaR is rarely used in NHS clinical practice due to toxicity concerns and patient intolerability, and therefore nearly all patients with R/R CLL who have previously been treated with a cBTKi for whom SoC (i.e., treatment with a BCL2i and/or cBTKi) is unsuitable and who have sufficient performance status are enrolled into clinical trials, where possible.”

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Additional comparative efficacy analysis

December 2025

File name	Version	Contains confidential information	Date
[ID6269] Pirtobrutinib in CLL_Additional Comparative Efficacy Analysis [noCON].docx	1	No	18 December 2025

1. Background and summary

Summary

- VenR identified as relevant comparator in post-cBTKi population in original Company Submission, however substantial heterogeneity meant an ITC was not possible
- Committee outcome ACM1: Cost-comparison analysis based on assumptions of similar effectiveness conducted; however, uncertainty remains
- Post-ACM gaps: stronger evidence for pirtobrutinib vs VenR (including updates from ongoing trials), a Ven-mono comparison, and clear guidance on cBTKi rechallenge.
- Lilly has conducted a Bayesian ITC/NMA (BRUIN CLL314 ↔ MURANO) for pirtobrutinib vs VenR which shows [redacted] (HR [redacted]; 95% CrI [redacted]), supporting the clinical similarity assumption for cost comparison.
- A cost comparison vs Ven-mono is prepared under the same framework (updated results will be appended.
- Taken together, the findings lessen uncertainty regarding pirtobrutinib versus VenR and support the similarity of effect assumptions used in the cost comparison

Background context

In the original Company Submission for pirtobrutinib in patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL), venetoclax with rituximab (VenR) was identified as a relevant comparator to pirtobrutinib for the population of adults with CLL who have previously been treated with a covalent BTKi (cBTKi), i.e. a post-cBTKi population.

However, a systematic literature review (SLR, detailed in Section 2.1 and Appendix B of the original Company Submission) found no relevant randomised controlled trials (RCTs) directly comparing pirtobrutinib with VenR in either the post-cBTKi population or the broader R/R CLL indication. A comprehensive feasibility assessment (FA, detailed in Section 2.10 of the original Company Submission) concluded that indirect treatment comparisons (ITCs) should not be conducted due to substantial heterogeneity in the distribution of treatment effect modifiers (TEMs), such as prior types and lines of treatment; these conclusions were supported by the External Assessment Group (EAG).

As a result, Lilly were unable to conduct cost-utility analyses for pirtobrutinib versus VenR in the post-cBTKi population. However, cost-comparison analyses were conducted for pirtobrutinib versus VenR, predicated on the assumption of similar effectiveness between the two treatments. Lilly acknowledged the limitations of the analyses, for which the key assumption was of similar clinical effectiveness between pirtobrutinib and VenR, in the absence of any strong data to support this assumption. Following the meeting, the Committee considered this to remain as an area of uncertainty with this appraisal.

Committee requests:

Following the ACM, Lilly note the Committee's remaining uncertainties with this appraisal, including the need for:

1. Further characterisation of the comparison between pirtobrutinib and VenR where possible, including updates from ongoing trials
2. A comparison with Ven-mono, which comprises any potentially useful available relative effect data, including RWE referenced by the clinical expert in the ACM comparing Ven-mono with VenR
3. Additional clarity around the issue of rechallenge with cBTKi therapies for patients who received fixed-duration venetoclax in combination with ibrutinib or discontinued a cBTKi therapy because of intolerance, although this was recognised as a smaller population/issue for decision-making

Evidence provided to address Committee uncertainty

1. Comparison between Pirtobrutinib and VenR

To address the key uncertainty of the similarity assumptions between pirtobrutinib and VenR underpinning the cost-comparison analysis, Lilly herein presents the results of an ITC of pirtobrutinib and VenR using newly available data from the Phase 3 BRUIN CLL-314 trial, which assessed the effectiveness of pirtobrutinib against ibrutinib in patients with CLL who were either treatment-naïve or who were BTKi-naïve but R/R to other previously received treatments (see Section 2 and Appendix A for further details).[1] The MURANO trial informed the efficacy for VenR in this ITC analysis. Unlike BRUIN CLL-321, which was conducted in an entirely post-BTKi population, MURANO was conducted in a predominantly BTKi-naïve population (<3% of patients were previously exposed). Therefore, MURANO is considered to be more similar to BRUIN CLL-314 than to BRUIN CLL-321.[1-3]

While this additional comparative efficacy analysis does not directly address the relative efficacy of pirtobrutinib versus VenR in the post-cBTKi population, Lilly considers that this may reduce decision-making uncertainty around the relative efficacy of pirtobrutinib versus VenR, as the ITC is conducted in a similar patient population for both treatments (see Appendix A.2 for further details).

2. Comparison between Pirtobrutinib and Ven-mono

With respect to the requested comparison of pirtobrutinib versus VenR proxied by real-world evidence (RWE) comparing venetoclax monotherapy (Ven-mono) to VenR, Lilly considers that the ITC comparing pirtobrutinib (using data from BRUIN CLL-314) with VenR (using data from MURANO) is a suitably more robust proxy to support the assumption of clinical similarity to VenR. Lilly acknowledge that the Committee concluded Ven-mono is another suitable comparator for the post-cBTKi population and present a cost-comparison analysis versus Ven-mono, underpinned by clinical similarity data presented in the Company clarification response (Question B1). Updated results will be provided in a subsequent appendix.

3. *Rechallenging with cBTKi*

Regarding the issue of rechallenge with cBTKi therapies, Lilly acknowledges the Committee's request for further clarity, but notes that no material from published literature or NHS data could be identified to inform current UK practice or outcomes for cBTKi rechallenge in this context. Further, since cBTKi rechallenge may only be relevant for a small subset of patients in the post-cBTKi population, Lilly concurs with the Committee that this issue has a smaller impact on the decision uncertainty in the appraisal than characterising the comparison between pirtobrutinib and VenR and Ven-mono. Cost-comparison analyses of pirtobrutinib versus cBTKi have therefore not been conducted.

Summary of the ITC analysis

The ITC presented herein for the comparison between pirtobrutinib and VenR is a Bayesian network meta-analysis (NMA). Studies selected for inclusion in the NMA were identified through the SLR and FA conducted for the original Company Submission (see Section 2.1 and Appendix B, and Section 2.10, respectively, for further details). In the interest of time, the only outcome assessed in the NMA was PFS as assessed by an Independent Review Committee (IRC). PFS by IRC assessment was chosen for comparability with the primary efficacy outcome of the BRUIN CLL-321 trial, ensuring relevance to the clinical evidence informing the cost-comparison analysis submitted at the clarification stage.[3]

Although OS data were available from BRUIN CLL-314, these data were considered very immature; therefore, NMAs for OS were not considered likely to be clinically meaningful at this time.[1]

In summary, to address the Committee's request for further characterisation of the comparison with VenR, Lilly conducted a Bayesian NMA using newly available data from BRUIN CLL-314 and relevant RCTs identified via an SLR. This analysis provided an indirect comparison of pirtobrutinib and VenR—and, by extension, Ven-mono—for patients with R/R CLL in the BTKi-naïve setting, using the efficacy outcome of PFS by IRC assessment. The NMA found [redacted] in expected PFS between VenR and pirtobrutinib (HR: [redacted]; 95% credible interval [CrI]: [redacted]). A better relative effect for VenR than pirtobrutinib would be implied only if the HR were <1 with the 95% CrI excluded 1.

These findings help address the decision uncertainty in the current appraisal regarding the comparative efficacy of pirtobrutinib versus VenR and lend greater confidence to the similarity of treatment effect assumptions underpinning the cost-comparison analyses. As mentioned earlier, results will be provided in a subsequent appendix.

Closing key takeaways:

- **Comparative efficacy (BTKi-naïve R/R CLL):** Bayesian NMA shows [redacted] between pirtobrutinib and VenR (HR: [redacted]; 95% CrI: [redacted])
- Analysis uses **PFS by IRC**; OS from BRUIN CLL 314 is immature; findings do **not** directly resolve post-cBTKi comparative efficacy
- **Ven-mono comparator:** Cost-comparison versus Ven-mono prepared under a similar effectiveness assumption, underpinned by clinical similarity data presented previously
- **Decision implication:** These findings **reduce uncertainty** and support using a **similar effectiveness assumption** for cost-comparison versus VenR and Ven-mono in BTKi-naïve R/R CLL
- Updated results will be provided in a subsequent appendix

2. Materials and methods

2.1. Identification and selection of relevant studies

The NMA discussed herein was based on the clinical SLR for R/R CLL that was included in the original Company Submission. The SLR was based on searches conducted up to February 2025; further details for the clinical SLR are provided in Section 2.1, Section 2.2 and Appendix B of the original Company Submission. In addition, newly available data from BRUIN CLL-314 were considered to assess the feasibility of conducting the NMA, as outlined in the below section.[1]

Given the time constraints for conducting the present analyses, no additional searches were undertaken to identify studies published after February 2025. As a simplifying assumption, it was therefore assumed that no new data had become available for the treatments considered in the FA conducted for the original Company Submission.

2.2. Similarity of studies selected for inclusion in NMA

As presented in Section 2.10 of the original Company Submission, a robust FA was conducted using data from BRUIN CLL-321 for pirtobrutinib and the available trial data for a range of active treatments to evaluate their suitability to inform ITCs in the post-cBTKi population.[2-7] The interventions included in the FA were aligned with global guidelines at the time of submission. The FA concluded that an ITC versus VenR was not feasible, primarily due to substantial heterogeneity in the distribution of important, known TEMs, including prior lines of therapy and prior treatment exposure.

For this NMA, the newly available data from BRUIN CLL-314 were assessed alongside the RCTs included in the FA conducted for the original Company Submission: MURANO, ALPINE, ASCEND, ELEVATE RR, and NCT02007044.[1-7] This review did not consider the DUO and RESONATE trials, which were included in the FA conducted for the original Company Submission, as these trials included ofatumumab, which has been discontinued for the treatment of CLL in the UK.[8-10]

Trial-level characteristics for the included studies are summarised in Table 1. Additional tables present treatment arm-level data on demographic and disease characteristics (Table 2), genetic mutations (Table 3), and prior treatments (Table 4). For completeness, data from BRUIN CLL-321, the pivotal study supporting the original Company Submission, are also presented in these tables for contextual comparison; however, BRUIN CLL-321 was not included in the NMA. All studies included in this NMA, with the exception of BRUIN CLL-314, data for which were not available at the time of the original Company Submission, are presented in Section 2.10 therein.

These data indicate that BRUIN CLL-314 is more closely aligned to the pivotal trial for VenR (MURANO) and the other trials that were included in the original FA than BRUIN CLL-321, particularly with respect to prior lines of therapy and previous exposure to BTKi, phosphoinositide 3-kinase inhibitor (PI3Ki) and BCL2i (Table 4). These factors were identified in the FA as among the most important known TEMs.[1-7]

Although some heterogeneity exists between BRUIN CLL-314 and the other trials, it was considered that the degree of similarity across key TEMs was sufficient to support the conduct of an NMA.[1-7] The results of NMA should nonetheless be interpreted with appropriate caution given the residual between-study differences.

Table 1: Trial-level characteristics

Trial	Phase	Intervention	Comparator	Blinding	Target population	Crossover	Primary outcome
BRUIN CLL-321[3a]	*3*	*Pirtobrutinib*	*Investigator's choice (IdelaR or BR)*	*Open-label*	*CLL/SLL*	*Yes*	*PFS*
BRUIN CLL-314[1]	3	Pirtobrutinib	Ibrutinib	Open-label	CLL/SLL	No	ORR
MURANO[2]	3	VenR	BR	Open-label	CLL	Yes	PFS
ALPINE[4]	3	Zanubrutinib	Ibrutinib	Open-label	CLL	NR	ORR
ASCEND[5]	3	Acalabrutinib	Investigator's choice (IdelaR or BR)	Open-label	CLL	Yes	PFS
ELEVATE RR[6]	3	Acalabrutinib	Ibrutinib	Open-label	CLL	NR	PFS
NCT02007044[7]	2	Ibrutinib + rituximab	Ibrutinib	Open-label	CLL	NR	PFS

Footnote: Details for BRUIN CLL-321 are presented for completeness; BRUIN CLL-321 was not included in this NMA.
Abbreviations: BR: bendamustine in combination with rituximab; CLL: chronic lymphocytic leukaemia; IdelaR: idelalisib in combination with rituximab; NMA: network meta-analysis; NR: not reported; ORR: overall response rate; PFS: progression-free survival; SLL: small lymphocytic lymphoma; VenR: venetoclax in combination with rituximab.

Table 2: Treatment arm-level demographic and disease characteristics

Trial	Treatment	N	Median age, years	Age >65 years	Male	Rai Stage I–II	Rai Stage III–IV	ECOG 0–1	ECOG 2
BRUIN CLL-321[3a]	*Pirtobrutinib*	*119*	*66*	*58.8%*	*69.7%*	*46.2%*	*42.8%*	*95.8%*	*4.2%*
BRUIN CLL-321[3a]	*Investigator's choice (IdelaR or BR)*	*119*	*68*	*67.2%*	*69.7%*	*43.7%*	*44.5%*	*89.9%*	*10.1%*
BRUIN CLL-314[1]	Pirtobrutinib	219	67	57.5%	66.2%	53.8%	45.2%	96.8%	3.2%
BRUIN CLL-314[1]	Ibrutinib	218	67	61.0%	66.1%	55.0%	43.4%	96.8%	3.2%
MURANO[2]	VenR	194	65	NR	70.1%	67.7%	23.1%	99.5%	0.5%
MURANO[2]	BR	195	66	NR	77.4%	73.6%	12.9%	99.0%	1.0%
ALPINE[4]	Zanubrutinib	327	67	NR	65.1%	55.7%	44.3%	NR	NR
ALPINE[4]	Ibrutinib	325	68	NR	71.4%	58.2%	41.5%	NR	NR

ASCEND[5]	Acalabrutinib	155	68	63.0%[b]	70.0%	58.0%	42.0%	87.0%	12.0%
ASCEND[5]	Investigator's choice (IdelaR or BR)	155	67	63.0%[b]	65.0%	58.0%	41.0%	86.0%	14.0%
ELEVATE RR[6]	Acalabrutinib	268	66	NR	69.0%	51.1%[c]	48.9%	92.2%	7.5%
ELEVATE RR[6]	Ibrutinib	265	65	NR	73.2%	49.4%[c]	50.6%	91.7%	8.3%
NCT02007044[7]	Ibrutinib + rituximab	104	65	NR	68.0%	60.0%	40.0%	100.0%	0.0%
NCT02007044[7]	Ibrutinib	104	65	NR	72.1%	63.0%	37.0%	100.0%	0.0%

Footnotes: [a] Details for BRUIN CLL-321 are presented for completeness; BRUIN CLL-321 was not included in this NMA. [b] Age ≥65 years. [c] Calculated assuming no unknown Rai status.
Abbreviations: BR: bendamustine in combination with rituximab; ECOG: Eastern Cooperative Oncology Group; IdelaR: idelalisib in combination with rituximab; NMA: network meta-analysis; NR: not reported; VenR: venetoclax in combination with rituximab.

Table 3: Treatment arm-level genetic mutations

Trial	Treatment	*IGHV* mutated	del11(q)	del17(p)	*TP53* mutated	del(17p) and/or *TP53* mutation
BRUIN CLL-321[3a]	*Pirtobrutinib*	*24.4%*	*16.0%*	*32.8%*	*27.7%*	*42.0%*
BRUIN CLL-321[3a]	*Investigator's choice (IdelaR or BR)*	*37.8%*	*21.0%*	*36.1%*	*21.8%*	*42.9%*
BRUIN CLL-314[1]	Pirtobrutinib	27.3%	NR	16.4%	42.9%	NR
BRUIN CLL-314[1]	Ibrutinib	29.9%	NR	16.1%	33.0%	NR
MURANO[2]	VenR	31.7%	NR	14.0%	11.1%	27.3%
MURANO[2]	BR	31.7%	NR	11.4%	14.6%	28.2%
ALPINE[4]	Zanubrutinib	26.9%	27.8%	13.8%	9.2%	22.9%
ALPINE[4]	Ibrutinib	26.5%	27.1%	15.4%	7.7%	23.1%
ASCEND[5]	Acalabrutinib	30.0%	25.0%	3.0%	11.0%	28.0%
ASCEND[5]	Investigator's choice (IdelaR or BR)	23.0%	28.0%	5.0%	13.0%	27.0%
ELEVATE RR[6]	Acalabrutinib	17.9%	62.3%	45.1%	37.3%	50.7%
ELEVATE RR[6]	Ibrutinib	10.6%	66.0%	45.3%	42.3%	50.9%
NCT02007044[7]	Ibrutinib + rituximab	NR	14.0%	29.0%	20.0%	NR
NCT02007044[7]	Ibrutinib	NR	26.0%	25.0%	28.0%	NR

Footnotes: [a] Details for BRUIN CLL-321 are presented for completeness; BRUIN CLL-321 was not included in this NMA.

Abbreviations: BR: bendamustine in combination with rituximab; IdelaR: idelalisib in combination with rituximab; NMA: network meta-analysis; NR: not reported; VenR: venetoclax in combination with rituximab.

Table 4: Treatment arm-level previous treatments

Trial	Treatment	Number of previous lines			Previous BTKi	Previous PI3Ki	Previous BCL2i
		Median	1-2 lines	3 or more lines			
BRUIN CLL-321[3a]	*Pirtobrutinib*	*3*	*42.8%*	*57.2%*	*100.0%*	*9.2%*	*50.4%*
BRUIN CLL-321[3a]	*Investigator's choice (IdelaR or BR)*	*3*	*43.7%*	*56.3%*	*100.0%*	*9.2%*	*52.1%*
BRUIN CLL-314[1, 11]	Pirtobrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRUIN CLL-314[1, 11]	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MURANO[2]	VenR	1	87.1%	12.9%	2.9%	NR	0.0%
MURANO[2]	BR	1	82.1%	17.9%	2.9%	NR	0.0%
ALPINE[4]	Zanubrutinib	1	85.0%	14.9%	0.0%	3.4%	2.1%
ALPINE[4]	Ibrutinib	1	79.0%	20.9%	0.0%	5.8%	2.5%
ASCEND[5]	Acalabrutinib	1	79.0%	11.0%	NR	NR	0.0%
ASCEND[5]	Investigator's choice (IdelaR or BR)	2	73.00%	15.0%	NR	NR	0.0%
ELEVATE RR[6]	Acalabrutinib	2	NR	NR	0.0%	NR	0.0%
ELEVATE RR[6]	Ibrutinib	2	NR	NR	0.0%	NR	0.0%
NCT02007044[7]	Ibrutinib + rituximab	1	73.0%	16.0%	0.0%	NR	0.0%
NCT02007044[7]	Ibrutinib	1	65.0%	21.0%	0.0%	NR	0.0%

Footnote: [a] Details for BRUIN CLL-321 are presented for completeness; BRUIN CLL-321 was not included in this NMA.
Abbreviations: BR: bendamustine in combination with rituximab; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton's tyrosine kinase inhibitor; IdelaR: idelalisib in combination with rituximab; NMA: network meta-analysis; NR: not reported; PI3Ki: phosphoinositide 3-kinase inhibitor; VenR: venetoclax in combination with rituximab.

2.3. Trials included in the network

Six trials were included in the network (Figure 1): BRUIN CLL-314, MURANO, ALPINE, ASCEND, ELEVATE RR, and NCT02007044.[1, 2, 4-7] An overview of BRUIN CLL-314 is provided in Appendix A, and details of the other RCTs included in the network are provided in Section 2.10 of the original Company Submission.[1, 2, 4-7]

Figure 1: Network of evidence for studies included in the NMA

Footnotes: Data from ASCEND are available for Investigator's choice of I+R or B+R, whereas data from MURANO are available for B+R only. Thus, the network assumes treatment equivalence between B+R and Investigator's choice of I+R or B+R.
Abbreviations: ACAL: acalabrutinib; B+R: bendamustine in combination with rituximab; IBRU: ibrutinib; I+R: idelalisib in combination with rituximab; NMA: network meta-analysis; PIRTO: pirtobrutinib; VEN+R: venetoclax in combination with rituximab; ZANU: zanubrutinib.

2.4. Methods of analysis of studies included in the NMA

2.4.1. Overview of analysis methods

Comparisons between pirtobrutinib and all treatment arms in eligible RCTs were conducted through a Bayesian mixed treatment comparison incorporating both direct and indirect evidence, as available. Analyses were conducted using the rjags package and were in accordance with the NICE Decision Support Unit (DSU) Technical Support Documents (TSDs).[12, 13]

For PFS by IRC assessment, the approach described by Woods *et al.* (2010)[14] was used to account for correlations in relative treatment effect estimates (HRs) arising from multi-arm trials. Per NICE DSU TSD 2,[12] observed log HRs were included in the model through a normal likelihood. Both fixed and random effects analyses were conducted, in line with NICE DSU TSD

2.[12] The posterior distributions were summarised by their median to reflect the estimate of the HRs), and the 2.5th and 97th percentile to capture the 95% CrIs of all pairwise comparisons.

Markov Chain Monte Carlo (MCMC) simulations were run for 80,000 burn-in simulations and monitored for a further 480,000 simulations with a thinning rate of 24 for all outcomes. Non-informative prior distributions were used for the model parameters. For treatment effects, priors were set to $N(0,100^2)$. For the random effects model, the prior distribution for the between-study variance was uniformly distributed as uniform (0,8). Missing values were not imputed, as outcome data were required for study eligibility.

Furthermore, the posterior distributions were used to estimate the probability that one treatment is better than another. This probability was calculated based on the proportion of MCMC cycles in which the specific treatment estimate is better than the comparator.[12] Based on the posterior distributions of each intervention, the probability for each treatment being ranked at a specific place (e.g. first, second, third) according to the outcome was estimated.

2.4.2. Model fit and diagnostic assessment

Model fit was evaluated using deviance information criterion (DIC) with lower DIC indicating better fit. When comparing two DIC values, a difference of five or more is regarded as a meaningful difference.[15] Convergence of chains was assessed by visual inspection of trace and autocorrelation plots and on the Gelman–Rubin–Brooks diagnostic (R <1.2). In case of non-convergence or slow convergence, the calculations were repeated with a use of an informative prior and higher number of iterations, burn-in and thinning. Heterogeneity was assessed visually by inspecting the magnitude and variability of the study results within each forest plot where the point estimate size was made proportional to the size of the study. The difference between fixed and random effects in treatment estimates was also assessed by visual inspection; outcomes were expected to be similar if between-study variability is low.

Consistency was assessed by evaluating model DIC. A leverage plot was used to assess influential data points by plotting standardised deviance residuals against leverage. A posterior mean deviance contribution plot was used to compare study-specific contributions under the two models. For each treatment contrast, summary statistics were computed under both models, including the posterior mean, median, standard deviation, and 95% CrI. These estimates allowed comparison between the inconsistency model and the consistency model to assess whether differences between direct and indirect evidence suggest meaningful inconsistency.

3. Results

3.1. Model fit statistics

The fixed and random effects models were compared using the previously discussed methods for evaluation of model fit and diagnostic assessment. However, ultimately, the primary analysis was conducted using a fixed effects model, primarily due to the extremely wide 95% CrIs observed with the random effects model, signifying uncertainty with the model estimates (see Appendix B). Since the DIC values were essentially the same between the models (12.03 for fixed effects versus 12.00 for random effects), this further supported the choice of the fixed effects model. A summary of model fit statistics is presented in Table 5 below.

Table 5: Model fit statistics

Analysis	Model	Dbar	Dhat	pD	DIC
PFS by IRC	RE	[redacted]	[redacted]	[redacted]	[redacted]
	FE	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Dbar: posterior mean residual deviance; Dhat: deviance at the posterior mean parameters; DIC: deviance information criterion; FE: fixed effects; IRC: Independent Review Committee; pD: effective number of parameters; PFS: progression-free survival; RE: random effects.

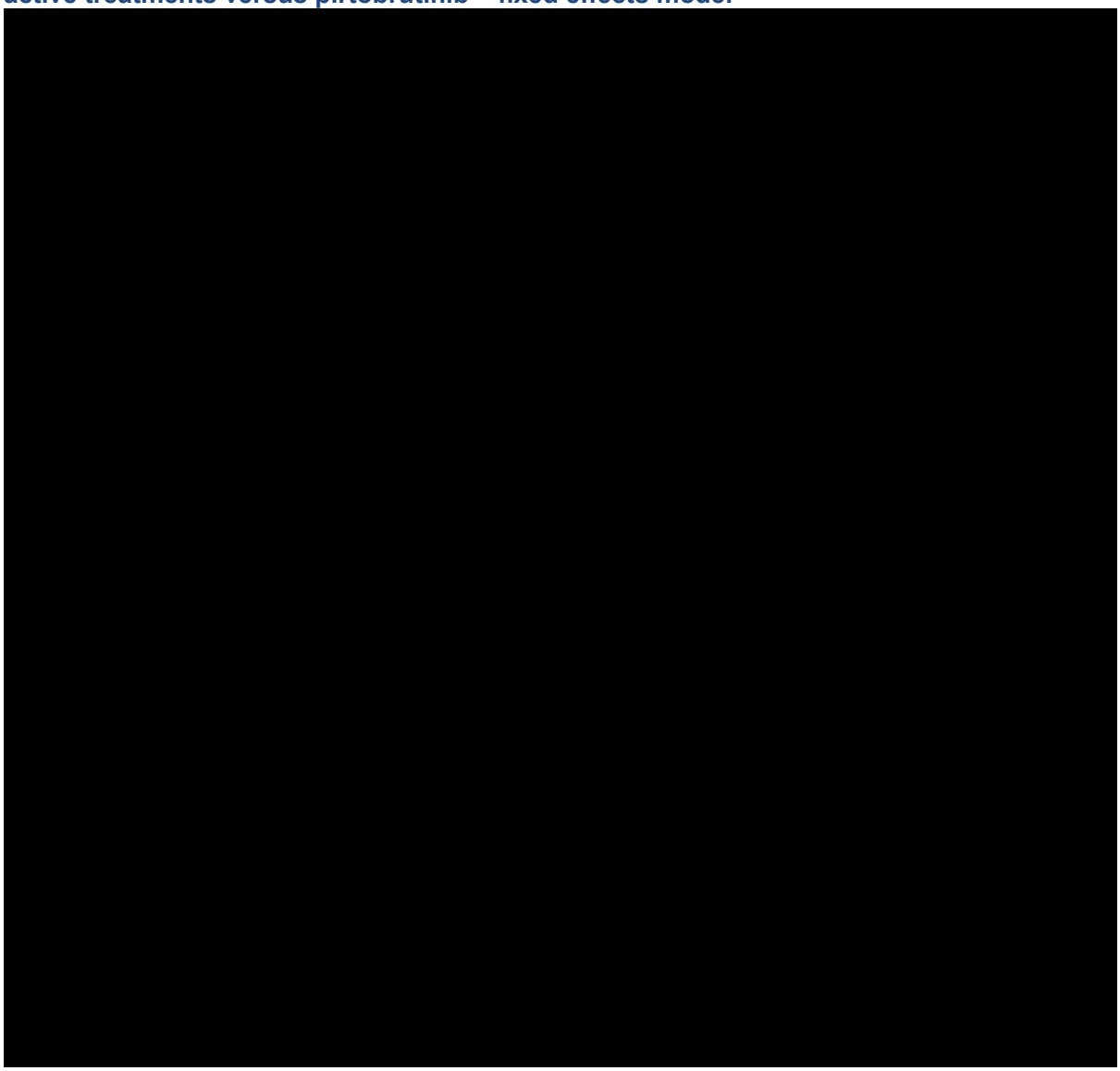
Additionally, the inconsistency assessment identified no evidence of inconsistency across the network. Furthermore, the DIC comparison between consistency and inconsistency models (both DIC = 12) suggests similar model fit, supporting the assumption of consistency in the network. Outputs of the inconsistency assessment are presented in Appendix C.

3.2. Summary of results

Only the details for the comparison of VenR and pirtobrutinib are discussed henceforth, given the objectives of this analysis, as discussed in Section 1. Results for the other comparisons included in the NMA are presented in the tables and figures below for completeness.

For PFS by IRC assessment, VenR versus pirtobrutinib showed an HR of [redacted] (95% CrI: [redacted], [redacted]). Figure 2 presents a forest plot of predictive posterior median HRs for PFS by IRC assessment of the active treatments included in the network versus pirtobrutinib. Pairwise median HRs and corresponding 95% CrIs for PFS by IRC assessment are reported in Table 6. Based on these results, [redacted], it may be concluded that there are [redacted] in expected PFS for pirtobrutinib compared with treatment with VenR in patients with R/R CLL in the BTKi-naïve setting.

Figure 2: Forest plot of predictive posterior median HRs for PFS by IRC assessment of active treatments versus pirtobrutinib – fixed effects model



Footnotes: Predictive posterior median HRs <1 (i.e. situated to the left of the dotted line), with a 95% CrI that does not include the value of 1, suggest a better relative effect on PFS for a given active treatment than pirtobrutinib, and *vice versa*.
Abbreviations: ACALA: acalabrutinib; BR: bendamustine in combination with rituximab; CrI: credible interval; HR: hazard ratio; I: ibrutinib; IR: ibrutinib in combination with rituximab; IRC: Independent Review Committee; PFS: progression-free survival; VENR: venetoclax in combination with rituximab; ZANU: zanubrutinib.

Table 6: PFS by IRC assessment pairwise median HRs (95% CrIs) – fixed effects model

		Comparator[a]						
		Pirtobrutinib	Ibrutinib	VenR	BR[b]	Zanubrutinib	Acalabrutinib	IbrutR
Intervention[a]	Pirtobrutinib	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VenR	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
	BR[b]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
	Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	IbrutR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Footnotes: [a] A pairwise median HR <1, with a 95% CrI that does not include the value of 1, suggests a better relative effect on PFS for the intervention than the comparator, and *vice versa*. [b] Data from ASCEND are available for Investigator's choice of IdelaR or BR, whereas data from MURANO are available for BR only. Thus, the network assumes treatment equivalence between BR and Investigator's choice of IdelaR or BR.
Abbreviations: BR: bendamustine in combination with rituximab; CrI: credible interval; HR: hazard ratio; IbrutR: ibrutinib in combination with rituximab; IdelaR: idelalisib in combination with rituximab; IRC: Independent Review Committee; PFS: progression-free survival; VenR: venetoclax in combination with rituximab.

4. Interpretation of the evidence

As discussed in Section 3.2, pirtobrutinib was observed to have comparable results for PFS in patients with R/R CLL in the BTKi-naïve setting versus VenR, based on the results of the NMA discussed herein. The efficacy results suggested by this NMA, combined with the established tolerability profile of pirtobrutinib, provide additional confidence in the value that pirtobrutinib can add in the R/R setting, where treatment options are needed that not only provide efficacy, but also allows for choice and selection based on factors that matter to patients (see Section 1.3 of original Company Submission).

A key strength of this analysis is that it was informed by a comprehensive clinical SLR and robust FA, which systematically identified and assessed relevant clinical trials in R/R CLL. In addition, the use of a NMA, which represents one of the more robust approaches to ITC, allowed randomisation within individual trials to be preserved. This enabled comparisons across a connected network of RCTs through common comparators, incorporating both direct and indirect evidence.

As with any additional comparative efficacy analysis, several limitations should be acknowledged. Although the patient population was R/R CLL, data permitting a feasible comparison were only available for the BTKi-naïve setting. Nevertheless, in the absence of suitable data for VenR in the post-cBTKi population, this analysis provides relevant contextual evidence on the relative efficacy between the two treatments. As this analysis was conducted in the same broader population (i.e. R/R CLL), with a similar stage of disease, data from the R/R population of BRUIN CLL-314 were considered suitable for inclusion in a network with VenR to explore the plausibility of the clinical similarity assumption applied in the post-cBTKi setting for the purposes of the cost-comparison analysis presented at clarification.

There is also uncertainty around the estimated relative treatment effect for pirtobrutinib versus VenR, reflecting the limited number of trials informing each comparator within the network. Related to this limited clinical evidence base, an assumption of treatment equivalence between Investigator's choice of IdelaR or BR, and BR only was required to connect the network via MURANO (VenR versus BR only) and ASCEND (acalabrutinib versus Investigator's choice of IdelaR or BR).[2, 5] In Section 2.10.1.2 of the original Company Submission, Lilly acknowledged the limited and conflicting evidence supporting this assumption; ASCEND demonstrated similarity between IdelaR and BR regarding PFS but BRUIN CLL-321 demonstrated more favourable outcomes for IdelaR, albeit neither trial was powered for this comparison.[2, 5] Thus, in the absence of strong data to the contrary, an assumption of clinical equivalence between IdelaR and BR is considered to introduce a level of uncertainty to the results of this NMA, though this is not considered to have a substantial impact on the overall conclusion regarding the relative efficacy between pirtobrutinib and VenR.

Lastly, there were also wide 95% CrIs for the point estimates for PFS by IRC assessment, but these should be interpreted alongside consideration of the similarity of point estimates of pirtobrutinib and VenR in this NMA and are considered to have little impact on the decision uncertainty in the current appraisal. This analysis is also limited in its assumption of proportional hazards (PHs), given the time constraints of this analysis.

5. Conclusions

Results of this Bayesian NMA of RCTs of patients with R/R CLL in the BTKi-naïve setting indicate that pirtobrutinib and VenR have comparable efficacy according to PFS by IRC assessment. This analysis is associated with several strengths, including systematic identification and assessment of relevant clinical evidence, and preservation of randomisation through the use of an NMA.[1] While the analysis has several limitations, few of these are relevant to drawing conclusions on the appropriateness of the cost-comparison analysis.

Additionally, the original NICE appraisal for VenR (TA561) adopted a cost-comparison approach against ibrutinib, based on an assumption of clinical similarity that was informed by ITCs conducted by the Company and EAG.[16] This assumption is also supported by the findings of a published NMA that indicated comparable efficacy between VenR and ibrutinib for PFS.[17]

In summary, the findings of this additional comparative efficacy analysis suggest that the assumption of clinical similarity between pirtobrutinib and VenR for the cost-comparison analysis presented in the Company Response to clarification is a reasonable assumption and an acceptable basis for Committee decision-making. Updated results will be provided in a subsequent appendix.

6. References

1. Woyach J, Qiu L, Grosicki S, et al. Pirtobrutinib vs ibrutinib in treatment-naïve and relapsed/refractory CLL/SLL: Results from the first randomized phase III study comparing a non-covalent and covalent BTK inhibitor. J Clin Oncol 2025.
2. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia (MURANO). New England Journal of Medicine 2018;378:1107-1120.
3. Sharman JP, Munir T, Grosicki S, et al. BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib versus Idelalisib plus Rituximab (IdelaR) or Bendamustine plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma ASH Annual Meeting, 2025.
4. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia (ALPINE). New England Journal of Medicine 2023;388:319-332.
5. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. Journal of Clinical Oncology 2020;38:2849-2861.
6. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial (ELEVATE RR). Journal of clinical oncology 2021;39:3441-3452.
7. Burger JA, Sivina M, Jain N, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia (NCT02007044). Blood, The Journal of the American Society of Hematology 2019;133:1011-1019.
8. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood, The Journal of the American Society of Hematology 2018;132:2446-2455.
9. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. American journal of hematology 2019;94:1353-1363.
10. National Institute for Care and Excellence (NICE). Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia [TA344]. 2015. Available at: https://www.nice.org.uk/guidance/ta344 [Accessed: 09 December 2025].
11. Eli Lilly and Company. Data on File. BRUIN CLL-314 CSR.
12. Dias S, Sutton, A. J., Ades, A. E., & Welton, N. J. (2011). NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. University of Sheffield. . Volume 2025, 2011.
13. Plummer M. rjags: Bayesian Graphical Models using MCMC. 2025. Available at: https://cran.r-project.org/web/packages/rjags/index.html [Accessed: 15 December 2025].
14. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol 2010;10:54.
15. Carlin B.P. & Louis T.A. Bayesian Methods for Data Analysis (3rd ed.). Chapman and Hall/CRC. https://doi.org/10.1201/b14884. 2008.
16. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. [TA561] Available at: https://www.nice.org.uk/guidance/ta561 [Accessed: 01 February 2025].
17. Monica M, Reczek M, Kawalec P. Network meta-analysis of novel targeted therapies for relapsed/refractory chronic lymphocytic leukemia. Ther Adv Med Oncol 2024;16:17588359241263710.
18. ClinicalTrials.gov. A Study of Pirtobrutinib (LOXO-305) Versus Ibrutinib in Participants With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) (BRUIN-CLL-314) Available at: https://clinicaltrials.gov/study/NCT05254743 [Accessed: 09 May 2025].
19. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.
20. Sharman JP, Munir T, Grosicki S, et al. Phase III Trial of Pirtobrutinib Versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor–

Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321). Journal of Clinical Oncology 2025:JCO-25-00166.
21. NICE. Appendix C: Methodology checklist: randomised controlled trials. Volume 2025, 2012.
22. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

Appendix A Overview of BRUIN CLL-314

A.1 BRUIN CLL-314: study design

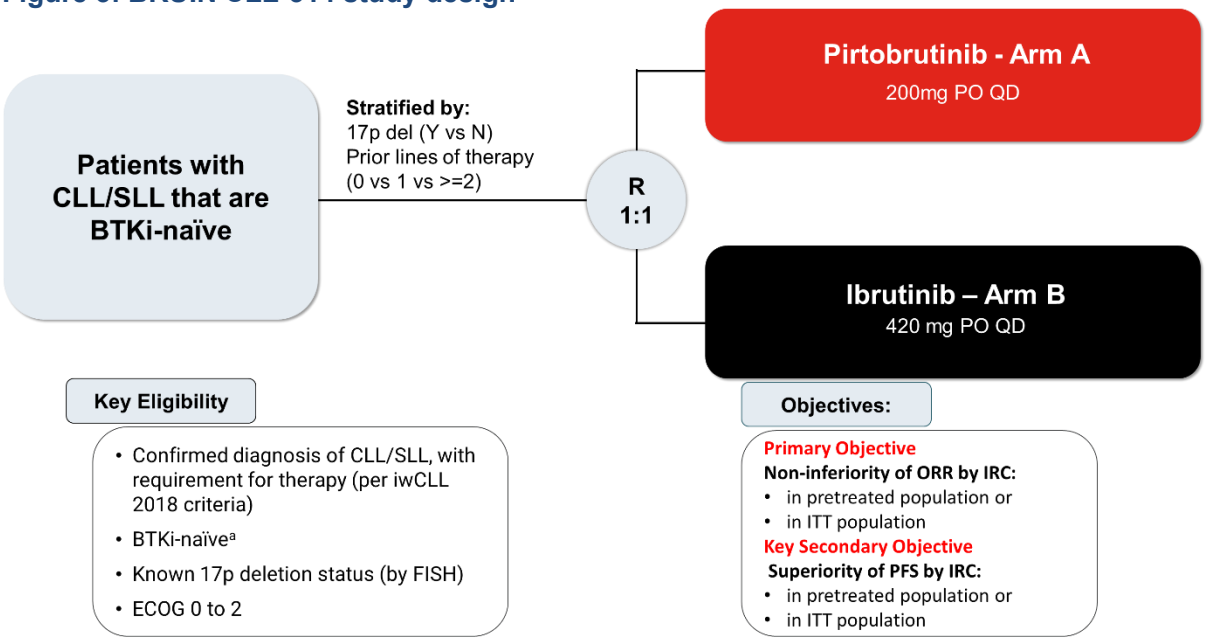
The trial of focus for this NMA is BRUIN CLL-314 (NCT05254743), an ongoing global, randomised, open-label Phase 3 trial in BTKi-naïve patients with CLL or small lymphocytic lymphoma (SLL) who were treatment-naïve or previously treated with other agents.[1, 18] BRUIN CLL-314 compares pirtobrutinib as continuous monotherapy with ibrutinib, a cBTKi.[1]

The study design schema for BRUIN CLL-314 is shown in Figure 3, and its key inclusion and exclusion criteria are presented in Table 7. In BRUIN CLL-314, patients were randomly assigned in a 1:1 ratio to one of the following treatments:[1]

- Pirtobrutinib 200 mg orally once daily (QD) in 28-day cycles until progressed disease (PD) or unacceptable toxicity
- Ibrutinib 420 mg orally QD in 28-day cycles until PD or unacceptable toxicity

The primary objective of BRUIN CLL-314 compared overall response rate (ORR) per International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) 2018 assessed by IRC of pirtobrutinib monotherapy versus ibrutinib monotherapy in patients with CLL/SLL (pre-treated population or ITT population).[1, 19] Secondary outcomes included PFS by IRC, PFS by Investigator, event-free survival, duration of response, time to next treatment and OS.[1] The previously treated population is a pre-specified subgroup in the trial, and primary and key secondary outcomes have been powered for both the ITT and previously treated populations.

Figure 3: BRUIN CLL-314 study design



Footnotes: [a] Planned: 30% treatment-naïve and 70% pre-treated; actual: 34% treatment-naïve and 66% pre-treated.
Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence *in situ* hybridisation; IRC: Independent Review Committee;

ITT: Intention to Treat; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; ORR: overall response rate; PFS: progression-free survival; PO: *per* os (orally); QD: *quaque die* (once daily); SLL: small lymphocytic lymphoma.
Source: Woyach *et al.* (2025).[1]

Table 7: Key inclusion and exclusion criteria for patients in BRUIN CLL-314

Inclusion criteria	Exclusion criteria
• Confirmed diagnosis of CLL/SLL requiring therapy as defined by iwCLL 2018 criteria • ECOG 0–2 • Adequate organ function • Platelets ≥50 × 10^9/L, haemoglobin ≥8 g/dL, and absolute neutrophil count ≥0.75 × 10^9/L • Kidney function: Estimated creatinine clearance ≥30 mL/min	• Known or suspected Richter's transformation to DLBCL, prolymphocytic leukaemia, or Hodgkin lymphoma at any time preceding enrolment • Prior exposure to BTKi (covalent or noncovalent) • Significant cardiovascular disease • Known or suspected transformation • Known or suspected history of CNS involvement by CLL/SLL • Major surgery within 4 weeks of planned start of study drug • Active uncontrolled autoimmune cytopenia • Use of ≥20 mg prednisone QD • Active second malignancy • Active or ongoing Hepatitis B or Hepatitis C or CMV • Concurrent use of investigational agent or anticancer therapy except hormonal therapy • Active uncontrolled systemic bacterial, viral, fungal, or parasitic infection • Known HIV infection, regardless of CD4 count • Clinically significant active malabsorption syndrome or inflammatory bowel disease • Patients requiring therapeutic anticoagulation with warfarin or another Vitamin K antagonist • Current treatment with strong cytochrome P450 (CYP) 3A4 (CYP3A4) inhibitors or inducers and/or strong P-gp inhibitors • Vaccination with a live vaccine within 28 days prior to randomisation

Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; CD4: cluster of differentiation 4; CLL: chronic lymphocytic leukaemia; CMV: cytomegalovirus; CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; HIV: human immunodeficiency virus; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; P-gp: P-glycoprotein corrected; QD: *quaque die* (once daily); SCT: stem cell transplantation; SLL: small lymphocytic lymphoma; ULN: upper limit of normal.
Source: Woyach *et al.* (2025).[1]

A.2 BRUIN CLL-314: summary of baseline characteristics (pre-treated population)

A summary of baseline patient demographics and disease characteristics for the pre-treated (R/R) population in BRUIN CLL-314 is presented in Table 8 below.[1]

Patients in the R/R population of BRUIN CLL-314 exhibited similar baseline demographic characteristics between the pirtobrutinib (N=219) and ibrutinib (N=218) treatment arms.[1] The median age was 67 years in both treatment arms, with 57.5% and 61.0% of patients aged ≥65 years in the pirtobrutinib and ibrutinib treatment arms, respectively. In both treatment arms, approximately one-third of patients were female, and two-thirds were male.

Likewise, the baseline disease characteristics were comparable between the two treatment arms of BRUIN CLL-314.[1] Rai stage at baseline was Stage 0–II in approximately half of patients (53.8% pirtobrutinib and 55.0% ibrutinib) and Stage III/IV in approximately 45% of patients (45.2% pirtobrutinib and 43.4% ibrutinib). Similarly, the majority of patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, reported in 96.8% of both treatment arms (ECOG PS 0: 53.9% pirtobrutinib and 49.1% ibrutinib; ECOG PS 1: 42.9% pirtobrutinib and 47.7% ibrutinib; ECOG PS 2: 3.2% in both treatment arms). Median disease duration at baseline for the pirtobrutinib and ibrutinib treatment arms was 7.29 and 7.45 years, respectively. Bulky disease (≥5 cm) was present in 31.5% and 38.1% of patients in the pirtobrutinib and ibrutinib treatment arms, respectively. Most patients had β_2-microglobulin >3.5 mg/L at baseline (66.2% pirtobrutinib and 62.4% ibrutinib).

Regarding molecular risk factors, the majority of patients had unmutated *IGHV* (72.7% pirtobrutinib and 70.1% ibrutinib). The del(17p) mutation was identified in 16.4% and 16.1% of patients in the pirtobrutinib and ibrutinib treatment arms, respectively, and *TP53* mutation was observed in 42.9% and 33.0% of patients treated with pirtobrutinib and ibrutinib, respectively. Complex karyotype was present in 45.2% and 40.0% of patients treated with pirtobrutinib and ibrutinib, respectively.

The median number of prior lines of systemic therapy was 1 (range: 1–9 for pirtobrutinib; 1–8 for ibrutinib), with [redacted]% and [redacted]% of patients in each arm, respectively, receiving one prior line and [redacted]% and [redacted]% having received two or more lines.

These baseline characteristics further support the above discussion that BRUIN CLL-314 is more closely aligned with the pivotal trial for VenR (MURANO) and the other trials that were included in the FA for the original Company Submission (Section 2.10), than BRUIN CLL-321 was to these trials, especially with regard to the distributions of previous lines of therapy.[1-7]

Table 8: Summary of baseline patient demographics and baseline disease characteristics for patients in BRUIN CLL-314 (R/R population)

	Pirtobrutinib (N=219)	Ibrutinib (N=218)
Age, years		
Median	67	67
Range	42–87	38–86
Age group, n (%)		
≥65 years	126 (57.5)	133 (61.0)
Sex, n (%)		
Female	74 (33.8)	74 (33.9)
Male	145 (66.2)	144 (66.1)
Region, n (%)		
North America	12 (5.5)	13 (6.0)
Europe	107 (48.9)	108 (49.5)
Asia	27 (12.3)	32 (14.7)
Other[a]	73 (33.3)	65 (29.8)

Rai Stage, n (%)		
Stage 0-II	112 (53.8)	104 (55.0)
Stage III/IV	94 (45.2)	82 (43.4)
Missing	2 (1.0)	3 (1.6)
Baseline ECOG PS, n (%)		
0	118 (53.9)	107 (49.1)
1	94 (42.9)	104 (47.7)
2	7 (3.2)	7 (3.2)
Duration of disease (years)		
Median (Q1, Q3)	7.29 (4.55, 10.75)	7.45 (3.84, 10.97)
Bulky disease, n (%)		
≥ 5cm	69 (31.5)	83 (38.1)
ß$_2$ microglobulin (mg/L) at baseline, n (%)		
≤3.5	66 (30.1)	76 (34.9)
>3.5	145 (66.2)	136 (62.4)
Missing/Unknown	8 (3.7)	6 (2.8)
***IGHV* mutation status, n (%)**		
Mutated	[redacted]	[redacted]
Unmutated	[redacted]	[redacted]
Missing/Unknown	[redacted]	[redacted]
17p deletion presence, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing/Unknown	[redacted]	[redacted]
***TP53* mutation status, n (%)**		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing/Unknown	[redacted]	[redacted]
Complex karyotype, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing/Unknown	[redacted]	[redacted]
Prior lines of systemic therapy, n (%)		
Median (Range)	1 (1–9)	1 (1–8)
1	148 (67.6)	150 (68.8)
≥2	71 (32.4)	68 (31.2)

Footnotes: [a] Other includes Australia/New Zealand, Middle East and South America.
Abbreviations: CLL: chronic lymphocytic leukaemia; *IGHV*: immunoglobulin heavy chain variable region; N: total number of participants; R/R: relapsed or refractory; *TP53*: tumour protein p53.
Source: Woyach *et al.* (2025);[1] Eli Lilly (Data on File). BRUIN CLL-314 CSR.[11]

A.3 BRUIN CLL-314: summary of results (pre-treated population)

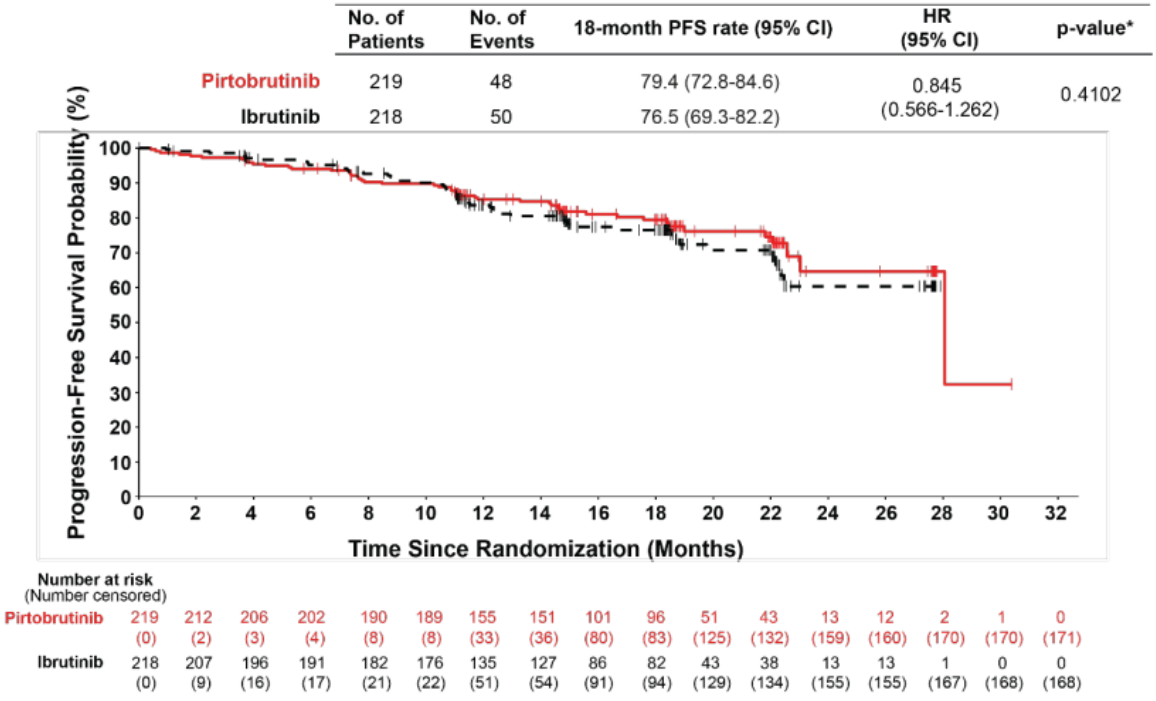
As discussed in Section 1, due to time limitations, the only outcome assessed in this NMA was PFS by IRC.[1] A summary of the results from BRUIN CLL-314 for PFS by IRC assessment are presented in Table 9 and Figure 4 below.

Table 9: Summary of PFS by IRC assessment in BRUIN CLL-314 (R/R population)

	Pirtobrutinib (N=219)	Ibrutinib (N=218)
Number of events, n (%)	48 (21.9)	50 (22.9)
Median follow-up, months (IQR)	[redacted]	[redacted]
18-month PFS rate (95% CI)	79.4 (72.8, 84.6)	76.5 (69.3, 82.2)
HR (95% CI)[a]	0.845 (0.566, 1.262)	
p-value[b]	0.4102	

Footnotes: [a] Based on the stratified Cox proportional hazards model. [b] 2-sided p-value based on stratified log-rank test.
Abbreviations: CI: confidence interval; HR: hazard ratio; IQR: interquartile range; IRC: Independent Review Committee; n: number of patients per category; N: number of patients in the population; PFS: progression-free survival; R/R: relapsed or refractory.
Sources: Woyach *et al.* (2025);[1] Eli Lilly (Data on File). BRUIN CLL-314 CSR.[11]

Figure 4: Kaplan–Meier curve of PFS by IRC assessment in BRUIN CLL-314 (R/R population)



Abbreviations: CI: confidence interval; HR: hazard ratio; IRC: Independent Review Committee; PFS: progression-free survival; R/R: relapsed or refractory.
Sources: Woyach *et al.* (2025).[1]

Additionally, while not included in the present analysis due to a lack of maturity of the data, results for OS from BRUIN CLL-314 indicate that there is no detriment in OS associated with

treatment with pirtobrutinib compared with ibrutinib in the R/R population, with an event rate of approximately 10% at data cut-off (pirtobrutinib: 10.0% [22/219]; ibrutinib: 9.6% [21/218]) and an HR of 0.96 (95% CI: 0.53, 1.76).[1]

Similarly, the incidence of treatment-emergent adverse events (TEAEs) of any Grade was comparable between treatment arms in the R/R population (96.3% for pirtobrutinib versus 97.2% for ibrutinib), as was the rate of Grade ≥3 TEAEs (56.0% versus 54.2%, respectively). Regarding adverse events (AEs) of special interest in the R/R population, similar frequencies were observed between the pirtobrutinib and ibrutinib arms, except for atrial fibrillation and atrial flutter, which were less frequent with pirtobrutinib (any Grade: 1.4%; Grade ≥3: 0.5%) compared with ibrutinib (any Grade: 10.2%; Grade ≥3: 3.7%). Conversely, a slightly higher frequency of neutropenia was observed with pirtobrutinib than with ibrutinib in the R/R population (any Grade: 35.8% versus 25.5%, respectively; Grade ≥3: 28.4% versus 19.9%, respectively).[1]

Overall, these data are in line with previous trial results regarding the efficacy and tolerability profiles of pirtobrutinib and ibrutinib, demonstrating comparable efficacy results in terms of PFS and OS, and similar overall tolerability profiles.[1, 6, 20]

A.4 BRUIN CLL-314: risk of bias assessment

The results of the risk of bias assessment for BRUIN CLL-314 using the NICE methodology checklist for RCTs are presented in Table 10.[1, 21] The risk of bias assessments for the other RCTs included in the network (MURANO, ALPINE, ASCEND, ELEVATE RR, and NCT02007044) were conducted using the Cochrane Risk of Bias Assessment for Randomised Trials Tool v2.0; the results of these assessments are presented in Appendix B.3 of the Company Submission.[2, 4-7, 22]

BRUIN CLL-314 was considered to carry a high risk of performance bias due to the trial's open-label design.[1] However, open-label trials are prevalent in CLL as they allow for practical assessment of treatment effects without the need for placebo controls, which are ethically unacceptable in this patient population. Additionally, all the other RCTs included in the network (MURANO, ALPINE, ASCEND, ELEVATE RR, and NCT02007044) likewise had open-label study designs.[2, 4-7]

Table 10: Risk of bias assessment for BRUIN CLL-314

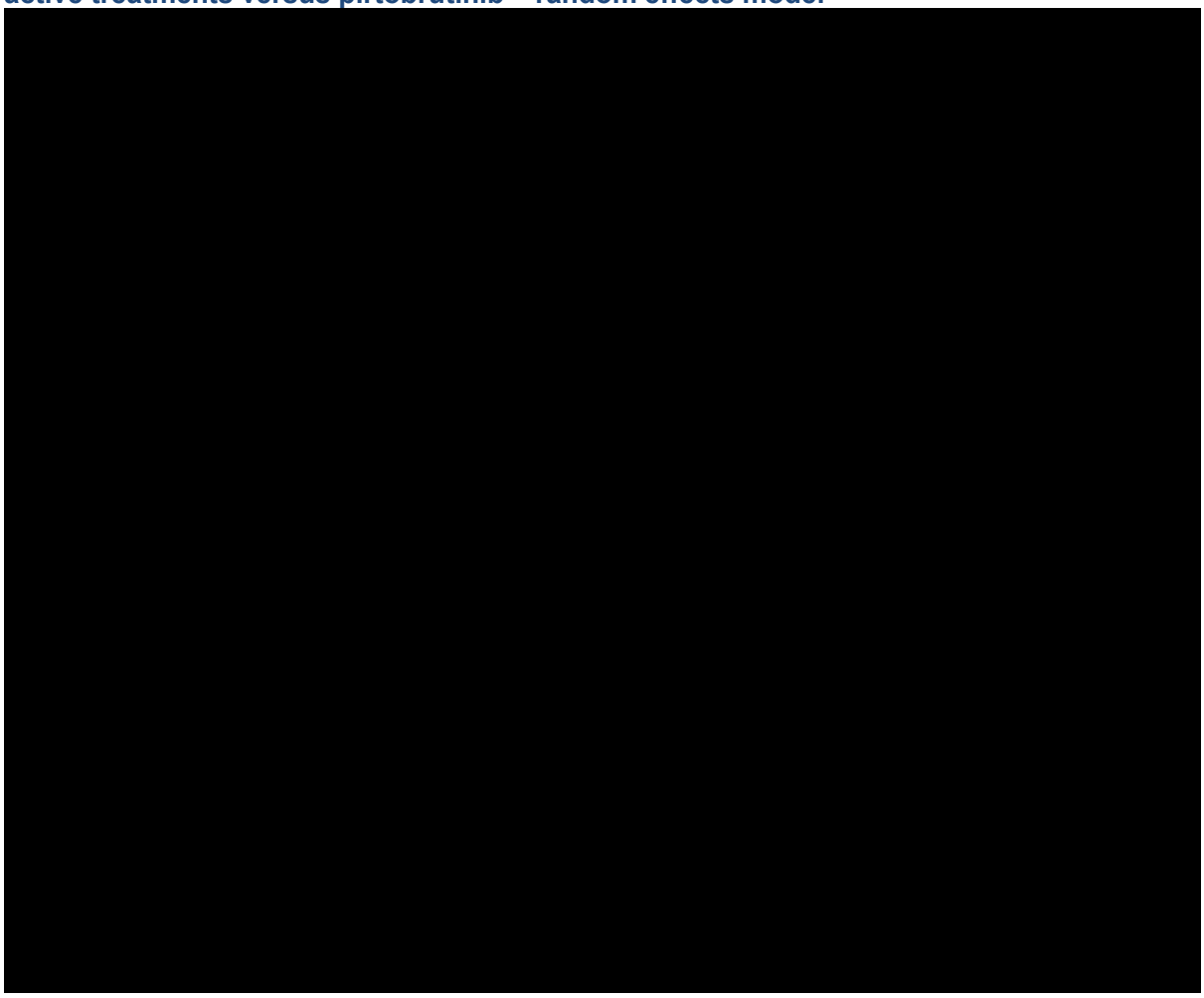
Bias domain and question	BRUIN-CLL-314	Rationale
A. Selection bias		
A1) An appropriate method of randomisation was used to allocate participants to intervention groups (which would have balanced any confounding factors equally across groups)	Yes	Patients were randomised in a 1:1 ratio via a web-based response system and stratified according to 17p deletion status and the number of prior lines of therapy
A2) There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	See above
A3) The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	Baseline characteristics, including key prognostic factors and treatment effect modifiers, were

		well balanced across the treatment arms.
Overall assessment	**Low risk of bias**	**-**
B. Performance bias		
B1) The comparison groups received the same care and support apart from the intervention(s) studied	Yes	-
B2) Participants receiving care and support were kept 'blind' to intervention allocation	No	The trial was an open-label study
B3) Individuals administering care and support were kept 'blind' to treatment allocation	No	See above
Overall assessment	**High risk of bias**	**-**
C. Attrition bias		
C1) All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	Duration of follow-up was similar between treatment arms
C2a) How many participants did not complete the intervention in each group?	N/A	Pirtobrutinib = 32; Ibrutinib = 35
C2b) The groups were comparable for intervention completion (that is, there were no important or systematic differences between groups in terms of those who did not complete the intervention)	Yes	
C3a) For how many participants in each group were no outcome data available?	N/A	Pirtobrutinib = 0; Ibrutinib = 0
C3b) The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	
Overall assessment	**Low risk of bias**	**-**
D. Detection bias		
D1) The study had an appropriate length of follow-up	Yes	Follow-up was sufficiently long to test the primary hypothesis (non-inferiority of ORR)
D2) The study used a precise definition of outcome	Yes	Primary and secondary outcomes were clearly defined
D3) A valid and reliable method was used to determine the outcome	Yes	Outcomes were clearly defined and align with those typically used in comparator trials for CLL
D4) Investigators were kept “blind” to participants' exposure to the intervention	No	The trial was an open-label study
D5) Investigators were kept “blind” to other important confounding factors	No	The trial was an open-label study
Overall assessment	**Low risk of bias**	**-**

Abbreviations: CLL: chronic lymphocytic leukaemia; ORR: overall response rate; RCT: randomised controlled trial.

Appendix B Additional model fit statistics: random effects model

Figure 5: Forest plot of predictive posterior median HRs for PFS by IRC assessment of active treatments versus pirtobrutinib – random effects model



Abbreviations: ACALA: acalabrutinib; BR: bendamustine in combination with rituximab; CrI: credible interval; HR: hazard ratio; I: ibrutinib; IR: ibrutinib in combination with rituximab; IRC: Independent Review Committee; PFS: progression-free survival; VENR: venetoclax in combination with rituximab; ZANU: zanubrutinib.

Appendix C Inconsistency assessment results

Table 11: Summary statistics for inconsistency and consistency – fixed effects model

	Inconsistency model				Consistency model			
	Mean	Median	SD	95% CrI	Mean	Median	SD	95% CrI
d[2,1]	[redacted]							
d[2,5]	[redacted]							
d[2,6]	[redacted]							
d[2,7]	[redacted]							
d[4,3]	[redacted]							
d[4,6]	[redacted]							

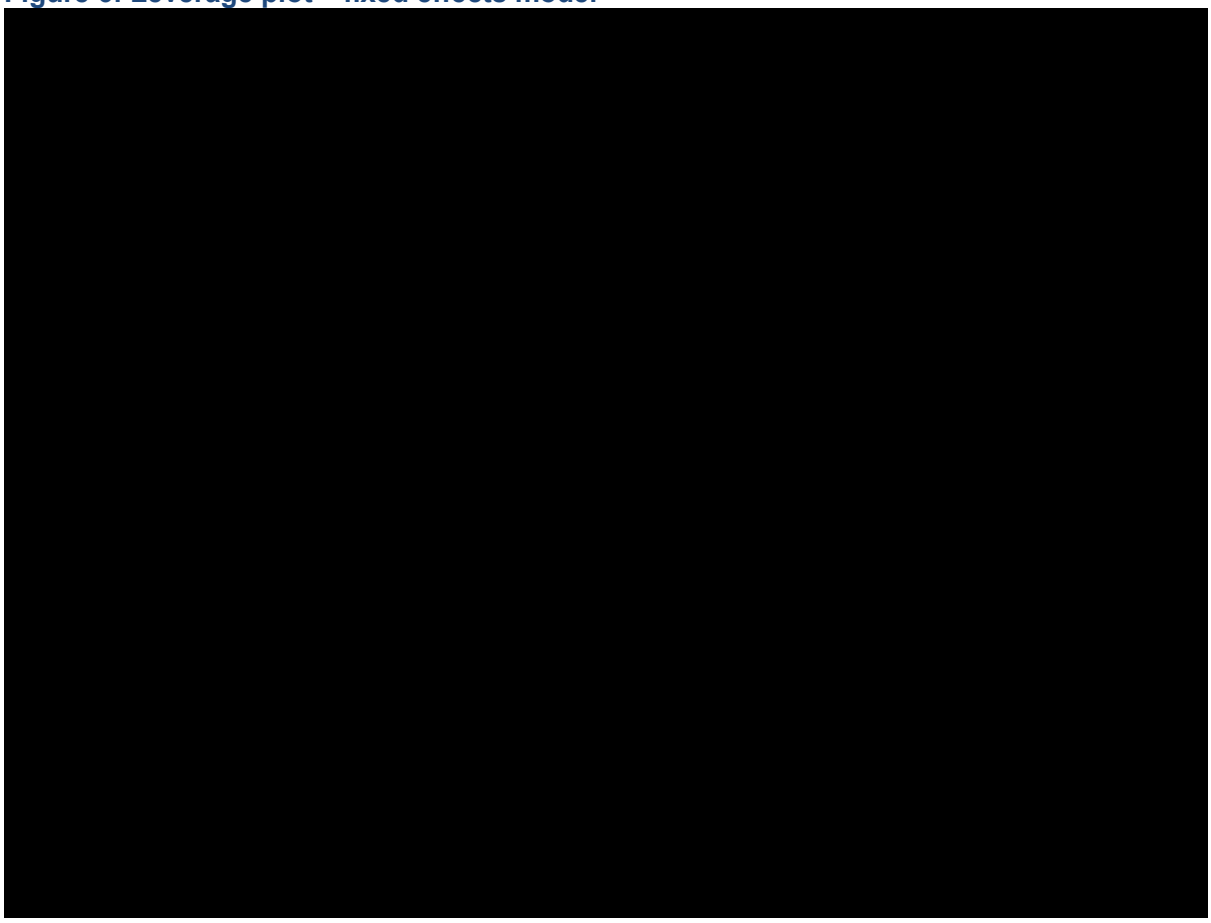
Abbreviations: CrI: credible interval; SD: standard deviation.

Table 12: Model fit statistics for inconsistency and consistency – fixed effects model

	Number of studies	Total number of treatments	Total number of data points	Dbar	Dhat	pD	DIC
Inconsistency model	6	7	6	[redacted]			
Consistency model	6	7	6	[redacted]			

Abbreviations: Dbar: posterior mean residual deviance; Dhat: deviance at the posterior mean parameters; DIC: deviance information criterion; pD: effective number of parameters.

Figure 6: Leverage plot – fixed effects model



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Updated cost comparison and cost-effectiveness results appendix

December 2025

File name	Version	Contains confidential information	Date
[ID6269] Updated cost comparison and cost-effectiveness results appendix [CON].docx	1	Yes	19 December 2025

Appendix A Cost-comparison results

Following ACM1, the PAS for pirtobrutinib has been updated. The PAS discount for pirtobrutinib is an updated discount from that which was submitted at the clarification stage as follows:

- 56 tablets of 100 mg = [redacted]
- 28 tablets of 50 mg = [redacted]

This document provides the revised analyses reflecting the new PAS price, including:

- Updated cost-comparison results for pirtobrutinib versus VenR, incorporating the latest PAS discount.
- The cost-comparison analysis for pirtobrutinib versus Ven-mono, as requested
- Updated cost-utility results for the dual-exposed population versus IdelaR, based on the new PAS price

A.1 Pirtobrutinib versus VenR

Results for the cost-comparison analysis of pirtobrutinib versus VenR for patients with R/R CLL in the post-cBTKi population are presented in Table 1 (with pirtobrutinib at the updated PAS price).

Table 1: Deterministic base case results for a lifetime horizon (pirtobrutinib updated PAS price; post-cBTKi population)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	[redacted]
VenR		

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; PAS: Patient Access Scheme; VenR: venetoclax in combination with rituximab.

A.2 Pirtobrutinib versus Ven-mono

A cost-comparison analysis between pirtobrutinib and Ven-mono has been conducted, as requested by the EAG. This cost-comparison has been conducted for adult patients with R/R CLL who have been previously treated with a BTKi, i.e. a post-cBTKi population, in line with the anticipated marketing authorisation for pirtobrutinib in the UK and the ITT population in BRUIN CLL-321.[19] As with the cost-comparison analysis that was submitted at the clarification stage for pirtobrutinib versus VenR, the cost-comparison analysis for pirtobrutinib versus Ven-mono likewise assumes treatment equivalence. As discussed in Sections **Error! Reference source not found.** and **Error! Reference source not found.** of the additional analyses document, Lilly considers this to be a reasonable assumption given the findings of the NMA presented in this additional comparative efficacy analysis and the findings of RWE studies of the comparable efficacy between VenR and Ven-mono.[4, 18]

The results from the cost-comparison analysis of pirtobrutinib and Ven-mono in the post-cBTKi population are presented in Table 2 (with pirtobrutinib at updated PAS price).

Table 2: Deterministic base case results for a lifetime horizon (pirtobrutinib updated PAS price; post-cBTKi population)

Treatment	Total treatment costs	Incremental costs
Pirtobrutinib	[redacted]	[redacted]
Ven-mono		

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; PAS: Patient Access Scheme; Ven-mono: venetoclax monotherapy.

Appendix B Updated cost-effectiveness analysis results

Results for the cost-utility analysis of pirtobrutinib versus IdelaR for patients with R/R CLL in the dual exposed population are presented in Table 1 (with pirtobrutinib at the updated PAS price).

Table 3: Revised probabilistic base-case results in patients with R/R CLL: dual-exposed population (at pirtobrutinib PAS price)

Comparator	Total costs	Total LYG[a]	Total QALYs	NMB	Incremental costs	Incremental LYG[a]	Incremental QALYs	ICER (£/QALY)
Pirtobrutinib	[redacted]	[redacted]	1.893	[redacted]	[redacted]	[redacted]	0.344	-£25,342
IdelaR	[redacted]	[redacted]	1.549	[redacted]				

Footnote: [a] Calculated deterministically.
Abbreviations: ICER: incremental cost-effectiveness ratio; Inv. Choice: investigator's choice; LYG: life-years gained; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life-year.

Appendix from Eli Lilly and Company (Lilly) assessing further evidence referred to in the External Assessment Group's (EAG's) critique of the additional evidence provided by Lilly post-ACM1 for pirtobrutinib for treating chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) after 1 or more BTK inhibitors (BTKis) [ID6269]

Lilly provides this Appendix to support the Committee with further evidence referred to in the EAG's critique of the post-ACM1 evidence submission. It summarises the real-world evidence (RWE) comparing venetoclax monotherapy (Ven-mono) with venetoclax with rituximab (VenR) and provides additional context for interpreting the post-ACM1 NMA. The aim is to present the additional evidence requested and provide the Committee with greater clarity to support their overall decision-making.

RWE context and relevance to the Ven-mono → VenR proxy referenced at ACM1

During ACM1, the clinical expert cited the retrospective cohort study by Mato *et al.* (2019), as a potential way to infer similarity between Ven-mono and VenR, with the intention of using the pirtobrutinib vs Ven-mono MAIC of as a proxy to support a pirtobrutinib vs VenR comparison.[1] Further consideration of this study was requested.

The study reports descriptive outcomes for Ven-mono (N=270) and a venetoclax combination arm (VENcombo = basket treatment arm of venetoclax with obinutuzumab [VenO] [N=13] and VenR [N=38]).[1] It showed similar clinical outcomes across regimens, including comparable overall response rates (81% vs 84%), complete remission rates (34% vs 32%), and no observed differences in PFS or OS (unadjusted HRs: PFS 1.0; 95% CI 0.6–1.8, and OS 1.2; 95% CI 0.6–2.3). These findings, while limited by the pooled comparator, do not conflict with the direction of effect observed in more robust comparative analyses such as the post-ACM1 NMA or MAIC.

While the study provides some useful contextual evidence on the comparative effectiveness of Ven-mono to VenR (and for pirtobrutinib by proxy), some limitations reduce the weight that can be placed on its findings. Because VenO and VenR were combined, the study does not provide comparative effectiveness for VenR alone; any indirect comparison must therefore treat the pooled VENcombo arm as a proxy for VenR.[1] In addition, VenO is used in untreated CLL and VenR in previously treated CLL in UK practice and published evidence shows differing efficacy between these regimens in untreated CLL, limiting suitability of the pooled comparator in evaluating pirtobrutinib in the post-cBTKi relapsed/refractory population. [1, 2, 3, 4]

Given these limitations, the RWE cannot address equivalence on its own but remains directionally consistent with the wider evidence base. Lilly therefore maintains the published unanchored matching-adjusted indirect comparison (MAIC) of pirtobrutinib versus Ven-mono offers a more robust assessment of the comparative efficacy than an adjusted or unadjusted comparison using the RWE data[1, 5] It followed best-practice methods, achieved good balance of baseline characteristics, and showed consistent results across sensitivity analyses. Point estimates were near unity for progression-free survival (PFS), no evidence of an overall survival (OS) detriment with pirtobrutinib, and overall safety outcome results numerically favouring pirtobrutinib.[5]

Lilly also maintains that the post-ACM1 NMA analysis that links pirtobrutinib and VenR through Phase III RCTs (BRUIN CLL-314 and MURANO) offers a more appropriate indirect comparison than is available from real-world data, preserving randomisation [1, 5-7].

To note, the Committee requested these data recognising the limitation that the NMA is based on a BTKi-naïve population rather than the post-cBTKi population. The NMA represents the only feasible approach given the absence of suitable post-cBTKi comparative data. It also helps reduce uncertainty related to prognostic markers and treatment-effect modifiers, addresses the evidence gaps highlighted

at ACM1, providing the Committee with pragmatic context to support decision-making where the available evidence is inherently limited. [6-8]

While wide CrI indicates uncertainty, in Bayesian analyses it does not determine decision relevance on its own and should be interpreted within the wider decision-making context rather than in isolation. To support interpretation, the post-ACM1 NMA derived posterior probabilities at clinically meaningful thresholds, indicating the likelihood that the treatment effect exceeds clinical meaningful values as assessed in clinical practice and reimbursement. Food and Drug Administration (FDA) guidance on non-inferiority recommends preserving a clinically meaningful proportion of the established treatment effect.[9] In MURANO, VenR demonstrated a substantial PFS benefit versus BR (HR 0.17; 95% CI 0.11–0.25), and using the upper limit of this interval a conservative loss-of-effect bound of 4 can be derived. The upper confidence limit for pirtobrutinib versus VenR in the post-ACM1 NMA is 2.24—well below this threshold—indicating that a substantial proportion of the established treatment effect is preserved. Consistent with best practice principles, this supports interpreting the NMA within a non-inferiority and cost-comparison framework. [9]

Furthermore, wide intervals are not unusual in CLL appraisals, and previous NICE decisions have considered them acceptable when interpreted within the totality of evidence. For example, in the recent CDF exit appraisal for VenO in first-line CLL (FCR-suitable; TA1119), confidence intervals spanning a wide range were still deemed consistent with decision-making when viewed alongside the broader evidence base.

Conclusion: The MAIC to Ven-mono and post-ACM1 NMA to VenR provide a coherent and directionally consistent evidence base of clinical equivalence to underpin the assumptions for a cost-comparison. It should be noted Lilly has taken a simplified approach focusing solely on acquisition costs and excludes administration costs that clinical experts expect to be lower for pirtobrutinib than for Ven-mono or VenR.[10]

References

1. Mato AR, Roeker LE, Eyre TA, et al. A retrospective comparison of venetoclax alone or in combination with an anti-CD20 monoclonal antibody in R/R CLL. Blood Adv 2019;3:1568-1573.
2. Walewska R, Eyre TA, Bloor A, et al. 2025 British Society for Haematology Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology 2025;n/a.
3. Bennett R, Seymour JF. Choosing between family members is always a balancing act. Haematologica 2023;108:1975-1978.
4. Eichhorst B, Niemann CU, Kater AP, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. N Engl J Med 2023;388:1739-1754.
5. Al-Sawaf O, Jen MH, Hess LM, et al. Pirtobrutinib versus venetoclax in covalent Bruton tyrosine kinase inhibitor-pretreated chronic lymphocytic leukemia: a matching-adjusted indirect comparison. Haematologica 2024;109:1866-1873.
6. Woyach J, Qiu L, Grosicki S, et al. Pirtobrutinib vs ibrutinib in treatment-naïve and relapsed/refractory CLL/SLL: Results from the first randomized phase III study comparing a non-covalent and covalent BTK inhibitor. J Clin Oncol 2025.
7. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia (MURANO). New England Journal of Medicine 2018;378:1107-1120.
8. Sharman JP, Munir T, Grosicki S, et al. BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib versus Idelalisib plus Rituximab (IdelaR) or Bendamustine plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma ASH Annual Meeting, 2025.
9. Food and Drug Administration (FDA). Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. 2016. Available at: https://www.fda.gov/media/78504/download [Accessed: 27 January 2026].
10. Eli Lilly and Company. Data on File. Clinical Validation Meeting Minutes.

EAG POST-ACM1 APPENDIX

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Post-ACM1 Appendix: EAG critique of the additional evidence provided by the company post-ACM1

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175978

Completed 15 January 2025

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

In the company submission (CS), the company only presented clinical effectiveness evidence for the comparison of pirtobrutinib versus investigator's choice (idelalisib with rituximab [IdelaR] or bendamustine with rituximab [BR]) for patients with relapsed or refractory chronic lymphocytic leukaemia (R/R CLL) who have previously been treated with one or more covalent Bruton's tyrosine kinase inhibitors (cBTKis).

The company provided no clinical effectiveness evidence for the comparisons of pirtobrutinib versus a cBTKi, venetoclax with rituximab (VenR) or best supportive care (BSC), which the External Assessment Group (EAG) considered were the most relevant comparators.

In the CS, the company only presented cost effectiveness results for the comparison of pirtobrutinib versus IdelaR. At clarification, the EAG requested that the company conduct cost-effectiveness analyses for pirtobrutinib versus the other relevant comparators (i.e., VenR, a cBTKi and BSC) using the pirtobrutinib and IdelaR survival data from the BRUIN CLL-321 trial[1] as a proxy in the absence of direct or indirect comparative clinical effectiveness data. In response to clarification, the company presented a cost comparison analysis for pirtobrutinib versus VenR only, assuming that pirtobrutinib and VenR had comparable efficacy.

Following the National Institute for Health and Care Excellence (NICE) Appraisal Committee Meeting 1 (ACM1), the NICE Appraisal Committee (AC) did not recommend pirtobrutinib and requested that the company provide:

- a comparison with venetoclax-monotherapy (Ven-mono) using all potentially useful available relative effect data, including the real world evidence (RWE) for the comparison of Ven-mono versus VenR referenced by the clinical expert during ACM1
- further characterisation of the comparison with VenR, where possible, including updates from ongoing trials
- further clarity around the issue of rechallenge with cBTKIs for people who had fixed-duration ibrutinib with venetoclax (VenI) or who discontinued treatment with a cBTKi due to intolerance.

In response to the NICE AC's request, the company provided:

- a network meta-analysis (NMA) for the comparison of pirtobrutinib versus VenR for patients with R/R CLL who had **not** previously been treated with a BTKi (i.e., patients who were BTKi-naïve)
- a cost-comparison analysis of pirtobrutinib versus Ven-mono.

This appendix includes the EAG's critique of the company's post-ACM1 evidence. In this appendix, references to the company's post-ACM1 document are to the report titled, "Additional comparative efficacy analysis" that the company submitted to NICE in response to the NICE AC's requests.

1.1 EAG critique of the additional evidence provided by the company to address the NICE AC uncertainties

1.1.1 Comparison of pirtobrutinib versus Ven-mono

The company did not provide additional clinical effectiveness evidence in response to the NICE AC's request for a comparison of pirtobrutinib versus Ven-mono using all potentially useful available relative effect data, including RWE comparing Ven-mono and VenR referenced by the clinical expert during ACM1. However, the company acknowledged that the NICE AC considered Ven-mono a relevant comparator for patients with R/R CLL who had been previously treated with a cBTKi and therefore provided updated cost effectiveness results from a cost-comparison analysis of pirtobrutinib versus Ven-mono, underpinned by the assumption that pirtobrutinib and Ven-mono have comparable efficacy (see Company's Updated Cost Comparison and Cost-Effectiveness Results Appendix). Cost effectiveness results for the company's deterministic and probabilistic base case analyses, and the EAG's deterministic exploratory analysis and deterministic and probabilistic base preferred analyses following ACM1, are presented in the EAG Confidential Appendix 2.

To support the assumption of comparable efficacy, the company referenced a published unanchored matching-adjusted indirect comparison (MAIC) which they previously referenced in response to clarification question B1. The published MAIC estimated the treatment effect of pirtobrutinib versus Ven-mono in patients with R/R CLL who had been previously treated with a cBTKi. The point estimate of the weighted PFS hazard ratio (HR) indicated similar efficacy for pirtobrutinib and Ven-mono (HR=1.01; 95% confidence interval [CI]: 0.58 to 1.73), while the OS HR numerically favoured pirtobrutinib over Ven-mono (HR=0.64; 95% CI: 0.25 to 1.67). The EAG highlights that the 95% CIs for these HRs were wide, including effect estimates that correspond with both clinically important benefit and clinically important harm. Therefore, the EAG considers that the unanchored MAIC does not provide conclusive evidence of comparable efficacy between pirtobrutinib and Ven-mono.

1.1.2 Clinical effectiveness evidence for the comparison of pirtobrutinib versus VenR

In response to clarification, the company presented a cost comparison analysis for pirtobrutinib versus VenR, underpinned by the key assumption that pirtobrutinib and VenR have comparable efficacy. However, the company was unable to present any clinical effectiveness evidence to support this assumption, as direct evidence (i.e., from a head-to-head trial of pirtobrutinib versus VenR) was not available and the company concluded that it was not feasible to conduct indirect treatment comparisons (ITCs) based on the existing evidence base. The EAG agreed that the company's decision not to perform any ITCs was appropriate.

Post-ACM1, the NICE AC requested "further characterisation of the comparison between pirtobrutinib and VenR where possible, including updates from ongoing trials" to address the key uncertainty of the similarity assumption for pirtobrutinib and VenR. The NICE AC also considered that clinical effectiveness evidence for the comparison of Ven-mono versus VenR, including RWE comparing Ven-mono and VenR referenced by the clinical expert during ACM1, when combined with evidence for the comparison of pirtobrutinib versus Ven-mono, may be informative for the comparison of pirtobrutinib versus VenR.

In response, the company has presented results from a network meta-analysis (NMA), henceforth referred to as the post-ACM1 NMA. The post-ACM1 NMA includes newly available data from the BRUIN CLL-314 trial[2] (data cut-off date [DCO]: 10 June 2025) and data from the MURANO trial[3] (the pivotal trial for VenR) and four other trials.[4-7]

The company considered, and the EAG agrees, that the BRUIN CLL-314 trial[2] population (100% BTKi-naïve) is more closely aligned to the populations of the MURANO trial[3] (≥97% BTKi-naïve) and the other trials included in the company's original feasibility assessment (all 100% BTKi-naïve), than the BRUIN CLL-321 trial[1] population (0% BTKi-naïve).

Although the trials included in the company's post-ACM1 NMA are more homogenous in terms of prior treatment with a BTKi than the trials included in the company's original feasibility assessment, the EAG highlights that none of the trials included in the company's post-ACM1 NMA were conducted in the population specified in the final scope[8] issued by NICE. As prior BTKi use has been identified as a treatment effect modifier (CS, p42), results from the company's NMA are applicable to the BTK-naïve population only and may not be generalisable to patients with R/R CLL who have previously been treated with a cBTKi.

The EAG also highlights that the company's NMA requires the assumption of comparable efficacy between IdelaR and BR. This assumption allows the MURANO trial[3] (VenR versus BR) and ASCEND trial[5] (acalabrutinib versus investigator's choice of IdelaR or BR) to be linked. The company states (company's post-ACM1 document, p15), and the EAG agrees, that clinical effectiveness evidence comparing these two treatments is limited and conflicting in nature. This assumption of clinical equivalence is considered by the company and EAG to introduce a level of uncertainty to the post-ACM1 NMA results.

The company performed the NMA for progression-free survival (PFS) only. The company considered, and the EAG agrees, that BRUIN CLL-314 trial[2] overall survival (OS) data are very immature and that NMAs including BRUIN CLL-314 trial[2] OS data would not be clinically meaningful.

Finally, the EAG highlights that although the point estimate of the HR for pirtobrutinib versus VenR indicates minimal difference in effectiveness between the two treatments (HR=[redacted]), the 95% credible interval (CrI) for this HR was wide (95% CrI: [redacted]), including effect estimates that correspond with both clinically important benefit and clinically important harm. Therefore, the EAG considers that the company's post-ACM1 NMA does not provide conclusive evidence of comparable efficacy between pirtobrutinib and VenR.

The company did not present clinical effectiveness evidence for the comparison of Ven-mono versus VenR, including RWE comparing Ven-mono and VenR referenced by the clinical expert during NICE ACM. The NICE AC considered that evidence for the comparison for Ven-mono versus VenR could be combined with evidence for the comparison of pirtobrutinib versus Ven-mono to inform the comparison of pirtobrutinib versus VenR. The company considered (company's post-ACM1 document, p3) that the post-ACM1 NMA results provided "a suitably more robust proxy to support the assumption of clinical similarity to VenR".

1.1.3 Rechallenge with a cBTKi

The company were unable to identify any evidence from published literature or NHS data regarding current NHS clinical practice or the clinical effectiveness of cBTKi rechallenge for patients with R/R CLL. The company considered (company's post-ACM1 document, p4) that "cBTKi rechallenge may only be relevant for a small subset of patients in the post-cBTKi population" and that the "issue has a smaller impact on the decision uncertainty in the appraisal than characterising the comparison between pirtobrutinib and VenR and Ven-mono". The company therefore did not provide cost-effectiveness estimates for the comparison of pirtobrutinib versus cBTKis.

Clinical advice to the EAG is that the following patients would be eligible for rechallenge with a cBTKi:

- patients who relapse after completing treatment with VenI in the first-line setting (i.e., a combined BTKi and B-cell lymphoma 2 inhibitor [BCL2i] therapy) but who are not refractory
- patients who discontinue prior treatment with a cBTKi due to intolerance.

For TA891,[9] clinical advice to the AC was that the fixed duration of VenI reduced the likelihood that patients treated with VenI would become resistant to either venetoclax or ibrutinib; an NHS England representative advised that rechallenge with a cBTKi or a BCL2i should be allowed for patients who had responded well to VenI in the first-line setting. Clinical advice to the EAG is that the proportion of patients who are eligible for rechallenge with a cBTKi is expected to increase over time.

2 REFERENCES

1. Eli Lilly and Company. Data on File. BRUIN CLL-321 CSR.
2. Woyach JA, Qiu L, Grosicki S, Wrobel T, Capra M, Czyz J*, et al.* Pirtobrutinib versus ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Journal of Clinical Oncology. 2025:Jco2502477.
3. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S*, et al.* Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. New England Journal of Medicine. 2018; 378:1107-20.
4. Brown JR, Eichhorst B, Hillmen P, Jurczak W, Kaźmierczak M, Lamanna N*, et al.* Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia (ALPINE). New England Journal of Medicine. 2023; 388:319-32.
5. Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M*, et al.* ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. Journal of Clinical Oncology. 2020; 38:2849-61.
6. Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR*, et al.* Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. Journal of Clinical Oncology. 2021; 39:3441-52.
7. Burger JA, Sivina M, Jain N, Kim E, Kadia T, Estrov Z*, et al.* Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. Blood. 2019; 133:1011-9.
8. National Institute for Care and Excellence. Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]. Final scope. Published 11 April 2025; Available from: https://www.nice.org.uk/guidance/gid-ta11298/documents/final-scope. Accessed 8 January 2026.
9. National Institute for Health and Care Excellence. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia. Technology appraisal guidance [TA891]. Published 31 May 2023; Available from: https://www.nice.org.uk/guidance/ta891. Accessed 8 January 2026.

EAG POST-ACM1 APPENDIX 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Post-ACM1 Appendix 2: EAG critique of the additional evidence provided by the company post-ACM1

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175978

Completed 17 February 2026

CONTAINS NO CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

Following the National Institute for Health and Care Excellence (NICE) Appraisal Committee Meeting 1 (ACM1), the NICE Appraisal Committee (AC) did not recommend pirtobrutinib and requested that the company provide:

- a comparison with venetoclax-monotherapy (Ven-mono) using all potentially useful available relative effect data, including the real world evidence (RWE) for the comparison of Ven-mono versus venetoclax with rituximab (VenR) referenced by the clinical expert during ACM1
- further characterisation of the comparison with VenR, where possible, including updates from ongoing trials
- further clarity around the issue of rechallenge with covalent Bruton's tyrosine kinase inhibitors (cBTKIs) for people who had fixed-duration ibrutinib with venetoclax (VenI) or who discontinued treatment with a cBTKi due to intolerance.

In response to the NICE AC's request, the company submitted a report titled, "Additional comparative efficacy analysis" and provided:

- a network meta-analysis (NMA) for the comparison of pirtobrutinib versus VenR for patients with R/R CLL who had **not** previously been treated with a BTKi (i.e., patients who were BTKi-naïve)
- a cost-comparison analysis of pirtobrutinib versus Ven-mono.

The EAG provided a critique of the company's post-ACM1 NMA in the EAG post-ACM1 Appendix.

In a subsequent appendix, the company has provided a summary and critique of the RWE comparing Ven-mono and VenR referenced by the clinical expert during NICE ACM1. The NICE AC considered that evidence for the comparison for Ven-mono versus VenR could be combined with evidence for the comparison of pirtobrutinib versus Ven-mono to inform the comparison of pirtobrutinib versus VenR.

In this EAG appendix, references to the company's post-ACM1 appendix are to the subsequent appendix that the company submitted to NICE presenting the RWE for the comparison of Ven-mono versus VenR.

1.1 EAG critique of the RWE for the comparison of Ven-mono versus VenR

In the company's post-ACM1 appendix, the company presented results from the Mato 2019 study,[1] a retrospective cohort study for the comparison of Ven-mono (n=270) versus venetoclax combination therapies (VENcombo; n=51) for patients with relapsed or refractory chronic lymphocytic leukaemia (R/R CLL). The VENcombo arm included treatment with either venetoclax plus obinutuzumab (VenO; n=13) or VenR (n=38).

In the Mato 2019 study,[1] overall response rates and complete remission rates were similar between the Ven-mono (81% and 34%, respectively) and VENcombo arms (84% and 32%, respectively). The PFS HR point estimate indicated no difference in effectiveness between Ven-mono and VENcombo (unadjusted HR=1.0; 95% confidence interval [CI] 0.6 to 1.8), however, the OS point estimate numerically favoured VENcombo (unadjusted HR 1.2, 95% CI 0.6 to 2.3).

The EAG considers that the Mato 2019 study[1] results are of limited use for this appraisal as:

- the Mato 2019 study[1] results are only reported for Ven-mono versus VENcombo (i.e., pooled comparator) and are not reported for Ven-mono versus VenR
- only a small number of patients received VenR (n=38)
- the 95% CIs for the PFS and OS HRs are wide and include effect estimates that correspond with both clinically important benefit and clinically important harm.

The EAG considers that the Mato 2019 study[1] results do not provide conclusive evidence of comparable efficacy between Ven-mono and VenR.

2 REFERENCES

1. Mato AR, Roeker LE, Eyre TA, Nabhan C, Lamanna N, Hill BT*, et al.* A retrospective comparison of venetoclax alone or in combination with an anti-CD20 monoclonal antibody in R/R CLL. Blood Advances. 2019; 3:1568-73.