Estimation of Utility Weights for Patients With Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) Previously Treated With a Covalent Bruton Kinase Inhibitor (cBTKi)

E Masoudi,[1] M-H Jen,[1] CN Graham,[2] A Erbe,[2] PT Maguire,[1] K-L Taipale,[1] C Qiao,[1] Z Zhang,[1] Y Han,[1] PL Graham-Clarke[1]

[1] Eli Lilly, Indianapolis, IN, United States;
[2] RTI Health Solutions, Durham, NC, United States

OBJECTIVES

- BRUIN-CLL-321 (LOXO-BTK-20020, J2N-OX-JZNN, NCT04666038) is a randomized, phase 3 trial comparing pirtobrutinib, a highly selective, noncovalent (reversible) BTKi, to investigator's choice of either IdelaR or BR in patients with CLL or SLL who were previously treated with cBTKis.
- The trial demonstrated that pirtobrutinib significantly improved PFS, EFS, and TTNT compared with the comparator arm (Sharman et al., 2025).
- To translate these clinical benefits into health economic value, CEAs are needed.
  CEAs depend on utility estimates to quantify patient quality of life.
- This study estimated preprogression utility values derived from the EQ-5D administered during the trial.

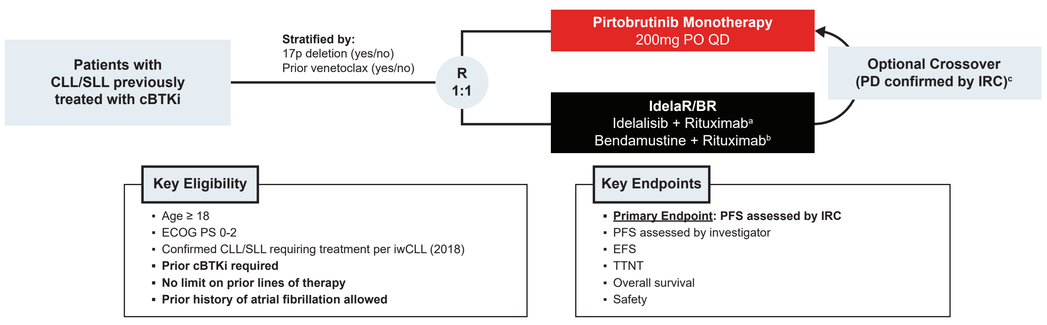
CONCLUSIONS

- This study has demonstrated that, among patients with heavily treated R/R CLL, utility weights improved after treatment initiation, with higher preprogression estimates from the linear mixed model compared with baseline values.
- The plausibility of the modelled utility estimates was supported by comparison with primary studies reporting utility weights (e.g., Cochrane et al., 2022; Cramer et al., 2018; Kosmas et al., 2015; Montillo et al., 2019) and with values used in previous NICE appraisals in R/R CLL (TA359, TA429, TA487, TA561, TA796, TA931).
- Overall, these results support the value of treatment in difficult-to-treat patients with R/R CLL and show improvements in health-related quality of life during therapy, as assessed by higher EQ-5D utility value.

STUDY DESIGN

- A total of 238 eligible patients were randomized 1:1 into Arm A (119 received pirtobrutinib as continuous monotherapy) and Arm B (119 received investigator's choice [82 IdelaR and 37 BR]).

Figure 1. BRUIN-CLL-321 Phase 3 Study Design



Treatment was given in 28-day cycles. PFS was assessed based on iwCLL guidelines (Hallek et al., 2018). [a] Idelalisib dosed at 150mg PO BID. Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 4 infusions at 500 mg/m^2 every 2 weeks, next 3 infusions at 500 mg/m^2 every 4 weeks. [b] Bendamustine (70 mg/m^2) was administered by IV D1, D2 of cycles 1-6. Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 5 infusions day 1 of cycle 2 through cycle 6 at 500 mg/m^2. [c] Eligible patients receiving investigator's choice of IdelaR/BR could crossover to receive pirtobrutinib monotherapy upon confirmation of PD by independent review committee per protocol.

BACKGROUND

BRUIN-CLL-321 Patient Population and Crossover

- This study is unique from other studies in R/R CLL:
  - This is the first randomized, prospective study to describe the efficacy and safety of available or investigational therapies in the post-cBTKi setting.
  - All patients had previously received a cBTKi, and approximately half also received another targeted agent, a BCL2i.
- Patients in the BRUIN-CLL-321 trial were heavily pretreated:
  - The median number of prior lines of therapy was 3 in both the pirtobrutinib and investigator's choice groups, with 14% and 15% of patients, respectively, having received more than 1 cBTKi. Prior studies in patients with R/R CLL report 1 (median) prior line of therapy, usually a chemotherapy-based regimen.
- In the investigator's choice group, 50/66 (76%) patients who experienced PD crossed over to pirtobrutinib.

BRUIN-CLL-321 EQ-5D-5L Assessments

- The EQ-5D-5L was administered at baseline and every 12 weeks until the EOT, PD, unacceptable toxicity, or treatment discontinuation.
- In the case of BR, as this is a time-limited treatment, EOT and collection of EQ-5D data were constrained to the maximum of six 28-day cycles.
- No patient-reported outcome data were collected during the crossover period.

METHODS

- EQ-5D-5L responses from the BRUIN-CLL-321 trial's ITT were transformed into utility weights using the NICE preferred mapping algorithm, which converts 5L responses to 3L utility values for the United Kingdom (Hernández Alava et al., 2023).
- Models were fit to estimate both pre- and postprogression utility weights.
- Linear mixed models, incorporating participants as a random effect, were employed to account for repeated measures. The restricted maximum likelihood estimation was used to fit the model, and the Kenward-Roger approximation method was used to estimate the degrees of freedom, standard errors, and covariance matrix.
- Baseline age and utility values, centered on population means, were included as fixed effect covariates to control for baseline variation.

RESULTS

- 238 patients were included in the ITT population.
  - Mean age was 66.3 years (SD = 9.06).
  - Mean baseline utility was 0.7574 (SD = 0.23) (Table 1).
- 158 patients were included in the EQ-5D-5L analysis population, resulting in 293 valid post-baseline assessments (Tables 2 and 3).
- Due to limited EQ-5D data captured after PD, estimates were deemed unreliable and were excluded from the analysis.
  - Only 73 valid assessments were available at the time of PD.
  - The trial did not collect EQ-5D data in Arm B beyond 6 weeks for patients treated with BR.
- The estimated preprogression utility from the linear mixed model was higher than the mean baseline utility, indicating an improvement in patient utility following treatment initiation (Table 4).
  - The coefficient for centered baseline utility indicates that patients with higher baseline utility had correspondingly higher postbaseline utility.
  - The coefficient for centered baseline age suggests no significant association between age at baseline and postbaseline utility.

Table 1. Mean Age and Mean Baseline Utility

Characteristic	Mean	SD	Median	Min	Max
Age (years)	66.32	9.06	66.00	42.00	82.00
EQ-5D-3L utility weight	0.7574	0.23	0.7849	−0.3861	0.9885

Table 2. EQ-5D-5L Analysis Population

Population	N (Arm A)	N (Arm B)	N (total)
ITT population	119	119	238
No EQ-5D-3L assessments[a]	4	16	20
Assessed post-event after subsequent anticancer therapy[a]	0	2	2
No adequate post-event after subsequent anticancer therapy[a]	0	1	1
Assessed post-study exit[a]	2	0	2
Assessed post-subsequent anticancer therapy without event[a]	0	1	1
Missing baseline assessment[a]	30	24	54
EQ-5D-5L analysis population	83	75	158

Arm A, Pirtobrutinib; Arm B, IdelaR or BR.
[a] Exclusion criteria are applied in a sequential manner.

Table 3. Summary of EQ-5D-5L Assessments

Health state[a]	Participants with ≥ 1 EQ-5D-3L assessment[b]	Number of EQ-5D-3L assessments	Number of EQ-5D-3L assessments at baseline	Number of EQ-5D-3L assessments at post-baseline
Progression free	157	377	157	220
Progression disease	43	74	1	73

[a] Prior to crossover for Arm B (Investigator's choice) over to Arm A (pirtobrutinib).
[b] A participant can contribute to more than 1 health state.

Table 4. Linear Mixed Model Coefficients for Preprogression Utility Weights (BRUIN-CLL-321)

Effect	Term	Estimate	Standard error	Statistic	Degrees of freedom	P value
Fixed	Intercept	0.81358[a]	0.01753	46.41492	94.94075	< 0.00001
Fixed	Baseline utility centered	0.48502	0.09747	4.97606	107.87134	< 0.00001
Fixed	Baseline age centered	−0.00069	0.00191	−0.35983	95.76981	0.71977
Random	SD of intercept	0.14680	Not applicable	Not applicable	Not applicable	Not applicable
Random	SD of observation	0.10994	Not applicable	Not applicable	Not applicable	Not applicable

[a] Intercept of the linear mixed model (ITT population), where utility weights are the response variable and the covariates are the centered EQ-5D-5L utility weight baseline scores (mean population baseline utility − participant baseline utility), centered age (mean population age − participant age), and the time period of observed utility weight is progression free.

LIMITATIONS

- PD utility weights could not be estimated due to the lack of data collection at time of progression; therefore, PD utility weights should be obtained from other sources for economic models.
- The EQ-5D analysis set may not fully represent the trial ITT population, as 80 of 238 ITT patients were excluded primarily due to missing baseline values or no EQ-5D assessments. This may limit generalizability of the utility estimates.
- For patients who were treated with BR, data collection was limited to 6 treatment cycles, limiting the ability to estimate preprogression utilities for patients who experienced disease progression after this time point.

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ABBREVIATIONS

Acronym	Definition
BCL2i	B-cell lymphoma 2 inhibitor
BID	twice daily
BR	bendamustine + rituximab
BTKi	Bruton tyrosine kinase inhibitor
cBTKi	covalent Bruton tyrosine kinase inhibitor
CEA	cost-effectiveness analysis
CLL	chronic lymphocytic leukemia
ECOG PS	Eastern Cooperative Oncology Group performance status
EFS	event-free survival
EOT	end of treatment
HTA	Health Technology Assessment
IdelaR	idelalisib + rituximab
IRC	independent review committee
ITT	intention-to-treat
IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
Min	minimum
Max	maximum
NICE	National Institute for Health and Care Excellence
PD	progressive disease
PFS	progression-free survival
PO	by mouth
PRO	patient-reported outcomes
QD	once daily
R	randomized
R/R	relapsed/refractory
SAP	statistical analysis plan
SD	standard deviation
SFU	safety follow-up
SLL	small lymphocytic lymphoma
TTNT	time to next treatment

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