Patient Reported Outcomes in BRUIN-CLL-321: A Phase 3 Trial of Pirtobrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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OBJECTIVE

- This study aims to assess the patient-reported outcomes from the BRUIN CLL-321 study, a phase 3, randomized, global trial assessing the safety and efficacy of pirtobrutinib monotherapy compared to IdelaR/BR in patients with CLL/SLL previously treated with a cBTKi

CONCLUSIONS

- While both groups experienced some improvements in PRO outcomes, compared to IdelaR/BR, patients treated with pirtobrutinib had more consistent improvement in CLL/SLL-related symptoms, physical function, and fatigue throughout the assessment period; all pirtobrutinib outcomes met a clinically meaningful threshold

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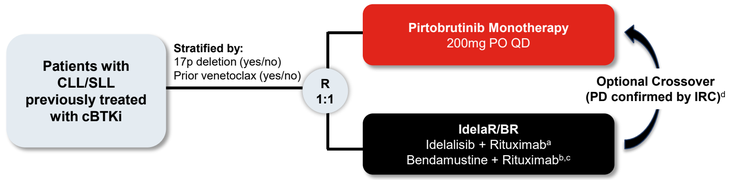
BACKGROUND

- Covalent Bruton Tyrosine Kinase inhibitors (cBTKi) are a mainstay of first- and second-line therapy in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), but there is an increasing need for new therapies in the post-cBTKi treatment setting
  - Pirtobrutinib is a highly selective non-covalent BTKi that inhibits BTK throughout the dosing interval, with low nM potency
- BRUIN CLL-321 is the first randomized phase III clinical trial assessing the safety and efficacy of treatment entirely in patients who have been previously treated with cBTKi
  - BRUIN CLL-321 established the superiority of pirtobrutinib in progression-free survival compared to IdelaR/BR
- PROs including symptom burden can provide helpful information to support benefit-risk assessment of a new treatment, such as pirtobrutinib
- Here we report PROs from the first randomized Phase 3 study in the post-cBTKi setting

BRUIN CLL-321 STUDY DESIGN



Key Eligibility

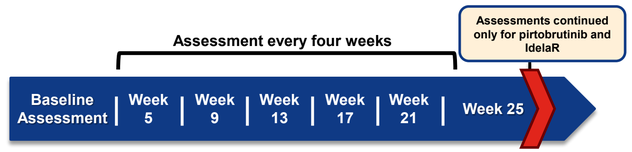
- Age ≥18
- ECOG PS 0-2
- Confirmed CLL/SLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**
- **Prior history of atrial fibrillation allowed**

Patient Reported Outcomes Endpoints

- Secondary and exploratory PRO endpoints were not alpha-controlled
- Secondary PRO Endpoints
  - Time to worsening of CLL/SLL-related symptoms and physical function, to be reported elsewhere
- Exploratory PRO endpoints
  - Longitudinal analyses of CLL/SLL-related symptoms (EORTC Item Library 87), physical function (EORTC QLQ-C30), and fatigue[e]

Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. [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) administered IV D1, D2 of cycles 1-6. [c]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. [d]Eligible patients receiving investigator's choice of IdelaR/BR could crossover to receive pirtobrutinib monotherapy upon confirmation of PD by IRC per protocol. [e]The Expanded Fatigue, comprised of the QLQ-C30 fatigue subscale plus three items from the EORTC item library 87. [f]Baseline is defined as the data collected at Week 1. [g]Excluding crossover period. [h]The MMRM model includes: change from baseline as the response variable, treatment, assessment time point, baseline value, deletion 17p presence, and receipt of prior venetoclax treatment as fixed effects, and patient as a random effect. Data cut of 29 August 2024 was used.

PATIENT-REPORTED OUTCOMES ANALYSIS AND METHODS



The analysis period was defined from baseline[f] through Week 25 for continuous pirtobrutinib and IdelaR treatment and through Week 21 (6 cycles of fixed-duration treatment) plus the safety follow-up assessment for BR[g]

- Changes from baseline were analyzed using a mixed model for repeated measures (MMRM)[h] for CLL/SLL-related symptoms, physical function, and fatigue
- Differences within each group and differences between treatment groups (based on adjusted least square means) were described over time adjusting for correlations across time points within patients and controlling for baseline values
- Thresholds for defining a clinically meaningful difference were based on those published by Cocks et al[1] for within-group changes over time and by Cocks et al[2] for between-group differences

PRO completion rate

- Of all patients randomized, 91 (76.5%) and 88 (73.9%), respectively, completed the baseline PRO assessments for an overall PRO completion rate of 75.2% at baseline

RESULTS

The dotted lines in the figures below represent clinically meaningful changes in the endpoint as defined by Cocks et al.; CLL/SLL related-symptoms and fatigue values below the line represent a clinically meaningful reduction, physical function values above the line represent a clinically meaningful improvement in physical function. P-value is nominal and not alpha-controlled. *=p<0.05.

Figure 1. Within-group change in CLL/SLL-related symptoms from baseline at each post-baseline assessment time point by treatment group

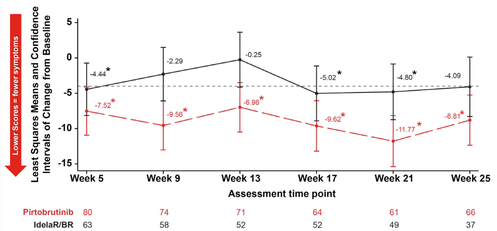


Figure 2. Within-group change in physical function from baseline at each post-baseline assessment time point by treatment group

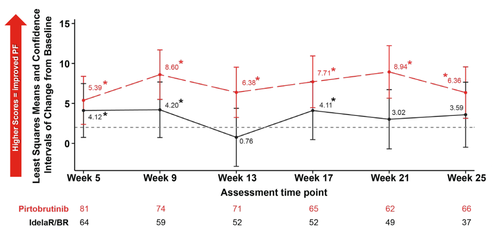


Figure 3. Within-group change in fatigue from baseline at each post-baseline assessment time point by treatment arm

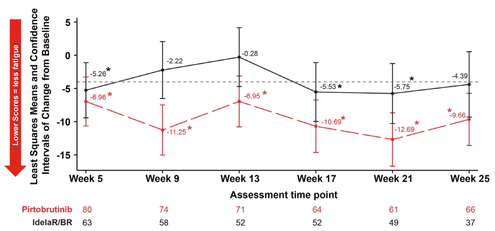


Figure 4. Differences in change from baseline in CLL/SLL-related symptoms between pirtobrutinib and IdelaR/BR

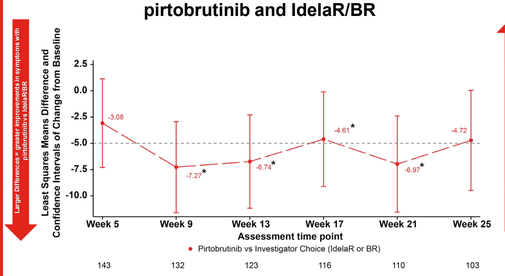


Figure 5. Differences in change from baseline in physical function between pirtobrutinib and IdelaR/BR

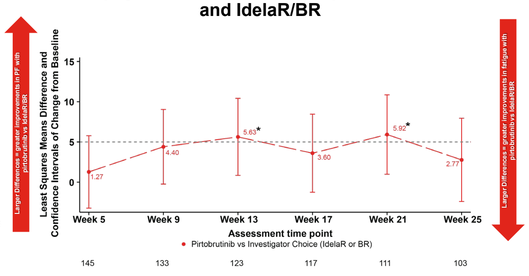
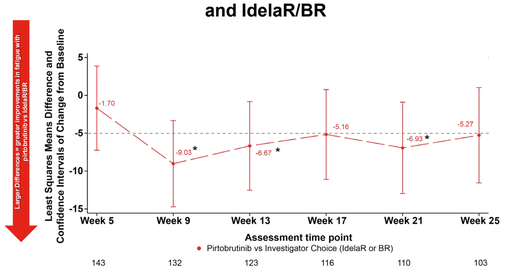


Figure 6. Differences in change from baseline in fatigue between pirtobrutinib and IdelaR/BR



SUMMARY OF RESULTS

238 patients were randomized (119 to each treatment arm)

- **PRO completion rate**
  - Overall baseline PRO completion rate 81.7%
  - 91 (79.8%) pirtobrutinib and 88 (83.8%) IdelaR/BR patients
- **Within-group change**
  - Patients treated with pirtobrutinib demonstrated a clinically meaningful improvement in
    - CLL/SLL-related symptoms (Figure 1)
    - physical function (Figure 2)
    - fatigue at all post-baseline visits (Figure 3)
- **Between-group change**
  - Clinically meaningful differences in pirtobrutinib versus IdelaR/BR were seen at multiple timepoints for changes from baseline in CLL/SLL-related symptoms (Figure 4), physical functioning (Figure 5), and fatigue (Figure 6)

Limitations

- The lack of data collection past Week 25 for patients receiving BR precludes the study of longer follow up for these patients
- The number of patients available for PRO assessment declined over time as patients experienced disease progression or treatment discontinuation, particularly notable in the IdelaR/BR group that experienced a higher rate of treatment discontinuation during the 25-week analysis period

References and Abbreviations

References:
1. Cocks, K., et al. (2012). Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. European Journal of Cancer, 48(11), 1713-1721. https://doi.org/10.1016/j.ejca.2012.02.059
2. Cocks, K., et al. (2011). Evidence-Based Guidelines for Determination of Sample Size and Interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Journal of Clinical Oncology, 29(1), 89-96. https://doi.org/10.1200/jco.2010.28.0107

Abbreviations: BID, twice daily; BR, bendamustine + rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IdelaR, idelalisib + rituximab; IRC, Independent Review Committee; iwCLL, international workshop on chronic lymphocytic leukemia; mg, milligram; PD, progressive disease; PFS, progression-free survival; PO, by mouth; QD, once daily; R, randomized; SLL, small lymphocytic lymphoma; PFS, progression-free survival; OS, overall survival; PF, physical function.

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