

Abstract Title : Pirtobrutinib vs bendamustine plus rituximab (BR) in patients with CLL/SLL: First results from a randomized phase III study Examining a non-covalent BTK inhibitor in untreated patients

Category: 600s - Hematologic Malignancy

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Authors

Wojciech Jurczak¹, Michal Kwiatek², Jaroslaw Czyz³, Ederson de Mattos⁴, Ki-Seong Eom⁵, Alexander Egle⁶, Anna Panovská⁷, Zhanet Grudeva-Popova⁸, Hsuan-Jen Shih⁹, Luis Felipe Casado Montero¹⁰, Paolo Sportoletti¹¹, Vu Minh Hua¹², James D'Olimpio¹³, Shinsuke Iida¹⁴, Rodrigo Ito¹⁵, Katherine Bao¹⁵, Anne Fink¹⁵, Weiji Su¹⁵, Amy Ruppert Stark¹⁵, Alejandro Levy¹⁵, Tomasz Wrobel¹⁶

¹ National Research Institute of Oncology, Krakow, Poland, ² AIDPORT Clinical Trials Hospital, Skorzewo, Poland, ³ Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Torun, Poland, ⁴ Hospital Amaral Carvalho Jau, São Paulo, Brazil, ⁵ Catholic Hematology Hospital, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea, Rep. of South, ⁶ Paracelsus University Hospital, Salzburg, Austria, ⁷ Masaryk University, Brno, Czech Republic, ⁸ Medical University of Plovdiv, Plovdiv, Bulgaria, ⁹ Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan, ¹⁰ HM CIOCC MADRID (Centro Integral Oncológico Clara Campal), Instituto de Investigación Sanitaria HM Hospitales, Madrid, Spain, ¹¹ Institute of Hematology Centro di Ricerca Emato- Oncologica (CREO), University of Perugia, Perugia, Italy, ¹² Liverpool Hospital, New South Wales, Australia, ¹³ Clinical Research Alliance, Westbury, United States, ¹⁴ Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, ¹⁵ Eli Lilly and Company, Indianapolis, IN, United States, ¹⁶ Wroclaw Medical University, Wroclaw, Poland

Abstract Body

Introduction: Pirtobrutinib is a highly selective, non-covalent (nc) Bruton tyrosine kinase inhibitor (BTKi) that has demonstrated safety and efficacy in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), including pts previously treated with a cBTKi. While cBTKi have significantly improved progression-free survival (PFS) for untreated pts with CLL/SLL, there are no Phase 3 data assessing a ncBTKi specifically in the treatment-naïve setting, and significant improvements in overall survival (OS) are uncommon with monotherapy cBTKi. A recent head-to-head phase 3 trial (BRUIN CLL-314 presented at this meeting, ASH abstract 25-2587; NCT05254743) showed a favorable overall response rate (ORR) and a positive PFS trend with pirtobrutinib compared to the cBTKi ibrutinib in a subset of pts with treatment-naïve CLL. Here we present the first results from a randomized, open-label, global phase 3 trial specifically assessing the efficacy and safety of pirtobrutinib versus bendamustine plus rituximab (BR) in treatment-naïve pts with CLL/SLL (BRUIN CLL-313; NCT05023980).

Methods: Pts with previously untreated CLL/SLL, without del(17p), were randomized 1:1 to receive pirtobrutinib monotherapy (200 mg QD) or 6 cycles of BR, stratified by IGHV mutation status (mutated vs unmutated) and Rai stage (low/intermediate vs high). Pts with known CLL/SLL CNS involvement, Richter transformation, or significant cardiovascular disease were excluded. Responses were evaluated using iwCLL 2018 criteria. The primary endpoint was PFS assessed by independent review committee (IRC), and a stratified log-rank test compared IRC-assessed PFS between pirtobrutinib and BR using a 2-sided alpha level of 0.05. OS was a key secondary endpoint, gated on IRC-assessed PFS, with a small alpha of 0.000001 spent at this interim OS analysis. Other secondary endpoints included investigator (INV)-assessed PFS and safety. Efficacy analyses were based on the intent-to-treat population. Pts assigned to BR were eligible to cross over to receive pirtobrutinib if they had IRC-confirmed disease progression (PD), met study eligibility requirements, and needed therapy per iwCLL criteria. The data cutoff was 11 July 2025.

Results: 282 pts were randomized to receive either pirtobrutinib (n=141) or BR (n=141). At a median follow-up of 28.1 months, the primary endpoint of IRC-assessed PFS was significantly improved with pirtobrutinib compared with BR (HR: 0.199; 95% CI: 0.107, 0.367; p<0.0001). The 24-month PFS rate was 93.4% (95% CI: 87.6, 96.5) for pirtobrutinib and 70.7% (95% CI: 61.5, 78.1) for BR. IRC-assessed PFS benefit was consistently observed with pirtobrutinib among prespecified, clinically relevant patient subgroups, including patients with mutated IGHV (HR: 0.293, 95% CI: 0.094, 0.910), and unmutated IGHV (HR: 0.172, 95% CI: 0.083, 0.357). The PFS by INV was consistent (HR: 0.186; 95% CI: 0.093, 0.371; p<0.0001). The OS HR for pirtobrutinib versus BR was 0.257 (95% CI: 0.070, 0.934; p=0.0261), despite an effective crossover rate of 52.9% (18/34 pts with INV-assessed PD). The median treatment duration was 32.3 months for 140 pts receiving pirtobrutinib and 5.6 months for 132 pts receiving BR. The incidence of grade ≥3 TEAEs was 40.0% with pirtobrutinib and 67.4% with BR. Grade 5 TEAEs occurred in 1 pt receiving pirtobrutinib and 4 pts receiving BR, with none considered pirtobrutinib related and 1 (tumor lysis syndrome) considered BR related. Discontinuation of pirtobrutinib and BR due to TEAE occurred in 6 (4.3%) and 20 (15.2%) pts, respectively. Two pts (1.4%) receiving pirtobrutinib had a TEAE of atrial fibrillation/flutter, including only 1 of 20 pts aged ≥75 years.

Conclusions: In BRUIN CLL-313, pirtobrutinib significantly improved IRC-assessed PFS versus BR for pts with treatment-naïve CLL/SLL with one of the largest treatment effects ever observed for a single-agent BTKi against this comparator. Pirtobrutinib was well tolerated, consistent with its known safety profile, with low rates of discontinuation and atrial fibrillation/flutter. While OS data remained immature, a notable trend favoring pirtobrutinib was observed, despite 52.9% of BR pts crossing over to receive pirtobrutinib after PD. Taken together, these data suggest that pirtobrutinib may be considered a potential new standard-of-care treatment for pts with untreated CLL/SLL, including older pts who may receive only one line of therapy.

Keywords: Research, Treatment Considerations, Diseases, Clinical Trials, CLL, Lymphoid Malignancies, Lymphoid Leukemias, Clinical Research

Disclosure : Wojciech Jurczak: AstraZeneca, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Janssen, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Roche, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Merck, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, BeOne Medicines Ltd, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Nurix Therapeutics Inc, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No,

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(Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Novartis, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Bristol Myers Squibb, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: 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company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Sandoz, Consultancy (Includes expert testimony): No,

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testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Rodrigo Ito: Eli Lilly and Company, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: Yes, Current Employment: Yes, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Katherine Bao: Eli Lilly and Company, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 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