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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-up and Subgroup Analysis With/Without Prior BCL2i from the Phase 1/2 BRUIN Study

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Background: The treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has benefited from covalent (c) Bruton tyrosine kinase inhibitors (BTKi), however, therapy can fail due to progression or intolerance. Sequential treatment with B-cell lymphoma 2 protein inhibitor (BCL2i) venetoclax, either as monotherapy or combined with an anti-CD20 monoclonal antibody, has been the primary treatment option for CLL/SLL patients (pts) whose disease has progressed on cBTKi. Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi that demonstrated promising efficacy in patients with relapsed or refractory CLL/SLL (Mato *et al*, NEJM, 2023). Here, we report on the efficacy of pirtobrutinib treatment in CLL/SLL in the post-cBTKi setting, including subgroups with or without prior BCL2i, using data from the BRUIN study (NCT03740529) with more than 2 years follow-up.

Methods: Pts with previously treated CLL/SLL were eligible for treatment with pirtobrutinib in the multicenter Phase 1/2 BRUIN study. Key endpoints included ORR (including partial response with lymphocytosis; PR-L) as assessed by an independent review committee per 2018 iwCLL response criteria, DoR, PFS, OS, and safety. A data cut of 05MAY2023 was utilized.

Results: In total, 282 pts with CLL/SLL who received prior cBTKi were included in this analysis. Median age was 69 years (range, 36-88), 68% were male, and median number of prior therapies was 4 (range, 1-11). Of 282 pts, 154 (55%) had not received prior-BCL2i therapy (Naïve; BCL2i-N) and 128 (45%) had (Exposed; BCL2i-E). BCL2i-N pts were exposed to fewer prior therapies than BCL2i-E pts (median prior therapies 3 and 5, respectively), including anti-CD20 antibody (83% and 97%), chemotherapy (74% and 89%), PI3K inhibitor (11% and 42%), CAR-T cell therapy (1% and 12%), and hematopoietic cell transplantation (1% and 6%). The ORR for all post-cBTKi pts was 72% (95% CI, 66.4-77.1), and ORR including PR-L was 82% (95% CI, 76.5-85.9). Post-cBTKi pts included a subgroup of 19 pts with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had ORR including PR-L of 89.5% (CI 95%, 66.9-98.7). The ORR including PR-L was 83.1% (95% CI, 76.2-88.7) for BCL2i-N pts, and 79.7% (95% CI, 71.7-86.3) for BCL2i-E pts. Median DoR was 18.4 months (95% CI, 15.3-20.4) for all cBTKi pre-treated pts, 24.9 months (95% CI, 18.4-32.0) for BCL2i-N, and 14.8 months (95% CI, 12.0-17.4) for BCL2i-E. With a median follow up of 27.5 months, the median PFS was 19.4 months (95% CI, 16.6-22.1) among all cBTKi pre-treated pts, 23.0 months (95% CI, 19.6-28.4) for BCL2i-N, and 15.9 months (95% CI, 13.6-17.5) for BCL2i-E (Figure). With a median follow up of 29.3 months, the median OS was not estimable for all cBTKi pre-treated pts, BCL2i-N, and BCL2i-E; the 24-month OS rates were 73.2% (95% CI, 67.4-78.2), 83.1% (95% CI,75.9-88.2), 60.6% (50.9-68.9), respectively.

In the CLL/SLL cohort (N=282), the most frequent treatment-emergent adverse events (TEAE), regardless of attribution, were fatigue (36.9%), diarrhea (28.4%), cough (27.3%) and contusion (26.2%). The most frequent Grade ≥3 TEAE was neutropenia/neutrophil count decreased (28.4%). Grade ≥3 TEAEs of hypertension (4.3%) and atrial fibrillation/flutter (1.8%) were infrequent. The AE profile of BCL2i-N and BCL2i-E pts was overall similar. Though Grade ≥3 neutropenia/neutrophil count decreased was higher in BCL2i-E pts (36.7% and 21.4%), this may have been attributed to the higher frequency of baseline neutropenia in BCL2i-E pts (27.3% and 11.0%). In total, 7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) pts had treatment-related AE leading to pirtobrutinib discontinuation.

Conclusion: Pirtobrutinib continues to demonstrate promising and durable efficacy in pts with post-cBTKi heavily pretreated CLL/SLL. ORR was high regardless of prior BCL2i status. Longer PFS was observed in BCL2i-N pts than BCL2i-E pts, likely due to the more heavily pretreated status of the BCL2i-E population which can be associated with poorer prognosis. Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BTKi-N and BTKi-E pts. These results suggest that continuation of BTK pathway inhibition following a cBTKi may be an important sequencing approach to consider in the treatment of CLL/SLL.

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OffLabel Disclosure: Pirtobrutinib is approved in the USA for treatment of relapsed or refractory MCL after at least 2 lines of systemic therapy, including prior BTKi.

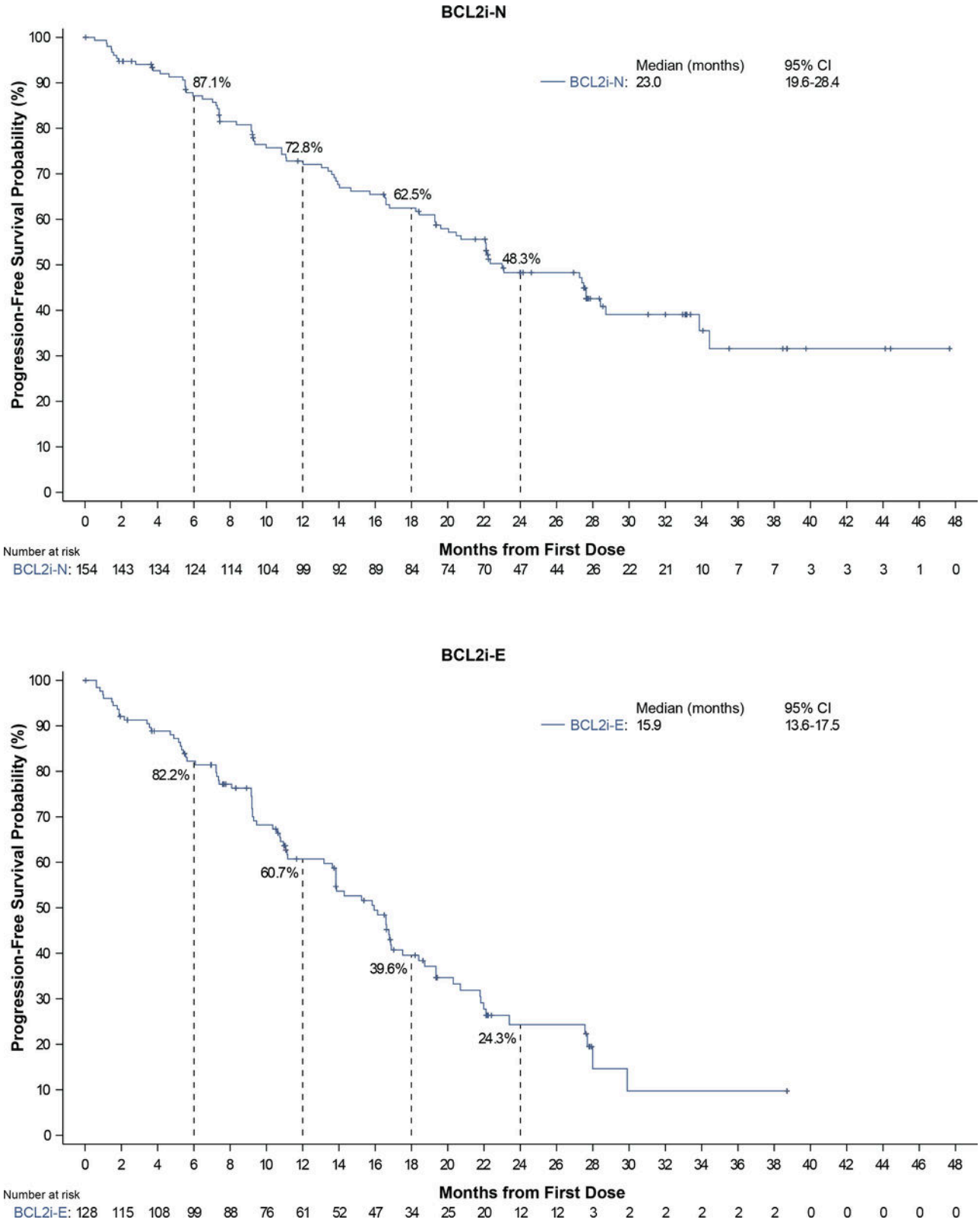

Figure 1

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