Pirtobrutinib, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results from the Phase 1/2 BRUIN Study

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Background:

Covalent BTK inhibitors (BTKi) have transformed the management of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but these treatments are not curative and many patients (pts) will require additional treatment. Covalent BTKi share pharmacologic liabilities (e.g. low oral bioavailability, short half-life) that collectively may lead to suboptimal BTK target coverage, for example in rapidly proliferating tumors with high BTK protein turnover such as accelerating CLL/SLL, ultimately manifesting as acquired resistance in some pts. To address these limitations, pirtobrutinib, a highly selective, non-covalent BTKi that inhibits both wild type (WT) and C481-mutated BTK with equal low nM potency was developed. In the phase 1/2 BRUIN study, pirtobrutinib achieved pharmacokinetic exposures that exceeded its BTK IC96 at trough, was well tolerated and demonstrated promising efficacy in CLL/SLL pts regardless of prior therapy, number of prior lines of therapy, or BTK C481 mutation status(Mato et al. Lancet 2021;397,10277:892-901).

Methods:

BRUIN is a phase 1/2 multicenter study (NCT03740529) of oral pirtobrutinib monotherapy in pts with advanced B-cell malignancies who have received >2 prior therapies. Pirtobrutinib was dose escalated in a standard 3+3 design in 28-day cycles. The primary objective for phase 1 was to determine the recommended phase 2 dose (RP2D) and the primary objective of phase 2 was overall response rate (ORR); secondary objectives included duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety and tolerability, and pharmacokinetics. Efficacy evaluable pts included all dosed pts who underwent their first response evaluation or discontinued therapy. Response was assessed every 8 weeks from cycle 3, and every 12 weeks from cycle 13 and was measured according to the iwCLL 2018 criteria, including PR with lymphocytosis (PR-L). Safety was assessed in all pts (CLL/SLL and NHL).

Results:

As of 27 September 2020, 323 pts with B-cell malignancies (170 CLL/SLL, 61 MCL, 26 WM, 26 DLBCL, 13 MZL, 12 FL, 9 RT, and 6 other [other transformation, B-PLL and hairy cell leukemia]) were treated on 7 dose levels (25-300mg QD). Among the 170 pts with CLL/SLL, the median age was 69 (range 36-88) years. Median number of prior lines of therapies was 3 (range 1-11). Majority of the CLL/SLL pts had received a prior BTKi (86%), an anti-CD20 antibody (90%), or a chemotherapy (82%); 21% had received a PI3K inhibitor and 34% a BCL2 inhibitor. High risk molecular features such as 17p deletion, TP53 mutation, and unmutated IGHV were present in 25% (20/81), 30% (27/91), and 88% (71/81) of pts, respectively. No DLTs were reported and MTD was not reached (n=323). 200mg QD was selected as the RP2D. Fatigue (20%), diarrhea (17%), and contusion (13%) were the most frequent treatment-emergent adverse events regardless of attribution or grade seen in >10% of pts (n=323). The most common adverse event of grade ≥3 was neutropenia (10%). Treatment-related hemorrhage and hypertension occurred in 5 (2%) and 4 (1%) pts, respectively. Five (1%) pts discontinued due to treatment-related adverse events. At the efficacy cutoff date, 139 CLL/SLL pts were efficacy-evaluable with a median follow up time of 6 months (range 0.16-17.8+). The ORR was 63% (95% CI 55-71) among the 139 efficacy evaluable pts with 69 PRs (50%), 19 PR-Ls (14%), 45 SDs (32%), and 1 PD (1%), and 5 (4%) pts discontinued prior to first response assessment. Among the 121 BTKi pretreated pts, the ORR was 62% (95% CI 53-71). Responses deepened over time with an ORR of 86% among the pts with at least 10 months follow-up. ORR was similar in pts who discontinued prior BTKi due to progression (67%), or adverse events or other reasons (52%). Of the 88 responding pts, all except 5 remained on therapy (4 progressed and 1 achieved a PR and electively discontinued treatment to undergo transplant). The longest-followed responding patient as of the data cutoff date had been on treatment for 17.8+ months.

Conclusion:

Pirtobrutinib demonstrated promising efficacy in heavily pretreated CLL/SLL pts following multiple prior lines of therapy, including a covalent BTKi and a BCL2 inhibitor, and in pts with BTK C481 mutations. Pirtobrutinib was well tolerated and exhibited a wide therapeutic index. Updated data, including approximately 100 new pts with CLL and an additional 10 months since the prior data cut will be presented.