(PS1690) UPDATED RESULTS FROM A PHASE 1B STUDY OF NON-COVALENT PAN-MUTANT BTK INHIBITOR DOCIRBRUTINIB (AS-1763) IN PATIENTS WITH PREVIOUSLY TREATED B-CELL MALIGNANCIES

Topic: 06. Chronic lymphocytic leukemia and related disorders - Clinical

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Background

Docirbrutinib is a highly selective, pan-mutant non-covalent BTK inhibitor (ncBTKi), which inhibits both wild-type and various c/ncBTKi-resistant mutations including C481x, T474x and L528x with IC_{50} values of <10 nM and shows strong anti-tumor activity in B-cell lymphoma cell lines harboring resistant BTK mutations including a kinase-dead BTK L528W. Here we present updated results from the ongoing Phase 1b study of docirbrutinib in B-cell malignancies including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Waldenström macroglobulinemia (WM), and marginal zone lymphoma (MZL) (NCT05602363).

Aims

To investigate the safety, efficacy and pharmacokinetics of docirbrutinib in Phase 1b study in B-cell malignancies.

Methods

This is a multicenter, open-label, Phase 1b study in patients (pts) with CLL/SLL or B-cell NHL who received ≥2 prior therapies including c/ncBTKis. The study includes dose escalation and expansion parts. The dose expansion part consists of three cohorts; Cohorts 1 and 2 include CLL/SLL and NHL pts, respectively, for determination of the recommended Phase 2 dose, and Cohort 3 includes CLL/SLL/MCL pts previously treated with a ncBTKi, pirtobrutinib, for exploratory efficacy evaluation.

Results

As of 9 Feb 2026, 53 pts (30 CLL/SLL, 8 MCL, 6 FL, 5 MZL, 4 WM) were assigned to 5 dose levels: 100 (n=3), 200 (n=3), 300 (n=23), 400 (n=21), and 500 mg twice daily (BID) (n=3). Median age was 69 years (range, 46-86). The median number of prior lines of therapy for CLL/SLL was 4 (range, 2-13) including cBTKi (30/30 [100%]), BCL2i (18/30 [60%]) and pirtobrutinib (2/30 [7%]), and that for NHL was 4 (range, 2-8) including cBTKi (3/8 [38%] for MCL, 1/6 [17%] for FL, 2/5 [40%] for MZL, 2/4 [50%] for WM) and pirtobrutinib (2/8 [25%] for MCL). For 30 CLL/SLL pts, baseline genetic features included IGHV-unmutated (29/29, 100%), del(17p)/TP53-mutated (10/29, 34%), del(11q) (4/27, 15%), BTK C481x (9/25, 36%), A428D (1/25, 4%), and L528W mutations (1/25, 4%), and PLCG2 mutation (1/25, 4%). Median treatment duration was 7.4 (range, 0.4-30.3) months for CLL/SLL and 3.5 (range, 0.4-22.4) months for NHL. Among all 53 pts, no drug-related atrial fibrillation or hypertension was reported. Drug-related ≥G3 adverse events (AEs) were reported in 5 pts (9%): neutropenia in 3 pts, ALT/AST increased in 1 pt, hematuria in 1 pt, hematoma on concomitant anticoagulation, anemia, and hemorrhagic shock in 1 pt. Due to drug-related AEs, 2 pts experienced dose interruption/reduction (ALT/AST elevation and fatigue), and 1 pt discontinued (hematoma). In the efficacy evaluable pts, excluding Cohort 3, overall response rate (ORR) was 56% (14/25; 12 partial response [PR] and 2 PR with lymphocytosis) for CLL/SLL, 75% (3/4; 2 complete response and 1 PR) for MCL, 100% (4/4; 4 PR) for WM, 50% (1/2; 1 PR) for MZL, and 0% (0/5) for FL. ORR for CLL/SLL pts assigned to the 400 mg BID dose level was 88% (7/8), including 5 pts double-exposed to cBTKi and BCL2i. The median progression free survival for CLL/SLL, MCL, WM and MZL have not yet been reached. In Cohort 3, the efficacy evaluation remains immature, as 3 of 4 pts have not yet reached the first post-dose assessment point.

Summary/Conclusion

Docirbrutinib demonstrated a favorable safety profile and robust efficacy in pts with CLL/SLL including those double-exposed to cBTKi and BCL2i and showed promising responses in pts with MCL and WM. Updated data will be presented at the annual meeting.