Safety and Efficacy of Pirtobrutinib in Relapsed/Refractory Waldenström Macroglobulinemia: Updated Results from the Phase 1/2 BRUIN Study

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Abstract

Covalent Bruton tyrosine kinase inhibitors (cBTKi) have advanced the treatment of Waldenström macroglobulinemia (WM), but effectiveness is limited by intolerance and resistance. In this multicenter Phase 1/2 BRUIN trial (NCT03740529), we report the safety and efficacy of pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor (BTKi) in patients with relapsed/refractory (R/R) WM, including after prior cBTKi therapy. Adults with previously treated WM were eligible for oral pirtobrutinib monotherapy in phase 1 dose escalation (25-300mg QD) or phase 2 (200mg QD). Key endpoints included investigator-assessed overall response rate (ORR) assessed by International Workshop on WM (IWWM-6) and modified IWWM-6 criteria, progression-free survival (PFS), overall survival (OS), and safety. Data cut-off was 05 May 2023. Of 80 patients included, median age was 69 (range: 42–84) years, 52 (65%) were male, and the median number of prior lines of systemic therapy received was 3 (range, 1–11). Sixty-three (79%) patients had received prior cBTKi treatment and 17 (21%) were cBTKi-naïve. ORR was 80.0% (95% confidence interval [CI], 69.6-88.1), 77.8% (95%CI, 65.5-87.3) in patients with prior cBTKi therapy, and 88.2% (95%CI, 63.6-98.5) for cBTKi-naïve patients. Median PFS overall was 22.1 months (95%CI 16.6–not estimable [NE]). Median OS was not reached. Grade ≥3 treatment-emergent adverse events of hypertension (3.8%), hemorrhage/hematoma (3.8%), and atrial fibrillation/flutter (1.3%) were infrequent. Treatment-related adverse events led to pirtobrutinib discontinuation in 4 (5.0%) and dose reduction in 2 (2.5%) patients. Pirtobrutinib was effective and tolerable in patients with R/R WM, including in those after prior cBTKi therapy.