A phase II study of pirtobrutinib and venetoclax in previously treated patients with Waldenström macroglobulinemia: An interim analysis

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Background: BTK inhibitors and BCL2 antagonists as monotherapy are highly active and well tolerated in Waldenström macroglobulinemia (WM). Non-covalent BTK inhibitors have shown efficacy in WM patients progressing on covalent BTK inhibitors. However, BTK inhibitor therapy has an indefinite duration with cumulative toxicity and risk of developing resistance. We initiated a prospective study evaluating the novel non-covalent BTK inhibitor pirtobrutinib in combination with the BCL2 antagonist venetoclax given as a fixed-duration regimen in previously treated WM.
Methods: This was an investigator-initiated, multicenter, prospective phase II study in symptomatic, previously treated WM patients (ClinicalTrials.gov ID NCT05734495). Study therapy was given in 4-week cycles. Intended therapy consists of pirtobrutinib at 200 mg/day on cycle 1. Venetoclax is added on cycle 2 at 100 mg/day for one week, 200 mg/day for one week, and 400 mg/day for two weeks, followed by pirtobrutinib 200 mg/day and venetoclax 400 mg/day given together for cycles 3-24. Patients undergo baseline laboratory studies, a bone marrow biopsy with *MYD88*, *CXCR4,* and *TP53* genotyping, and CT scans of the chest, abdomen, and pelvis to evaluate extramedullary disease. The outcome of interest was attaining a very good partial response (VGPR) or better. Responses are assessed using modified IWWM6 criteria. Assumptions included H0 15%, H1 35%, 2-sided alpha 0.03, and power 0.85 for a sample size of 42 patients. The null hypothesis will be rejected if 12 or more patients attain a VGPR or better. For this interim analysis, if 3 VGPR or better events or fewer were observed in the first 16 patients, the study should be stopped early because of futility, with a probability of stopping early of 79%.
Results: Between May 2023 and June 2024, 16 (8 males; 8 females) patients have been enrolled. Baseline characteristics include median age 67 (range 57-76 years), median number of previous therapies 1 (range 1-3), previous covalent BTK inhibitor 9 (56%), previous rituximab-containing regimens 11 (69%), median serum IgM 2,401 (range 551-7,249 mg/dL), median hemoglobin 8.6 (range 6.6-11.5 g/dL), median bone marrow involvement 80% (20-90%), lymphadenopathy (>1.5 cm) 7 (44%), and splenomegaly (>15 cm) 2 (13%). *MYD88 L265P* was detected in 14 patients (88%), *CXCR4* mutations in 6 (38%), and *TP53* mutations in 1 (6%). The median study follow-up is 6 months (range 3-12). VGPR was attained in 9 patients (56%), partial response in 5 (31%), and minor response in 2 (13%), for an overall response rate of 100%. No complete responses were observed. *CXCR4* mutations (33% v 70%; p=0.35) and previous exposure to covalent BTK inhibitors (33% v 86%; p=0.05) might be associated with lower VGPR rates. The median time to VGPR was 1.9 months (95% CI 0.9-2.2). *CXCR4* mutations (p=0.32) and previous exposure to covalent BTK inhibitors (p=0.50) did not seem to impact time to VGPR. At best response, median serum IgM decreased to 254 (range 35-3786 mg/dl; p<0.001), median hemoglobin increased to 12.1 (range 8.2-16.2 g/dl); p<0.001), and median bone marrow involvement decreased to 0% (range 0-40%; p<0.001) when compared to baseline. Of the seven patients with lymphadenopathy, 5 (71%) had improvement or resolution, and of the two patients with splenomegaly, 2 (100%) had improvement

or resolution. Two patients had disease progression at two and five months; both had *MYD88 WT* disease. The 6-month progression-free survival rate is 84% (95% CI 49-96%), and the 6-month overall survival rate is 93% (95% CI 61-99). There have been no arrhythmia events thus far.
Conclusion: The combination of pirtobrutinib and venetoclax appears active in symptomatic, previously treated WM patients with a VGPR rate of 56%, exceeding the futility rate. *CXCR4* mutations and previous exposure to covalent BTK inhibitors might impact VGPR rates. Accrual will continue to enroll 26 additional patients.