Two-year follow-up after ibrutinib and venetoclax in symptomatic, treatment-naive patients with Waldenström macroglobulinemia

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Background: BTK inhibitors and BCL2 antagonists as monotherapy are highly active and well tolerated in Waldenström macroglobulinemia (WM). We initiated a prospective study evaluating ibrutinib and venetoclax in treatment-naive WM. Study therapy was stopped on March 31, 2022, after four ventricular arrhythmia events, including two grade 5 events as previously reported. Herein, we present follow-up data 2 years after stopping therapy to assess the response durability of the combination in WM.

Methods: This was an investigator-initiated, multicenter, prospective phase II study in symptomatic treatment-naïve WM patients (ClinicalTrials.gov ID NCT04273139). Study therapy was given in 4-week cycles. Intended therapy consisted of ibrutinib at 420 mg/day on cycle 1. Venetoclax was 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 ibrutinib 420 mg/day and venetoclax 400 mg/day given together for cycles 3-24. All patients underwent baseline laboratory studies, a bone marrow aspiration and biopsy with *MYD88* and *CXCR4* genotyping, and CT scans of the chest, abdomen, and pelvis with intravenous contrast to evaluate extramedullary disease. Responses were assessed using modified IWWM6 criteria.

Results: Between July 2020 and January 2022, 45 (30 males and 15 females) patients were enrolled. Baseline characteristics were median age 67 (range 40-82 years), median serum IgM 4297 (range 572-9211 mg/dL), median hemoglobin 10.2 (range 7.8-15.3 g/dL), median bone marrow involvement 60% (5-90%), lymphadenopathy (>1.5 cm) 25 (56%), and splenomegaly (>15 cm) 13 (29%). *MYD88 L265P* was detected in all patients, and *CXCR4* mutations were detected in 17 patients (38%; 10 nonsense, and 7 frameshift). The median time on treatment was 10.2 months (range 1.9-20.8) before treatment was halted. No patient completed the 24 planned treatment cycles. Three patients discontinued therapy before study therapy was stopped: one because of grade 4 ventricular arrhythmia, one because of an intracranial bleed possibly related to study therapy in a patient with a previously unknown benign brain lesion, and one because of transformation to DLBCL. Very good partial response (VGPR) was attained in 19 patients (42%), partial response in 24 (53%), and minor response in 2 (4%), for an overall response rate of 100%. *CXCR4* mutations were associated with numerically lower VGPR rates (29% v 50%; p=0.18).

The median study follow-up was 36 months (range 34-39). There were 23 (51%) progression events, two treatment-emergent deaths three and four months into study therapy, and one death of unknown cause two years after stopping study therapy. Six patients (13%) started a new treatment. At 36 months, the progression-free survival (PFS) rate was 51% (95% CI 35-65), the therapy-free survival (TFS) rate was 88% (95% CI 74-95), and the overall survival (OS) rate was 93% (95% CI 79-98). *CXCR4* mutations did not impact PFS (p=0.86), TFS (p=0.49), or OS (p=0.20). The median time after end of therapy (EOT) was 26 months (95% CI 25-27). There were 20 progression events after EOT, and the 24-month PFS rate after EOT was 56% (95% CI 40-69). *CXCR4* mutations (p=0.70), time

on therapy ≥12 months (p=0.47), and VGPR attainment at EOT (p=0.62) did not impact PFS after EOT. No treatment-emergent events, especially arrhythmia, were observed after treatment stopped. Twenty-two patients (49%) underwent a bone marrow biopsy two years after EOT. No emergent mutations in *BTK* were detected. Mutations in *BCL2* will be assessed at a later time.

Conclusion: Despite early treatment truncation due to unexpected ventricular arrhythmia, the combination of ibrutinib and venetoclax was active in symptomatic, treatment-naive WM patients and is associated with durable responses after stopping therapy. *CXCR4* mutations, time on study treatment, or VGPR attainment did not impact PFS after EOT. No treatment-emergent toxicities occurred after EOT, including arrhythmia or the emergence of *BTK* mutations.