Combination treatment with novel BCL-2 inhibitor sonrotoclax (BGB-11417) and zanubrutinib induces high rate of complete remission for patients with relapsed/refractory mantle cell lymphoma

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ABSTRACT

Objectives: Mantle cell lymphoma (MCL) is an aggressive and rare B-cell non-Hodgkin lymphoma subtype. Despite advanced treatment, most patients experience relapsed/refractory (R/R) disease and require novel therapies to improve clinical outcomes. The combination of BCL2 and Bruton tyrosine kinase (BTK) inhibition with venetoclax + ibrutinib has shown efficacy in patients with R/R MCL. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax. Zanubrutinib, a next-generation BTK inhibitor, has shown improved PFS and OS and is approved for R/R MCL. Here, safety and efficacy data for patients with R/R MCL treated with sonrotoclax + zanubrutinib in the ongoing BGB-11417-101 (NCT04277637) study are reported.

Methods: Patients with R/R MCL (≥1 prior therapy) received zanubrutinib (standard dose: 320 mg QD or 160 mg BID) 8-12 weeks before starting sonrotoclax in a dose escalation cohort (target sonrotoclax doses: 80, 160, 320, or 640 mg QD) according to a ramp-up schedule designed to mitigate potential risk of tumor lysis syndrome (TLS). This was followed by 2 sonrotoclax expansion cohorts at 160 mg and 320 mg. Patients were treated until progression or unacceptable toxicity. The primary endpoint was safety (treatment-emergent adverse events [TEAEs] reported per CTCAEs v5.0), and a secondary endpoint was ORR (per Lugano 2014 criteria). TLS was assessed per Howard 2011 criteria.

Results: As of October 31, 2023, 35 patients with R/R MCL were enrolled across different cohorts (80 mg, n=6; 160 mg, n=12; 320 mg, n=14; 640 mg, n=3). The median age was 68 years (range, 45-85 years), and 23 patients (66%) were men. The median number of prior treatments was 1 (range, 1-3), 11/35 patients (31%) had a prior autologous stem cell transplant, and 3 patients were previously treated with a BTK inhibitor. Dose escalation occurred per protocol at all defined doses. The maximum tolerated dose was not reached with a maximum assessed dose of 640 mg. No DLTs occurred and the sonrotoclax 160 mg and 320 mg dose levels were chosen for expansion cohorts. Three patients were still in the zanubrutinib lead-in phase and 29 had started sonrotoclax. Nine patients discontinued from study

treatment. Six patients discontinued both study drugs (progressive disease [PD], n=3; AE, n=2 [MDS and diarrhea]; patient withdrawal, n=1). Three patients did not complete the zanubrutinib lead-in phase due to early progression (PD). Five patients died due to PD (including 3 during zanubrutinib lead-in). TEAEs occurring in ≥20% patients who received sonrotoclax + zanubrutinib were neutropenia (31%), contusion (29%), thrombocytopenia (23%), and diarrhea (23%). Neutropenia was the most common grade ≥3 TEAE (20%). No cases of laboratory or clinical TLS occurred and no cases of atrial or ventricular fibrillation were reported. For 27 response-evaluable patients, the ORR was 85%, which included 18 complete responses (CRs; 67%). For response-evaluable patients in dose-expansion cohorts, the CR rate and ORR, respectively, was 91% (10/11) and 91% (10/11) in the 320 mg cohort, and 44% (4/9) and 88% (8/9) in 160 mg cohort. The median time to CR was 6.4 months. Among 2 response-evaluable patients with previous progression on a BTK inhibitor, 1 CR and 1 PD was observed.

Conclusions: Sonrotoclax in combination with zanubrutinib is generally well tolerated and has demonstrated promising efficacy in R/R MCL, including deep and durable responses. Further expansion of the 320 mg cohort is currently ongoing.