Safety and efficacy results of a phase 1 study of the novel BCL2 inhibitor sonrotoclax (BGB-11417) for relapsed/refractory Waldenström macroglobulinemia

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ABSTRACT

Introduction: Sonrotoclax (BGB-11417), a novel BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax. Updated safety and efficacy of sonrotoclax in patients with relapsed/refractory (R/R) Waldenström's macroglobulinemia (WM) from the BGB-11417-101 (NCT04277637) study are presented.

Methods: Patients with R/R WM (≥1 prior therapy) received sonrotoclax (planned dose escalation: 80, 160, 320, or 640 mg QD) with dose ramp-up to mitigate tumor lysis syndrome (TLS) risk. The primary endpoint was safety per CTCAE v5.0. The secondary endpoint was ORR (minor response [MR] or better per modified Owens 2013 criteria). TLS was assessed per Howard 2011 criteria.

Results: As of Oct 31, 2023, 17 patients with R/R WM were enrolled (80 mg, n=6; 160 mg, n=8; 320 mg, n=3). Patients had a median age of 68 years (range, 48-87 years) and a median of 2 (range, 2-9) prior treatments. Ten patients had a prior BTK inhibitor (noncovalent, n=1; covalent, n=9) and 14 had prior anti-CD20. Median follow-up was 10.6 (range, 1-24) months. Six patients discontinued treatment (progressive disease [PD], n=4; AEs, n=2 [multifocal neurological syndrome and COVID-19, neither were considered related to sonrotoclax by the investigator]), and 4 patients died on study (PD, n=2; COVID-19 pneumonia, n=1; pneumonia, n=1). TEAEs occurring in ≥20% of patients were anemia (n=6; 35%), COVID-19 (n=6; 35%), pyrexia (n=5; 29%), neutropenia (n=4; 24%), and pruritus (n=4; 24%). Anemia was the most common grade ≥3 TEAE (n=4; 24%). One patient in the 160-mg dose group experienced a DLT of grade 3 febrile neutropenia, which resolved after 2 days without dose reducing during ramp-up (day 2, 10 mg sonrotoclax). No TLS occurred up to the highest dose tested (320 mg). No atrial or ventricular fibrillation occurred. No deaths or AEs leading to treatment discontinuation were determined by the investigator to be treatment related. In 17 response-evaluable patients, across dose levels, overall, major, and very good partial response (VGPR) rates were 76% (13/17), 41% (7/17), and 12% (2/17), respectively (**Figure**). In 7 patients who had a BTK inhibitor as their last treatment, the ORR was 70% (MR, n=2; PR, n=1; VGPR, n=2). In the 320-mg cohort, the median follow-up was 3.3 (range, 1-5) months and ORR was 100% (n=3), with 1 VGPR.

Conclusions: Sonrotoclax monotherapy was well tolerated and had encouraging preliminary antitumor activity in this heavily pretreated R/R WM population. Based on these findings, further evaluation of sonrotoclax monotherapy in patients with R/R WM is ongoing in a potentially pivotal phase 2 study.