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

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Background: BCL2, a key regulator of apoptosis, is overexpressed in many hematologic malignancies, including Waldenström's macroglobulinemia (WM), and plays a significant role in cell survival. In previous studies, the BCL2 inhibitor venetoclax demonstrated antitumor activity in patients with WM (Castillo 2022), but it is not approved for the treatment of this disease. Therefore, a need remains for development of BCL2 inhibitors for treatment of patients with WM whose disease progresses on standard treatments. Sonrotoclax (BGB-11417), a novel BCL2 inhibitor, is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax. Sonrotoclax monotherapy is being studied in dose escalation in the ongoing BGB-11417-101 (NCT04277637) study in B-cell malignancies.

Aims: To report updated safety and efficacy data for patients with relapsed/refractory (R/R) WM treated with sonrotoclax in BGB-11417-101.

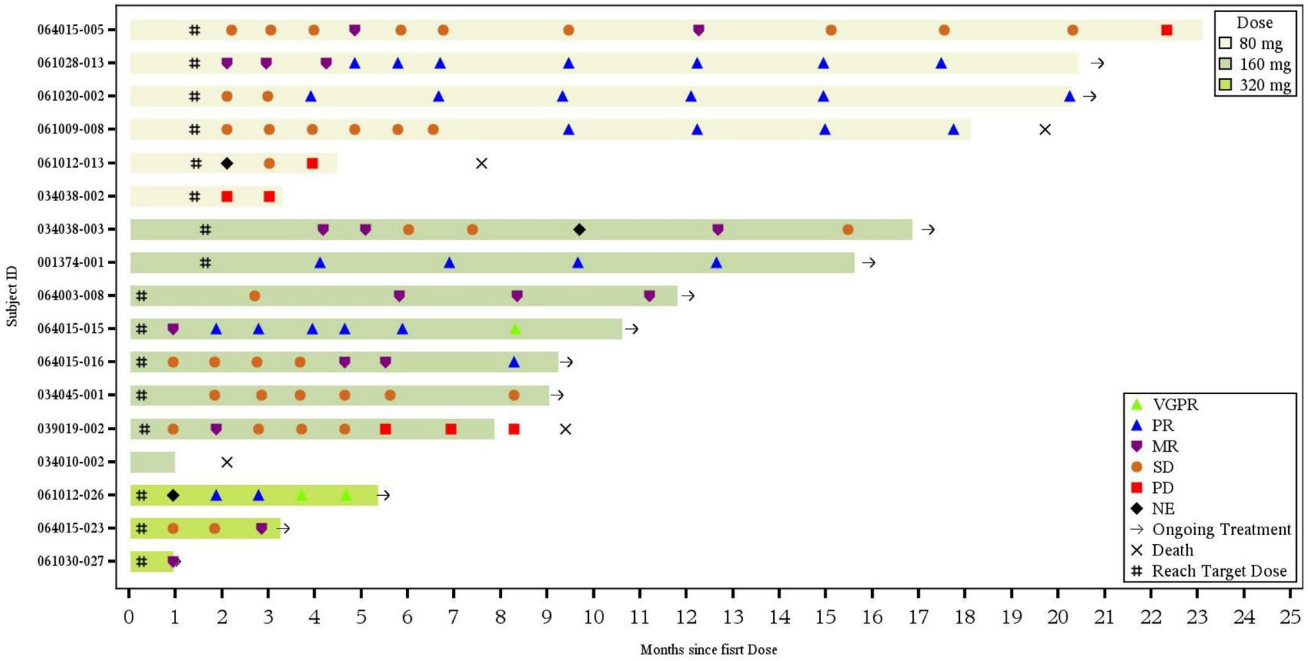
Methods: Patients with R/R WM (≥1 prior therapy) received sonrotoclax (planned dose escalation: 80, 160, 320, or 640 mg QD) with a ramp-up schedule to the intended dose to

mitigate potential risk of tumor lysis syndrome (TLS). Patients were treated until progression or unacceptable toxicity. The primary endpoint is safety reported per CTCAE v5.0 and the secondary endpoint is ORR (minor response [MR] or better per Modified Owens 2013 criteria). TLS was assessed per Howard 2011 criteria.

Results: As of Oct 31, 2023, a total of 17 patients with R/R WM have been enrolled in 3 dose-escalation cohorts (80 mg, n=6; 160 mg, n=8; 320 mg, n=3); none were enrolled in the 640–mg cohort as of the cutoff date). Overall, the median age (range) was 68 (48-87) years. The median number of prior treatments (range) was 2 (1-9); 10 patients were previously treated with a BTK inhibitor (1 noncovalent, 9 covalent) and 14 were previously treated with anti-CD20. Median follow-up (range) was 10.6 (1-24) months. Six patients discontinued treatment: 4 due to progressive disease (PD) and 2 due to adverse events (AEs; multifocal neurological syndrome and COVID-19). Four patients died while on study: 2 due to PD, 1 due to COVID-19 pneumonia, and 1 due to pneumonia. Treatment-emergent AEs (TEAEs) that occurred in ≥20% of patients who received sonrotoclax 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%). No DLTs or cases of TLS occurred up to the highest dose tested (320 mg). No cases of atrial or ventricular fibrillation were reported. No deaths or AEs leading to discontinuation of therapy were determined to be related to study treatment by the investigator. All 17 patients were evaluable for response assessments. The overall, major, and very good partial response (VGPR) rates were 76% (13/17), 41% (7/17), and 12% (2/17), respectively (Figure). Seven patients had a BTK inhibitor as their last therapy and achieved an ORR of 70% (MR, n=2; PR, n=1; VGPR, n=2). For all patients in the 320–mg cohort, the median follow-up (range) was 3.3 (1-5) months and the ORR was 100% (n=3), with 1 VGPR.

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

Figure. Treatment responses and duration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Dose
80 mg
160 mg
320 mg
VGPR
PR
MR
SD
PD
NE
Ongoing Treatment
Death
Reach Target Dose
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Months since fisrt Dose