UPDATED 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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Background: BCL2 is overexpressed in many hematologic malignancies, including Waldenström macroglobulinemia (WM). Venetoclax, the first-generation BCL2 inhibitor, has antitumor activity in patients with WM, but it is not approved for the treatment of this disease. A need remains for development of BCL2 inhibitors for treatment of patients with WM whose disease progresses on standard treatments. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Sonrotoclax monotherapy is being studied in the dose-escalation portion of the ongoing BGB-11417-101 (NCT04277637) study in B-cell malignancies.

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

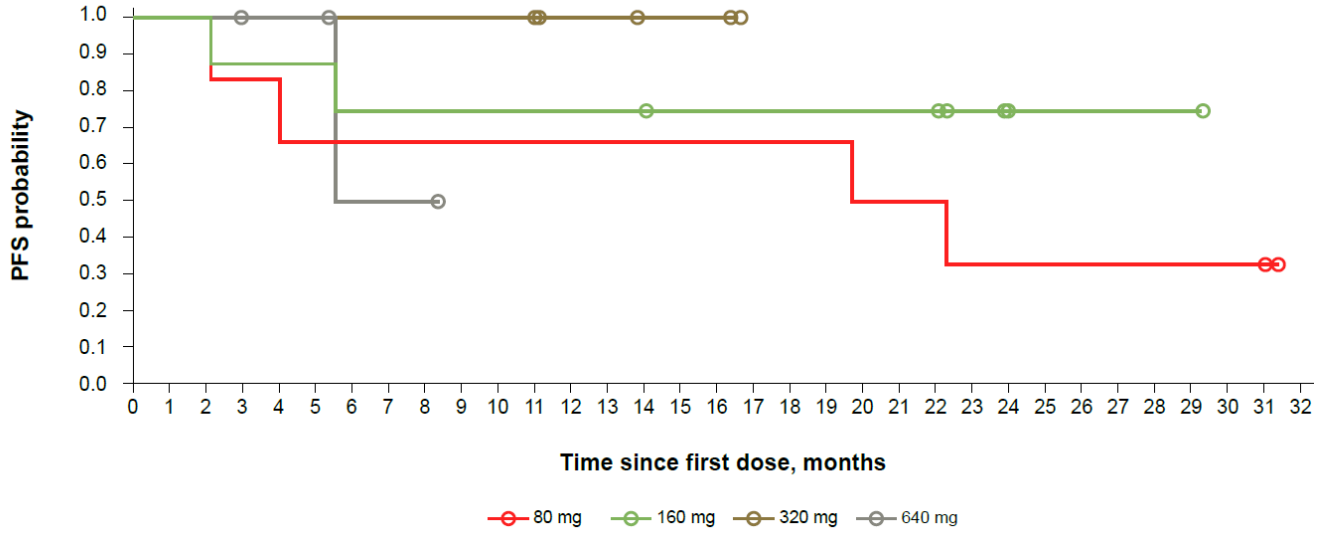
Methods: Patients with R/R WM (≥1 prior therapy) received sonrotoclax (80, 160, 320, or 640 mg QD) with a ramp-up schedule to the intended dose to mitigate potential risk of tumor lysis syndrome (TLS). Patients were treated until progression or unacceptable toxicity. The

primary endpoint is safety reported per CTCAE v5.0 and the secondary endpoint is overall response rate (ORR; minor response [MR] or better per modified Owens 2013 criteria). TLS was assessed per Howard 2011 criteria.

Results: As of December 6, 2024, a total of 23 patients with R/R WM were enrolled in 4 dose-escalation cohorts (80 mg, n=6; 160 mg, n=8; 320 mg, n=5; 640 mg, n=4). Median age was 69 years (range, 48-87 years). The median number of prior treatments was 3 (range, 1-9); 14 patients were previously treated with a BTK inhibitor (noncovalent, n=1; covalent, n=13) and 22 were previously treated with anti-CD20. Median follow-up was 18.6 months (range, 2.1-37.2 months). Nine patients discontinued treatment: 6 due to progressive disease (PD) and 3 due to treatment-emergent adverse events (TEAEs; multifocal neurological syndrome, COVID-19 pneumonia, and hemolysis [treatment-related]). Six patients died while on study due to PD (n=4), COVID-19 pneumonia (n=1), and pneumonia (n=1); no deaths were related to study treatment. TEAEs that occurred in ≥20% of patients who received sonrotoclax were anemia (n=8; 34.8%), COVID-19 (n=8; 34.8%), and neutropenia, nausea, and pyrexia (n=5; 21.7% each). Anemia was the most common grade ≥3 TEAE (n=5; 21.7%). No cases of TLS occurred up to the highest dose tested (640 mg). No cases of atrial or ventricular fibrillation were reported. In 23 patients, the overall, major, and very good partial response (VGPR) rates were 78.3% (18/23), 60.9% (14/23), and 13.0% (3/23), respectively. With a median follow-up of 22.1 months (range, 11.2-24.0), median progression-free survival was not reached (95% CI, 19.7-NE) (**Figure**). Nine patients had a BTK inhibitor as their last therapy and achieved an ORR of 66.7% (MR, n=1; PR, n=4; VGPR, n=1). In the 320 mg cohort, with a median follow up of 14.2 months (range, 12.8-18.6 months), all patients responded and had a major response rate of 80%, including 1 VGPR.

Summary/Conclusion: Sonrotoclax monotherapy has encouraging antitumor activity, with ORRs of 78.3% across dose levels and 100% at sonrotoclax RP2D (320 mg) in heavily pre-treated patients with R/R WM and has demonstrated a tolerable safety profile across all dose levels tested. Based on the 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. PFS in Patients with WM Treated With Sonrotoclax Monotherapy



No. at risk:

80 mg	6	6	6	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	3	3	3	2	2	2	2	2	2	2	2	0
160 mg	8	8	8	7	7	7	6	6	6	6	6	6	6	6	6	5	5	5	5	5	5	5	5	3	2	1	1	1	1	1	0	0	0
320 mg	5	5	5	5	5	5	5	5	5	5	5	5	3	3	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
640 mg	4	4	4	3	3	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

PFS, progression-free survival; WM, Waldenström macroglobulinemia.