Monotherapy With Second-Generation BCL2 Inhibitor Sonrotoclax (BGB-11417) Is Well Tolerated with High Response Rates in Patients with Relapsed/Refractory Marginal Zone Lymphoma: Data from an Ongoing Phase 1 Study

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ABSTRACT

Background: Marginal zone lymphoma (MZL) is an uncommon type of non-Hodgkin lymphoma (NHL) that is generally considered incurable, with most patients experiencing a relapse after remission. Development of novel MZL therapies that are effective and tolerable is needed. Sonrotoclax (BGB-11417) is a next-generation BH3 mimetic which binds and inhibits BCL2 with a potency >10x that of venetoclax in biochemical assays.

BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation and dose-expansion study looking at a wide array of B-cell malignancies. Previous interim analyses indicate sonrotoclax is well tolerated as monotherapy at all doses tested, up to 640 mg once daily (QD). This analysis investigated the safety, tolerability, and efficacy of sonrotoclax in patients with relapsed/refractory (R/R) MZL.

Methods: Patients with R/R MZL received sonrotoclax (dose escalation: 40, 80, 160, 320, or 640 mg QD) with a 3-day ramp-up to the intended dose, followed by expansions at 640 mg and 320 mg. Dose-limiting toxicity (DLT), predefined in the protocol for each dose cohort, was evaluated during dose ramp-up through day 21 at the intended dose. The primary objective was to determine the safety and tolerability of sonrotoclax; a secondary objective for the expansion phase was to evaluate the activity of BGB-11417 as measured by the overall response rate (ORR, defined as partial response [PR] or better). Responses were assessed per Lugano criteria 2014. Adverse events (AEs) were reported per CTCAE v5.0 and tumor lysis syndrome (TLS) was assessed per Howard (2011) criteria.

Results: As of April 24, 2023, 13 patients with MZL had received sonrotoclax across dose-escalation and -expansion cohorts (n=1, 40 mg; n=2, 160 mg; n=10, 640 mg). Overall, median age was 73 years (range: 54-85) and the median number of prior treatments was 1 (range: 1-3). Four patients progressed on Bruton tyrosine kinase inhibitors (BTKi), of which three had BTKi as last prior therapy.

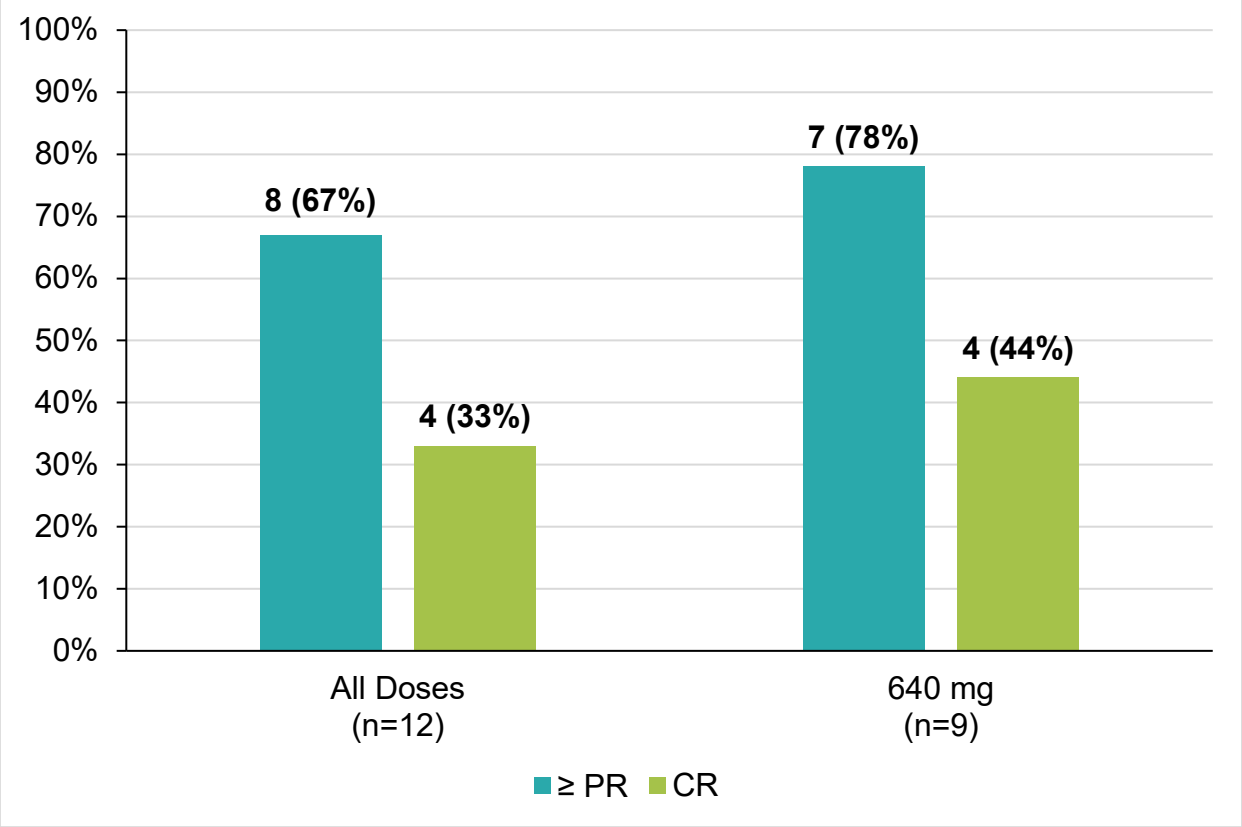
Dose escalation occurred per protocol at all defined doses. The maximum tolerated dose was not achieved with a maximum assessed dose of 640 mg; one DLT of febrile neutropenia was observed in the 160 mg cohort. Dose expansion was completed with the recommended phase 2 dose of 640 mg. Median follow-up was 7.8 months (range, 2.6-36.6 months).

Treatment-emergent AEs (TEAEs) occurring in ≥20% of patients were nausea (39%) and pyrexia, diarrhea, and constipation (31% each). The most common grade ≥3 TEAEs were neutropenia, febrile neutropenia/neutropenic sepsis, and TLS (n=2 [15%] each). Five patients discontinued treatment (n=3, progressive disease; n=1, AE [infection]; n=1, withdrawal). No TEAEs leading to death occurred. Two patients in the 640-mg cohort experienced laboratory TLS following the initial ramp-up dose. The first patient (baseline: nodes, 60 mm; spleen, 21 cm; white blood cells [WBC], 46.9 × 10^9/L) had laboratory TLS (elevated potassium, phosphate, and urate) after a 160 mg dose, which resolved within 24 hours with intravenous hydration and supportive care without sequela or dose modification. Following a protocol amendment, patients with circulating tumor cells received an additional 3-day ramp-up starting at 40 mg. A second patient (baseline: nodes, 28 mm; spleen, 20 cm; WBC, 352 × 10^9/L) had laboratory TLS (elevated phosphate and urate) after initial 40- and 80-mg doses. Both episodes resolved within 24 hours without sequela or change in dosing.

Overall, 12 patients were assessable for response; ORR was 67% (n=8), including four patients (33%) with complete response (CR). Nine of the 10 patients treated at 640 mg were assessable for response, where the ORR was 78% (n=7), including four patients (44%) who achieved a CR (Figure). Responses of PR or better were observed in all four patients with previous progression on BTKi (n=3, CR; n=1, PR).

Conclusions: These data confirm sonrotoclax monotherapy had a tolerable safety profile across all doses tested and encouraging antitumor activity in patients with MZL. Two patients had laboratory TLS following the initial doses that resolved. No clinical TLS were observed, indicating that TLS can be mitigated with current measures, including revised ramp-up. An exploratory 320-mg cohort is currently enrolling.

Figure: Overall Response Rates by Lugano Criteria in Patients With R/R MZL Treated With Sonrotoclax Monotherapy



CR, complete response; MZL, marginal zone lymphoma; PR, partial response; R/R, relapsed/refractory.