Monotherapy with second-generation BCL2 inhibitor sonrotoclax (BGB-11417) is well tolerated, with high response rates in relapsed/refractory (R/R) marginal zone lymphoma (MZL): Data from an ongoing phase 1 study

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ABSTRACT

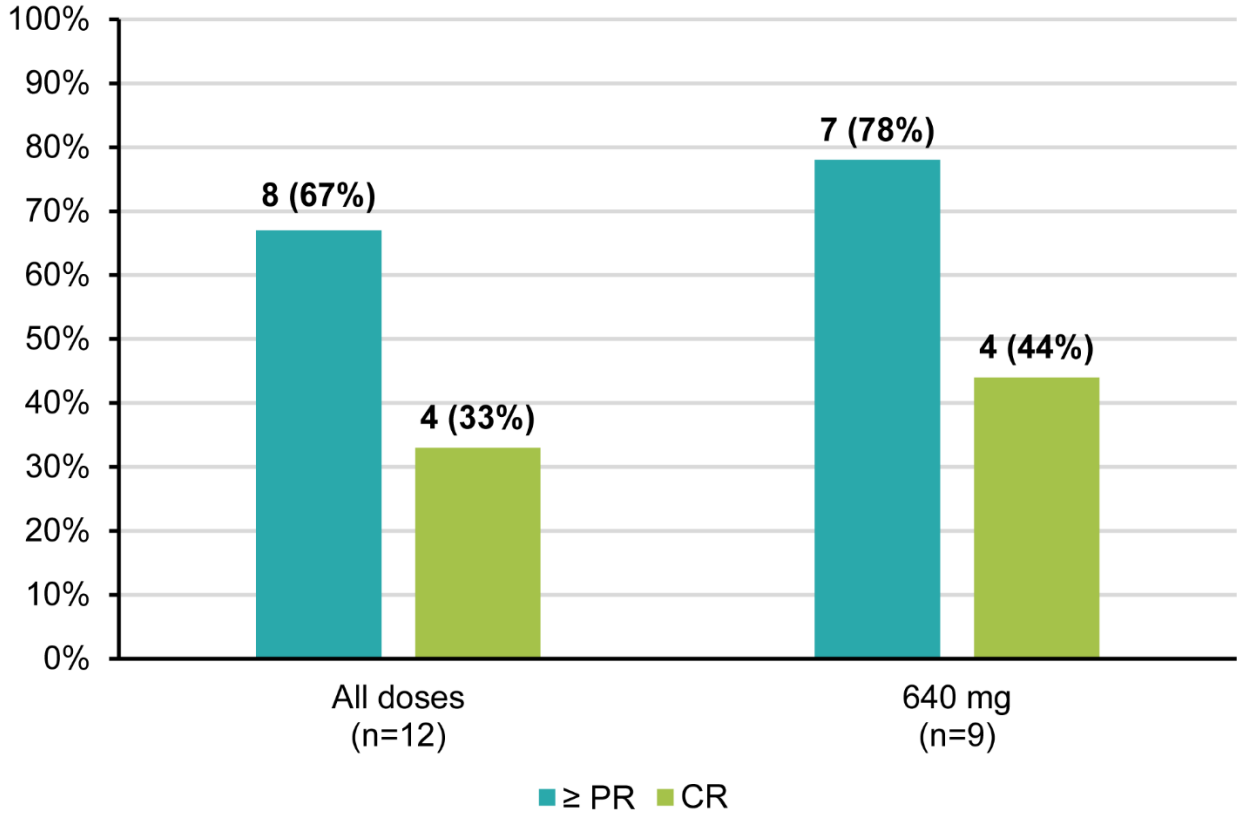
Background: Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and potent inhibitor of BCL2 than venetoclax in biochemical assays. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study in pts with B-cell malignancies. Presented here are safety and efficacy data for sonrotoclax in pts with R/R MZL.

Methods: Pts received sonrotoclax (dose escalation: 40, 80, 160, 320, or 640 mg QD) with a 3-day dose ramp-up. Expansions at 640 and 320 mg followed. DLTs were evaluated from ramp-up through day 21 at the intended dose. The primary endpoint was safety per CTCAE v5.0; a secondary endpoint for dose-expansion was ORR (defined as partial response [PR] or better) per Lugano 2014 criteria. TLS was assessed per Howard 2011 criteria.

Results: As of April 24, 2023, 13 pts with MZL had received sonrotoclax across the dose-escalation and -expansion cohorts (40 mg, n=1; 160mg, n=2; 640 mg, n=10). Overall, median age was 73 years (range, 54-85); the median number of prior tx was 1 (range, 1-3). Four pts progressed on BTK inhibitors (BTKi); 3 had BTKi as their last therapy. Dose escalation occurred per protocol at all defined doses. MTD was not reached up to 640 mg. One DLT of febrile neutropenia was observed at 160 mg. Expansion was completed with the recommended phase 2 dose of 640 mg. Median follow-up was 7.8 mo (range, 2.6-36.6). TEAEs occurring in ≥20% of pts 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 pts discontinued tx (progression, n=3; AE [infection], n=1; withdrawal, n=1). No TEAEs led to death. Two pts in the 640-mg cohort had laboratory TLS after initial ramp-up doses: 1 after 160 mg and 1 after initial doses of 40 and 80 mg. All TLS events resolved within 24 hrs without sequela or dose change. Of 12 response-evaluable pts, the ORR was 67%, including 4 CRs (33%). Of 9 response-evaluable pts treated at 640 mg, the ORR was 78%, including 4 CRs (44%; Figure). Responses were observed in all 4 pts with prior progression on BTKi (CR, n=3; PR, n=1).

Conclusions: Sonrotoclax monotherapy had a tolerable safety profile and encouraging antitumor activity across tested doses in pts with MZL. Two pts had laboratory TLS following initial doses that resolved. No clinical TLS was observed. 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.