Sonrotoclax (BGB-11417) monotherapy in patients with relapsed/refractory marginal zone lymphoma: an ongoing phase 1 study

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ABSTRACT

Background: Sonrotoclax (BGB-11417) inhibits BCL2 with a potency >10x that of venetoclax in biochemical assays. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/2 dose-escalation/expansion in patients with B-cell malignancies. Data are presented for the relapsed/refractory marginal zone lymphoma (MZL) cohort.

Methods: Patients received one of the following sonrotoclax target doses: 40mg/80mg/160mg/320mg/640mg QD; a 3-day ramp-up was used; expansions at 640mg and 320mg followed. Dose-limiting toxicities (DLTs) at the intended dose were evaluated. The primary endpoint was safety; a secondary endpoint for expansion was ORR. Responses were assessed per Lugano 2014 criteria. Tumor lysis syndrome (TLS) was assessed per Howard (2011) criteria.

Results: As of 24Apr2023, 13 patients received sonrotoclax across groups (40mg, n=1; 160mg, n=2; 640mg, n=10). Of 4 patients with progression on Bruton tyrosine kinase inhibitors (BTKi), 3 had BTKi as last prior therapy. The maximum tolerated dose was not achieved with doses ≤640mg. One DLT occurred (febrile neutropenia, 160mg group) which resolved after 2 days without dose modification. The recommended phase 2 dose after dose expansion was 640mg. Median follow-up was 7.8 months (range, 2.6-36.6). Treatment-emergent AEs (TEAEs) in ≥20% of patients were nausea (39%) and pyrexia, diarrhea, and constipation (31% each). Most common grade ≥3 TEAEs were neutropenia, febrile neutropenia/neutropenic sepsis, and TLS (15% each). Five patients discontinued treatment (n=3, progressive disease; n=1, AE [infection]; n=1, withdrawal); no TEAEs led to death. Two patients (640mg group) experienced laboratory TLS following the initial ramp-up dose. The first patient had elevated potassium, phosphate, and urate after a 160mg dose, which resolved within 24 hours with intravenous hydration and supportive care without sequela or dose modification. After protocol amendment, patients with circulating tumor cells received an additional 3-day ramp-up starting at 40mg. A second patient had elevated phosphate and urate after initial 40mg and 80mg doses. Both episodes resolved within 24 hours without sequela or dosing change. In 12 assessed patients, the ORR was 67% (n=8), including 4 (33%) CR. Nine evaluable patients treated at 640mg had an ORR of 78% (n=7), including 4 (44%) CR. All patients with previous progression on BTKi had CR (n=3) or PR (n=1).

Conclusions: Sonrotoclax monotherapy was tolerable across tested doses and had encouraging antitumor activity in patients with MZL. Two patients had laboratory TLS following initial dosing that

resolved. No clinical TLS was observed, indicating that TLS can be mitigated with current measures, including revised ramp-up. An exploratory 320mg group is currently enrolling.