

Sonrotoclax (BGB-11417) monotherapy in patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) previously treated with a Bruton tyrosine kinase (BTK) inhibitor: Early results from a phase 1/2 study

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Introduction: MCL is a rare, incurable subtype of B-cell non-Hodgkin lymphoma characterized by a continuous pattern of relapse after initial therapy. While BTK inhibitors are standard of care treatments for R/R MCL and are effective in first line, the population of patients with BTK inhibitor resistance is growing and optimal treatment regimens for patients with disease progression after BTK inhibitors who are ineligible for chimeric antigen receptor-T cell therapy are unknown. Sonrotoclax (BGB-11417), a next-generation B-cell lymphoma 2 (BCL2) inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Here, initial phase 1/2 safety and efficacy data are presented for patients with R/R MCL with previous BTK inhibitor exposure and treated with sonrotoclax monotherapy.

Methods: BGB-11417-201 (NCT05471843) is an ongoing multicenter, open-label, dose-escalation/expansion study. Eligible adult patients have histologically confirmed MCL per WHO 2016 classification and measurable disease. Patients must have received prior anti-CD20–based therapy and ≥ 1 BTK inhibitor. In the part 1 dose-escalation and safety expansion, sonrotoclax was orally administered once daily with ramp-up to the target doses of 160 mg and 320 mg. The part 2 efficacy expansion used sonrotoclax at the recommended phase 2 dose (RP2D) and implemented a simplified ramp-up schedule. The primary endpoints were dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs) and tumor lysis syndrome (TLS) for part 1, and independent review committee (IRC)-assessed overall response rate (ORR; partial response or better) per 2014 Lugano classification for part 2.

Results: As of February 4, 2025, a total of 125 patients were enrolled to receive either sonrotoclax 160 mg (n=10) or 320 mg (part 1, n=12; part 2, n=103). No DLTs were observed in part 1; sonrotoclax 320 mg was chosen as the RP2D based on safety and efficacy evaluation. Results are reported for the 320-mg group. Median study follow-up was 10.1 months (range, 0.1-23.3 months). At the data cutoff date, 31.3% of patients (n=36) remained on treatment. Median age was 68 years (range, 39-85 years), 75.7% of patients (n=87) were male, and 40.0% (n=46) had bulky disease (longest diameter \geq 5 cm). At study entry, 87.8% of patients (n=101) had stage III/IV MCL, 69.6% (n=80) had an intermediate or high MCL International Prognostic Index, 53.0% (n=61) had Ki67 \geq 30%, and 50.4% (n=58) had bone marrow involvement. The median number of prior lines of therapy was 3 (range, 1-8), and 68.7% (n=79) discontinued their last line of therapy due to progressive disease. Eighteen patients (15.7%) received \geq 2 prior BTK inhibitors.

In 103 efficacy-evaluable patients of part 2 in the 320-mg group, the ORR by IRC was 53.4% (n=55; ORR by INV, 48.5% [n=50]) and complete response (CR) rate by IRC was 14.6% (n=15; CR rate by INV, 17.5% [n=18]). Median time to response by both IRC and INV was 1.9 months (range, 1.6-6.5 months). Median duration of response (DOR) was 15.8 months both by IRC (95% CI, 7.2 months-NE) and INV (95% CI, 7.4 months-NE) with median follow-up (mFU) of 7.4 and 9.3 months, respectively. The median progression-free survival was 6.5 months by IRC (95% CI, 4.0-9.1 months; mFU, 9.0 months) and 6.3 months by INV (95% CI, 3.7-9.1 months; mFU, 11.8 months). Median overall survival was not reached.

In the 320-mg group (n=115), TEAEs of any grade occurring in \geq 20% of patients were hematologic toxicities. The most common grade \geq 3 TEAE was neutropenia (grouped term, 19.1%). Overall, 36.5% of patients (n=42) had a serious TEAE; the most common was pneumonia (7.0%). TEAEs led to treatment discontinuation in 16 patients (13.9%) and death in 15 patients (13.0%). Overall, 42 deaths (36.5%) occurred, most due to disease progression (n=29). Clinical TLS occurred in 2 patients (1.7%) and laboratory TLS in 6 (5.2%). All recovered without sequelae.

Conclusions: Preliminary results indicate that once daily sonrotoclax 320 mg monotherapy is well tolerated in patients with R/R MCL previously treated with a BTK inhibitor. Clinically meaningful benefits, including median DOR of 15.8 months, were seen in patients with high unmet needs and advanced, aggressive disease. These results support sonrotoclax as a promising treatment option for patients with R/R MCL.