Preliminary safety and antileukemic activity of sonrotoclax (BGB-11417), a potent and selective BCL2 inhibitor, in patients with relapsed/refractory acute myeloid leukemia

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ABSTRACT

Objectives: B-cell lymphoma 2 (BCL2), a key regulator of apoptosis, is overexpressed in many hematologic malignancies. Although treatment with the BCL2 inhibitor venetoclax has improved outcomes in some patients with newly diagnosed acute myeloid leukemia (AML), it is not approved in relapsed/refractory (R/R) AML. Historically, available salvage regimens for R/R AML have produced CR/CRh rates of 5%-35% and overall survival of 3-9 months, depending on the regimen and the presence/absence of targetable mutations. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 vs venetoclax. Presented here are preliminary safety and antileukemic activity of sonrotoclax + azacitidine in patients with R/R AML in BGB-11417-103 (NCT04771130; EudraCT: 2021-003285-12).

Methods: BGB-11417-103 is an ongoing, phase 1b/2, global, multicenter, dose finding and expansion study evaluating sonrotoclax + azacitidine in patients with AML, myelodysplastic syndrome (MDS), or MDS/myeloproliferative neoplasm. Patients who received prior BCL2 inhibitors were excluded. Prior HMA was allowed. In cycle 1, a 4-day ramp-up of sonrotoclax began at one-eighth of the target dose. Dose-limiting toxicities (DLTs) were assessed up to day 28 for nonhematologic toxicities and day 42 or cycle 2 initiation for hematologic toxicities. Treatment-emergent AEs (TEAEs) were graded per CTCAE v5.0. The primary endpoint was safety and tolerability of the combination. Response assessment was conducted according to the European Leukemia Net (ELN) 2017 criteria.

Results: As of September 25, 2023, a total of 39 patients with R/R AML (13% with HMA failure) were enrolled across dose escalation and expansion cohorts and were included in the safety evaluation. Ten remain on treatment. Median age in all enrolled patients was 63 (range, 29-80) years and 59% had ELN 2017 adverse risk AML. Median number of prior lines of therapy was 1 (range, 1-4). Seven dose cohorts have been evaluated in R/R AML so far: sonrotoclax 40 mg x 10 days, 80 mg x 10 days, 160 mg x 10 days, 160 mg x 21 days, 160 mg x 28 days, 320 mg x 14 days, or 320 mg x 21 days + azacitidine (75 mg/m^2 x 7 days). At a median follow-up of 6.3 months, 1 patient had a DLT (grade 4 thrombocytopenia; 320 mg x 14 days). All patients had ≥1 TEAE. The most common grade ≥3 nonhematologic TEAEs were vomiting, hypokalemia, and hypotension (all 8%); common grade ≥3 hematologic TEAEs were neutropenia (49%), anemia (36%), febrile neutropenia (36%), and thrombocytopenia (33%). Grade ≥3 infections occurred in 46% of patients. Six patients (15%) had TEAEs leading to sonrotoclax dose reductions. The most common

TEAE class leading to sonrotoclax discontinuation was infection (5%). No cases of tumor lysis syndrome occurred. Three ongoing patients had not reached the first response assessment timepoint as of the data cutoff date; thus, 36 patients were included in the efficacy analysis. CR and CR/CRh rates were 28% and 47%, respectively. Median time to CR and CR/CRh was 2.8 and 1.5 months, respectively. Median duration for both CR and CR/CRh was 13.1 months. Eight patients (21%) proceeded to allogeneic stem cell transplant. Preliminary median overall survival was 11.8 (95% CI, 7.4-NE) months.

Conclusions: In this ongoing dose escalation phase 1b/2 trial, sonrotoclax + azacitidine was generally well tolerated. This combination demonstrated promising antileukemic activity in patients with R/R AML including in the lowest dose cohorts. Further evaluation in patients with R/R AML is ongoing.