**Preliminary Safety and Antileukemic Activity of Sonrotoclax (BGB-11417), a Potent and Selective BCL2 Inhibitor, in Treatment-Naive Patients with Acute Myeloid Leukemia**

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**Background**: B-cell lymphoma 2 (BCL2), a key regulator of apoptosis, is overexpressed in many hematologic malignancies. The BCL2 inhibitor venetoclax + azacitidine (AZA) has improved outcomes for treatment-naive (TN) patients (pts) with newly diagnosed acute myeloid leukemia (AML) unfit for intensive chemotherapy (TN unfit AML), with median overall survival (OS) of 14.7 months and complete remission in 36.7%. However, primary or secondary resistance is common, and long-term survival is suboptimal. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a selective and pharmacologically potent inhibitor of BCL2. In ongoing phase 1 studies, sonrotoclax has been well tolerated with preliminary antitumor activity in B-cell malignancies, AML/myelodysplastic syndrome (MDS), and multiple myeloma.

**Aims:** To present preliminary safety and antileukemic activity of sonrotoclax + AZA in TN unfit AML pts 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 + AZA in pts with AML (TN unfit [≥65 years old or with comorbidities] or relapsed/refractory [R/R]), MDS, or MDS/myeloproliferative neoplasm. Among TN unfit AML pts, dose cohorts were evaluated to explore sonrotoclax 40 mg x 10 days, 80 mg x 10 days, 160 mg x 10 days, 160 mg x 28 days, 320 mg x 21 days, or 320 mg x 14 days + AZA

(75 mg/m$^2$ x 7 days). For cycle 1, a 4-day sonrotoclax ramp-up was incorporated starting at one-eighth the target dose. Dose-limiting toxicities (DLTs) were assessed up to day 28 for nonhematologic toxicities and day 42 for hematologic toxicities (unless cycle 2 was initiated). Treatment-emergent adverse events (TEAEs) were graded per CTCAE v5.0. Response assessment was conducted per European Leukemia Net 2017 criteria.

**Results**: As of September 25, 2023, 42 enrolled TN pts with AML received study drug across dose escalation and expansion cohorts and were included in efficacy analyses; 16 (38%) remain on treatment. Median age was 75 years and median follow-up was 9.6 months (Table by cohort). All pts had ≥1 TEAE. The most common grade ≥3 nonhematologic TEAEs were pneumonia (17%) and hypokalemia (14%); common grade ≥3 hematologic TEAEs were neutropenia (64%), thrombocytopenia (48%), febrile neutropenia (48%), and anemia (43%). Grade ≥3 infections occurred in 52% of pts. The most common TEAE leading to dose reduction was neutropenia (n=4, sonrotoclax reduction; n=9, AZA reduction). The most common TEAE class leading to sonrotoclax discontinuation was infection (n=5). No deaths due to treatment-related TEAEs or clinical tumor lysis syndrome (TLS) occurred; 1 pt had laboratory TLS (160 mg x 10 days, cycle 2, hyperuricemia and hyperphosphatemia, resolved in 4 days). Mortality rate within 30 days was 2% (1 pt). CR and CR/CRh rates were 50% and 62%, with median time to response of 1.7 and 1.3 months, respectively; median duration of response for both was 18.8 months. Preliminary median OS was 20.6 (95% CI, 9.5-NE) months, with 64% OS at 12 months.

**Summary/Conclusion**: In this phase 1b/2 dose escalation and expansion study, sonrotoclax + AZA was generally well tolerated with promising antileukemic activity in TN unfit AML pts. Efficacy was seen starting at the lowest dose cohort. The study is ongoing in escalation, and the recommended phase 2 dose is still being determined.

**Table. Baseline Characteristics and Preliminary Antileukemic Activity in TN Pts With Unfit AML**

| | Sonrotoclax | | | | | |
|---|---|---|---|---|---|---|
| | **40 mg QD × 10 days** | **80 mg QD × 10 days** | **160 mg QD × 10 days** | **160 mg QD × 28 days** | **320 mg QD × 21 days** | **Total** |
| | **n=9** | **n=11** | **n=8** | **n=9** | **n=4** | **n=42[a]** |
| Age, median (range), years | 72.0 (64-91) | 77.0 (67-85) | 78.0 (70-87) | 70.0 (65-80) | 76.0 (72-81) | 75.0 (64-91) |
| Secondary AML, n (%) | 3 (33.3) | 0 | 2 (25.0) | 3 (33.3) | 1 (25.0) | 9 (21.4) |
| Favorable risk (ELN17), n (%) | 0 | 3 (27.3) | 1 (12.5) | 1 (11.1) | 1 (25.0) | 6 (14.3) |
| Adverse risk (ELN17), n (%) | 5 (55.6) | 3 (27.3) | 3 (37.5) | 4 (44.4) | 0 | 16 (38.1) |
| *IDH1/2* mutations, n (%) | 1 (11.1) | 1 (9.1) | 1 (12.5) | 0 | 0 | 3 (7.1) |
| Study follow-up time, median (range), months | 9.5 (0.5-23.3) | 20.5 (0.3-27.9) | 14.1 (1.4-21.4) | 9.8 (5.1-18.2) | 6.1 (5.1-6.5) | 9.6 (0.3-27.9) |
| DLT, n (%)[b] | 0 | 2 (20.0)[c] | 0 | 0 | 0 | 2 (5.6) |
| Relative dose intensity of sonrotoclax, median, % | 80.1 | 89.2 | 95.3 | 63.3 | 85.6 | 88.7 |
| Best overall response | | | | | | |
| CR, n (%) | 4 (44.4) | 8 (72.7) | 4 (50.0) | 4 (44.4) | 1 (25.0) | 21 (50.0) |
| Duration of CR, median (95% CI), months[d] | NR (6.8-NE) | 17.0 (0.6-NE) | NR (8.7-NE) | 4.4 (NE-NE) | NR (NE-NE) | 18.8 (7.5-NE) |
| CR/CRi, n (%) | 6 (66.7) | 8 (72.7) | 6 (75.0) | 6 (66.7) | 4 (100.0) | 30 (71.4) |
| CR/CRh, n (%) | 5 (55.6) | 8 (72.7) | 5 (62.5) | 5 (55.6) | 3 (75.0) | 26 (61.9) |
| Duration of CR/CRh, median (95% CI), months[d] | NR (6.8-NE) | 17.9 (0.6-NE) | NR (8.7-NE) | 5.3 (4.4-NE) | NR (NE-NE) | 18.8 (7.5-NE) |

AML, acute myeloid leukemia; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DLT, dose limiting toxicity; ELN17, 2017 European LeukemiaNet criteria; NE, not estimable; NR, not reached; pt, patient; QD, once daily; TN, treatment naive.

[a] Included 1 additional pt treated with 320 mg × 14 days who received 2 cycles of treatment.

[b] Percentages were calculated from the DLT evaluable population: total n=36, 80 mg × 10-day cohort n=10.

[c] Grade 4 neutropenia and grade 4 thrombocytopenia, n=1; grade 4 thrombocytopenia, n=1.

[d] Medians were estimated using the Kaplan-Meier method, with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.