UPDATED SAFETY AND ANTILEUKEMIC ACTIVITY DATA FOR SONROTOCLAX (BGB-11417), A POTENT AND SELECTIVE BCL2 INHIBITOR, IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

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Background: Treatment with venetoclax, a B-cell lymphoma 2 (BCL2) inhibitor, has improved outcomes in patients with newly diagnosed acute myeloid leukemia (AML), but it is not approved for relapsed/refractory (R/R) AML. Salvage regimens for R/R AML have complete remission (CR)/CR with incomplete hematologic recovery rates of ~21% and median overall survival of 6.1 months. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation.

Aims: To present updated safety and antileukemic activity data for sonrotoclax + azacitidine in patients with R/R AML in a phase 1b/2 study.

Methods: BGB-11417-103 (NCT04771130) is an ongoing, global, dose-escalation/expansion study of sonrotoclax + azacitidine in patients with AML, myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasm. Prior hypomethylating agent (HMA) treatment was allowed, but prior BCL2 inhibitor treatment was exclusionary. In cycle 1, a 4-day sonrotoclax ramp-up began at one-eighth the target dose. Dose-limiting toxicities (DLTs) were assessed up to day 28 (nonhematologic events) and day 42 or cycle 2 initiation (hematologic events). Treatment-emergent AEs (TEAEs) were assessed per CTCAE v5.0. The primary objective was to assess safety and tolerability. Antileukemic activity was assessed per European Leukemia Net (ELN) 2017 criteria.

Results: As of November 5, 2024, 68 patients with R/R AML were enrolled across 9 dose-escalation/expansion cohorts; 11 remain on treatment. At a median follow-up of 5.7 months (range, 0.1-37.8 months), 1 patient had a DLT (grade 4 thrombocytopenia; 320 mg × 14 days). TEAE frequency and severity were similar across doses. The most common grade ≥3 nonhematologic TEAEs were hypokalemia (8.8%), sepsis (7.4%), and vomiting (5.9%); common grade ≥3 hematologic TEAEs were neutropenia (82.4%), thrombocytopenia (50.0%), febrile neutropenia (38.2%), and anemia (29.4%). Grade ≥3 infection occurred in 41.2% of patients. TEAEs led to sonrotoclax dose reductions (most common: neutropenia, 10.3%) and discontinuations (most common: infection, 5.9%) in 11.8% of patients each. No tumor lysis syndrome occurred. Median time to recovery from grade 3 and 4 neutropenia that occurred after CR/CR with partial hematologic recovery (CRh) was 8.5 days (IQR, 7-15 days). Fifteen patients (22.1%) proceeded to allogeneic stem cell transplant. In 67 efficacy-evaluable patients, CR and

CR/CRh rates were 25.4% and 41.8%, respectively, and the median time to CR and to CR/CRh was 1.9 months and 1.6 months (data for total population and 14-day cohorts in **Table**). Of the 20 measurable residual disease (MRD)–evaluable patients with CR/CRh, 10 (50.0%) attained MRD-negative status ($<10^{-3}$ by flow cytometry). In the 14-day cohorts with comparable follow-up, an exploratory exposure-response analysis showed that the CR rates at the end of cycle 2 in the 3rd (highest) tertile of sonrotoclax exposure were considerably higher than in lower tertiles [1st: 11%; 2nd: 10%; 3rd: 40%].

Summary/Conclusion: In BGB-11417-103, a phase 1b/2 trial, sonrotoclax + azacitidine was well tolerated and demonstrated promising antileukemic activity in patients with R/R AML. Further evaluation in patients with R/R AML is ongoing.

Table. Baseline characteristics, safety, and clinical response in patients with R/R AML

	Sonrotoclax dose + Azacitidine (75 mg/m^2 × 7 days)			
	80 mg QD × 14 days (n=8)[a]	**160 mg QD × 14 days (n=9)**	**320 mg QD × 14 days (n=13)**	**Total (N=68)[b]**
Baseline characteristics				
Age, median (range), years	57.5 (48-83)	53.0 (27-72)	64.0 (43-81)	60.0 (27-83)
Secondary AML, n (%)	1 (12.5)	4 (44.4)	1 (7.7)	11 (16.2)
No. of prior lines of therapy, median (range)	1 (1-4)	1 (1-4)	1 (1-3)	1 (1-6)
Prior HMA for AML, n (%)	3 (37.5)	2 (22.2)	3 (23.1)	12 (17.6)
Favorable risk (ELN17), n (%)	0	2 (22.2)	5 (38.5)	14 (20.6)
Adverse risk (ELN17), n (%)	4 (50.0)	4 (44.4)	7 (53.8)	38 (55.9)
Positive recurrent genetic abnormality, n (%)				
IDH1/ IDH2	2 (25.0)	1 (11.1)	1 (7.7)	16 (23.5)
FLT3	2 (25.0)	0	2 (15.4)	10 (14.7)
NPM1	1 (12.5)	1 (11.1)	1 (7.7)	11 (16.2)
TP53 aneuploidy or -17/abn(17p)	2 (25.0)	0	1 (7.7)	7 (10.3)
Follow-up, median (range), months	4.6 (0.1-8.0)	3.3 (1.5-8.9)	4.0 (0.9-14.8)	5.7 (0.1-37.8)
Safety[c]				
Grade ≥3 neutropenia	7 (87.5)	7 (77.8)	11 (84.6)	56 (82.4)
Grade ≥3 thrombocytopenia	3 (37.5)	4 (44.4)	8 (61.5)	34 (50.0)
Grade ≥3 infections	0	6 (66.7)	4 (30.8)	28 (41.2)
Clinical response				
Response rates, n/N (%)				
CR at end of cycle 2	2/7 (28.6)	0	4/13 (30.8)	12/67 (17.9)
CR	2/7 (28.6)	0	4/13 (30.8)	17/67 (25.4)
CR/CRi	3/7 (42.9)	1/9 (11.1)	8/13 (61.5)	29/67 (43.3)
CR/CRh	2/7 (28.6)	1/9 (11.1)	7/13 (53.8)	28/67 (41.8)
MRD-negative, n/N (%)[d]	0	1/9 (11.1)	5/13 (38.5)	14/67 (20.9)

AML, acute myeloid leukemia; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; ELN17, 2017 European LeukemiaNet criteria; HMA, hypomethylating agent; MRD, measurable residual disease; NE, not estimable; NR, not reached; QD, once daily; R/R, relapsed/refractory.

[a] One ongoing patient had not reached the first response/MRD assessment as of the data cutoff date. [b] Total includes data for all 9 dose cohorts, 6 of which are not presented here. [c] Grouped terms: neutropenia (neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic sepsis, neutropenic infection); thrombocytopenia (thrombocytopenia, platelet count decreased); infections (infection and infestations by system organ class). [d] MRD assessed by multiparameter flow cytometry (MRD negative: ≥1 post-treatment sample was below the cutoff [≤1 residual leukemic blasts per 1,000 leukocytes, or 10^{-3}]).