UPDATED SAFETY & ANTILEUKEMIC ACTIVITY DATA OF SONROTOCLAX (BGB-11417), A POTENT AND SELECTIVE BCL2 INHIBITOR, IN TREATMENT-NAIVE PATIENTS WITH ACUTE MYELOID LEUKEMIA UNFIT FOR INTENSIVE CHEMOTHERAPY

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Background: B-cell lymphoma 2 (BCL2) inhibitor venetoclax + azacitidine (AZA) has improved outcomes in treatment-naive patients (pts) with newly diagnosed acute myeloid leukemia unfit for intensive chemotherapy (TN unfit AML), with median overall survival of 14.7 mo and complete remission in 36.7% of pts. However, primary or secondary resistance and dose modifications are common. 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. 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 clinical safety and antileukemic activity data for sonrotoclax + AZA in pts with TN unfit AML in a phase 1b/2 study.

Methods: BGB-11417-103 (NCT04771130) is an ongoing, global, dose-escalation/expansion study of sonrotoclax + AZA in pts with AML, MDS, or MDS/myeloproliferative neoplasm. Pts with TN unfit AML (≥65 years old or with comorbidities) with no prior BCL2 inhibitor treatment (tx) were included. In cycle 1, a 4-day (d) sonrotoclax ramp-up began at 1/8th the target dose. Dose-limiting toxicities (DLTs) were assessed up to d28 (nonhematologic events) and d42 or cycle 2 initiation (hematologic events). Tx-emergent adverse events (TEAEs) were assessed per CTCAE v5.0. Primary objective was to assess safety and tolerability. Antileukemic activity was assessed per European LeukemiaNet 2017 criteria.

Results: As of November 5, 2024, 79 enrolled pts with TN unfit AML were treated across 8 dose escalation/expansion cohorts; 22 remain on tx. Median follow-up was 5.8 mo (range, 0.3-41.2) (data for total population and 14-d cohorts in **Table**). TEAE frequency and severity were similar across doses. The most common (≥20%) grade ≥3 TEAEs were neutropenia (88.6%), thrombocytopenia (64.6%), anemia (43.0%), febrile neutropenia (38.0%), and pneumonia (20.3%); 20 pts (25.3%) had a TEAE leading to sonrotoclax dose reduction (most common: neutropenia, 20.3%), and 11 (13.9%) discontinued sonrotoclax due to a TEAE (most common: infection, 7.6%). Grade ≥3 infection occurred in 38 pts (48.1%). Median time to recovery for grade ≥3 neutropenia after CR/CRh was 8d (IQR: 6.0-15.0). Two deaths due to tx-related TEAEs occurred (anemia [80 mg × 14d]; neutropenic sepsis [160 mg × 14d]); 4 pts had tumor lysis syndrome (including 2 clinical) that resolved in ≤4d without sequelae. Mortality rate within 30d was 3.8% (n=3). Rates of >2 dose reductions or discontinuation due to disease relapse were highest in cohorts with >14d dosing durations. CR and CR/CRh rates were 49.4% and 59.5%, respectively, with median times to response of 1.7 and 1.3 mo. Of 40 measurable residual disease (MRD)–evaluable pts with CR/CRh, 23 (57.5%) attained MRD-negative

(<10^{-3}) status by flow cytometry. Among 14-d cohorts with comparable follow-up, exploratory exposure-response analysis showed that CR rate for 1st tertile corresponding to PK exposure associated with 80-mg dose is ~2-fold lower than CR rate for 2nd and 3rd tertile.

Summary/Conclusion: In BGB-11417-103, a phase 1b/2 trial, sonrotoclax + AZA was more tolerable in cycles with shorter tx duration and had promising antileukemic activity, with the potential for deeper responses at higher exposures. TEAE frequency and severity were similar across all cohorts. Further evaluation in pts with TN unfit AML is ongoing.

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

	Sonrotoclax dose + AZA (75 mg/m^2 x 7 days)			
	80 mg QD × 14 days (n=13)	**160 mg QD × 14 days (n=11)**	**320 mg QD × 14 days (n=14)**	**Total[a] (n=79)**
Baseline characteristics				
Age, median (range), years	74.0 (68-83)	71.0 (65-79)	73.0 (66-89)	74.0 (64-91)
Secondary AML, n (%)	1 (7.7)	3 (27.3)	3 (21.4)	17 (21.5)
Favorable risk (ELN17), n (%)	4 (30.8)	2 (18.2)	1 (7.1)	12 (15.2)
Adverse risk (ELN17), n (%)	3 (23.1)	6 (54.5)	7 (50.0)	34 (43.0)
Recurrent genetic abnormality, n (%)				
IDH1/IDH2	2 (15.4)	2 (18.2)	1 (7.1)	8 (10.1)
FLT3	2 (15.4)	1 (9.1)	2 (14.3)	10 (12.7)
NPM1	3 (23.1)	0	1 (7.1)	9 (11.4)
TP53 aneuploidy or -17/abn (17p)	1 (7.7)	1 (9.1)	2 (14.3)	10 (12.7)
Follow-up, median (range), months	4.1 (0.6-8.3)	4.4 (1.1-6.5)	3.2 (1.4-14.8)	5.8 (0.3-41.2)
DLT, n (%)[b]	0	1 (9.1)[c]	1 (7.7)[c]	4 (5.8)
Tumor lysis syndrome, n (%)	0	1 (9.1)	2 (14.3)	4 (5.1)
Relative dose intensity of sonrotoclax, median, %	94.4	90.0	82.9	88.3
Cycle length, median, days	29	40	35	34
Duration of neutropenia events after first CR/CRh, median (IQR), days	8 (7-12)	14 (5-17)	8 (5-12)	8 (6-15)
Safety[d]				
Grade ≥3 neutropenia	12 (92.3)	9 (81.8)	11 (78.6)	70 (88.6)
Grade ≥3 thrombocytopenia	8 (61.5)	7 (63.6)	8 (57.1)	51 (64.6)
Grade ≥3 infections	6 (46.2)	4 (36.4)	5 (35.7)	38 (48.1)
Clinical response				
Response rates, n (%)				
CR	5 (38.5)	5 (45.5)	6 (42.9)	39 (49.4)

CR/CRi	7 (53.8)	6 (54.5)	10 (71.4)	53 (67.1)
CR/CRh	7 (53.8)	6 (54.5)	7 (50.0)	47 (59.5)
MRD negative, n (%)[e]	4 (30.8)	3 (27.3)	4 (28.6)	28 (35.4)
Discontinued due to relapse, n (%)	1 (7.7)	0	0	13 (16.5)

AML, acute myeloid leukemia; AZA, azacitidine; 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; MRD, measurable residual disease; NE, not estimable; NR, not reached; QD, once daily; TN, treatment naive.

[a] Total includes data for all 8 dose cohorts, 6 of which are not presented here. [b] Percentages were calculated from the DLT-evaluable population (n=69). [c] Grade 4 thrombocytopenia, n=1. [d] 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). [e] 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}]).