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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Background: 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 (pts) 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. Here we present data with sonrotoclax + azacitidine in pts with R/R AML.

Aims: To present preliminary safety and antileukemic activity of sonrotoclax + azacitidine in pts 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 pts with AML, myelodysplastic syndrome (MDS), or MDS/myeloproliferative neoplasm. Pts 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 pts 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). Baseline characteristics are noted in Table 1. 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 pt had a DLT (grade 4 thrombocytopenia; 320 mg x 14 days). All pts 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 pts. Six pts (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 pts 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 pts (21%) proceeded to allogeneic stem cell transplant. Preliminary median overall survival was 11.8 (95% CI, 7.4-NE) months.

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

Table. Baseline Characteristics and Preliminary Antileukemic Activity in Pts With R/R AML

	Sonrotoclax							
	40 mg QD × 10 days	**80 mg QD × 10 days**	**160 mg QD × 10 days**	**160 mg QD × 21 days**	**160 mg QD × 28 days**	**320 mg QD × 14 days**	**320 mg QD × 21 days**	**Total**
	n=7	**n=6**	**n=8**	**n=4**	**n=9**	**n=3**	**n=2**	**n=39**
Age, median (range), years	64.0 (36-80)	70.0 (54-78)	52.5 (36-71)	53.0 (43-60)	57.0 (29-69)	64.0 (54-74)	70.0 (67-73)	63.0 (29-80)
Secondary AML, n (%)	0	2 (33.3)	1 (12.5)	0	1 (11.1)	0	1 (50.0)	5 (12.8)
HMA failure, n (%)	0	1 (16.7)	1 (12.5)	0	2 (22.2)	0	1 (50.0)	5 (12.8)
Favorable risk (ELN17), n (%)	1 (14.3)	1 (16.7)	1 (12.5)	0	2 (22.2)	0	0	5 (12.8)
Adverse risk (ELN17), n (%)	3 (42.9)	4 (66.7)	3 (37.5)	3 (75.0)	5 (55.6)	3 (100.0)	2 (100.0)	23 (59.0)
Positive recurrent genetic abnormality, n (%)								
ASXL1	2 (28.6)	0	0	0	2 (22.2)	1 (33.3)	1 (50.0)	6 (15.4)
IDH1	0	2 (33.3)	2 (25.0)	0	1 (11.1)	1 (33.3)	0	6 (15.4)
NPM1	2 (28.6)	1 (16.7)	2 (25.0)	0	3 (33.3)	1 (33.3)	0	9 (23.1)
TP53 aneuploidy	0	0	0	1 (25.0)	0	0	1 (50.0)	2 (5.1)
Follow-up time, median (range), months	15.4 (9.2-24.0)	16.8 (1.5-28.1)	6.8 (0.2-22.3)	0.3 (0.0-1.0)	4.9 (1.2-15.7)	1.4 (1.0-1.9)	4.3 (2.6-6.0)	6.3 (0.0-28.1)
Efficacy evaluable	**n=7**	**n=6**	**n=8**	**n=1**	**n=9**	**n=3**	**n=2**	**n=36**
CR, n (%)	2 (28.6)	3 (50.0)	2 (25.0)	1(100.0)	2 (22.2)	0	0	10 (27.8)
Duration of CR, median (95% CI), months[a]	7.7 (2.3-NE)	18.0 (1.9-NE)	20.5 (NE-NE)	NR (NE-NE)	0.1 (NE-NE)	–	–	13.1 (0.1-NE)
CR/CRi, n (%)	4 (57.1)	4 (66.7)	3 (37.5)	1 (100.0)	3 (33.3)	2 (66.7)	0	17 (47.2)
CR/CRh, n (%)	5 (71.4)	4 (66.7)	3 (37.5)	1 (100.0)	3 (33.3)	1 (33.3)	0	17 (47.2)
Duration of CR/CRh, median (95% CI), months[a]	8.6 (4.0-NE)	18.0 (1.9-NE)	20.5 (NE-NE)	NR (NE-NE)	NR (0.1-NE)	NR (NE-NE)	–	13.1 (0.1-NE)

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; NE, not estimable; NR, not reached; pt, patient; QD, once daily; R/R, relapsed/refractory.

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