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

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ABSTRACT

Introduction: Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 vs venetoclax in biochemical assays. Preliminary safety and antileukemic activity of sonrotoclax + azacitidine (AZA) in pts with R/R AML from the ongoing phase 1b/2 BGB-11417-103 (NCT04771130; EudraCT: 2021-003285-12) study are presented.

Methods: Eligible pts had AML, myelodysplastic syndrome (MDS), or MDS/ myeloproliferative neoplasm. Prior HMA, but not prior BCL2 inhibitor, were allowed. In cycle 1, a 4-day sonrotoclax ramp-up began at 1/8 of the target dose. DLTs were assessed up to day 28 for nonhematologic toxicities and day 42 or cycle 2 initiation for hematologic toxicities. The primary endpoint was safety per CTCAE v5.0. Response was assessed per European Leukemia Net (ELN) 2017 criteria.

Results: As of 25Sep2023, 39 pts with R/R AML (HMA failure, 13%) were enrolled across 7 dose cohorts (**Table**). Pts had a median of 1 (range, 1-4) prior treatment and 59% had adverse-risk AML per ELN 2017 criteria. Ten remain on treatment. 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. TEAEs led to sonrotoclax dose reduction in 6 pts (15%). The most common TEAE class leading to sonrotoclax discontinuation was infection (5%). No TLS occurred. In 36 efficacy-evaluable pts, 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 of CR and CR/CRh was 13.1 months. Eight pts (21%) proceeded to allogeneic stem cell transplant. Preliminary median OS was 11.8 (95% CI, 7.4-NE) months.

Conclusions: In this dose-escalation trial, sonrotoclax + AZA was generally well tolerated and demonstrated promising antileukemic activity in pts with R/R AML, including in the lowest-dose cohort. 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.