Preliminary safety and antileukemic activity of sonrotoclax (BGB-11417), a potent and selective BCL2 Inhibitor, in treatment-naive (TN) patients with acute myeloid leukemia (AML)

Authors: Uwe Platzbecker,[1] Jake Shortt,[2] Shuh Ying Tan,[3] Sophie Leitch,[4] James Mao-Chun Liang,[5] Chun Yew Fong,[6] Sundra Ramanathan,[7] Qiubai Li,[8] Pau Montesinos,[9] Courtney DiNardo,[10] Jinhua Zhong,[11] Wai Y. Chan,[12] Rui Li,[13] Oleg Zernovak,[12] Amit Agarwal,[12] Andrew H. Wei[13]

Affiliations: [1]Universitaetsklinikum Leipzig Aör, Leipzig, Germany; [2]Monash Health and Monash University, Clayton, VIC, Australia; [3]St Vincent's Hospital, Melbourne, VIC, Australia; [4]Te Whatu Ora Health New Zealand - Waitemata, Wellington, New Zealand; [5]Middlemore Hospital, Auckland, New Zealand; [6]Austin Health, Melbourne, Australia; [7]St George Hospital, Kogarah, NSW, Australia; [8]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [9]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [10]MD Anderson Cancer Center, Houston, TX, USA; [11]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [12]BeiGene USA, Inc, San Mateo, CA, USA; [13]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, Melbourne, VIC, Australia

ABSTRACT

Introduction: Sonrotoclax (BGB-11417) 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 patients (pts) with newly diagnosed AML in the ongoing phase 1b/2 BGB-11417-103 (NCT04771130; EudraCT: 2021-003285-12) study are presented.

Methods: Eligible pts had TN AML and were unfit for intensive chemotherapy (aged ≥65 years or with comorbidities). In cycle 1, a 4-day sonrotoclax ramp-up began at one-eighth of the target dose. DLTs were assessed up to day 28 for nonhematologic toxicities and day 42 or cycle 2 initiation for hematologic toxicities. TEAEs were graded per CTCAE v5.0. Response was assessed per European Leukemia Net 2017 criteria.

Results: As of 25Sept2023, 42 pts were treated across dose escalation and expansion cohorts (**Table**) and were included in efficacy analyses; 16 (38%) remain on treatment. Median age was 75 years, and median follow-up was 9.6 mo. 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 (sonrotoclax, n=4; AZA, n=9). The most common TEAE class leading to sonrotoclax discontinuation was infection (n=5). No deaths due to treatment-related TEAEs or clinical TLS occurred; 1 pt had laboratory TLS (160 mg x 10 days, cycle 2; resolved in 4 days). The mortality rate within 30 days was 2% (1 pt). CR and CR/CRh rates were 50% and 62%, respectively; median time to response was 1.7 and 1.3 mo, respectively, and median duration of response was 18.8 mo for both. Preliminary median OS was 20.6 mo (95% CI, 9.5-NE), with 64% OS at 12 mo.

Conclusions: In this dose escalation and expansion study, sonrotoclax + AZA was generally well tolerated, with promising antileukemic activity in TN unfit AML pts, including in the lowest-dose cohort. Dose escalation is ongoing, and the recommended phase 2 dose is 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.