Preliminary Safety and Antileukemic Activity of Sonrotoclax (BGB-11417), a Potent and Selective BCL2 Inhibitor, in Treatment-Naive Patients With Acute Myeloid Leukemia

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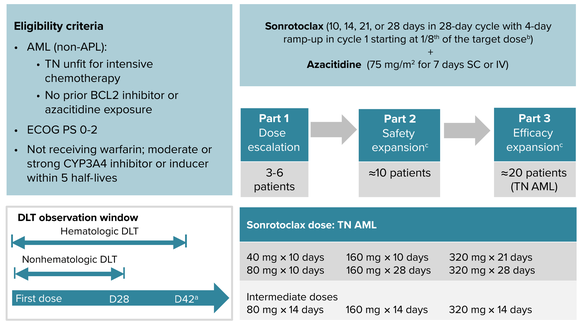
INTRODUCTION

- Acute myeloid leukemia (AML) is the most common acute form of leukemia in adults and has an aggressive disease course[1,2]
- The B-cell lymphoma 2 (BCL2) inhibitor venetoclax + azacitidine has improved outcomes in treatment-naive (TN) patients with AML unfit for intensive chemotherapy compared with azacitidine alone[3]; however, relapse is common and prognosis is suboptimal[4,5]
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no accumulation[6]
- In ongoing phase 1 studies, sonrotoclax has been well tolerated, with preliminary antitumor activity in B-cell malignancies, AML/myelodysplastic syndromes (MDS), and multiple myeloma[7-9]
- Here, we present the preliminary safety and antileukemic activity of sonrotoclax + azacitidine in TN patients with unfit AML in BGB-11417-103, a phase 1b/2 study

METHODS

- BGB-11417-103 (NCT04771130; EudraCT: 2021-003285-12) is an ongoing, global, multicenter, dose-finding and -expansion study evaluating sonrotoclax ± azacitidine in patients with AML, MDS, or MDS/myeloproliferative neoplasms (**Figure 1**)
- The primary and key secondary endpoints were safety per CTCAE v5.0 and CR + CR with partial hematologic recovery (CRh) rate per the 2017 European LeukemiaNet criteria and partial hematology recovery criteria for AML
- An exploratory objective was minimal residual disease (MRD) status, assessed by multiparameter flow cytometry (patients were MRD negative if 1 sample was below the cutoff [≤1 residual leukemic blasts per 1,000 leukocytes or 10^{-3}] at any time on the study)
- Sonrotoclax was administered orally once daily for a limited duration with an initial 4-day ramp-up to mitigate potential risk of tumor lysis syndrome (TLS), and azacitidine (75 mg/m^2 for 7 days/cycle) was administered subcutaneously or intravenously

Figure 1. BGB-11417-103 Study Design

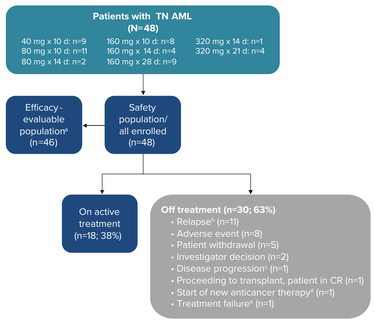


[a] Or cycle 2 initiation. [b] As a precautionary measure for TLS monitoring, patients were hospitalized during the ramp-up period. [c] Safety monitoring committee reviews available data to determine dose escalation in part 1, dose expansion to part 2, and the final RP2D to start part 3.
CYP3A4, cytochrome P450 3A4; HMA, hypomethylating agent; non-APL, nonacute promyelocytic leukemia.

RESULTS

- As of March 31, 2024, a total of 48 patients with TN AML were enrolled and had received sonrotoclax + azacitidine treatment and 18 (38%) remain on treatment (**Figure 2**)
- In all patients with TN AML, the median study follow-up was 10.5 (range, 0.3-34.0) months and the median age was 75 years (**Table 1**)
- The median number of treatment cycles was 7, with the longest average cycle duration (median, 35.1 days) in the azacitidine + sonrotoclax 160 mg x 28 day cohort (**Table 2**)
- The median dose intensity relative to the assigned dose of sonrotoclax was >80% except in the azacitidine + sonrotoclax 160 mg x 28 day and 320 mg x 21 day cohorts

Figure 2. Patient Disposition



Data cutoff: March 31, 2024. [a] The efficacy-evaluable population included patients who (1) completed ≥1 treatment cycle (initiated the second cycle) or 42 days, whichever is earlier, or discontinued treatment during the first cycle or (2) had ≥1 response assessment. Two patients have yet to complete cycle 1 and were excluded from the efficacy-evaluable population. [b] Hematologic relapse (after CR/CRi) defined as bone marrow blasts ≥5%, reappearance of blasts in the blood, or development of extramedullary disease. [c] Defined as evidence for an increase in bone marrow blast percentage and/or increase in absolute blast counts in the blood, both per ELN2017 response criteria. [d] Patient switched therapy while in CRi. [e] Defined as no CR or CRi after 6 cycles of sonrotoclax + azacitidine according to ELN2017.
CRi, CR with incomplete hematologic recovery; ELN, European LeukemiaNet.

Table 1. Baseline Patient Characteristics

	Sonro 40 mg × 10 d (n=9)	Sonro 80 mg × 10 d (n=11)	Sonro 80 mg × 14 d (n=2)	Sonro 160 mg × 10 d (n=8)	Sonro 160 mg × 14 d (n=4)	Sonro 160 mg × 28 d (n=9)	Sonro 320 mg × 14 d (n=1)	Sonro 320 mg × 21 d (n=4)	All TN AML (N=48)
	Aza								
Study follow-up, median (range), months	9.5 (0.5-29.4)	20.6 (0.3-34.0)	1.5 (1.1-1.9)	14.1 (1.4-27.6)	0.9 (0.5-1.6)	13.6 (5.1-24.4)	7.6 (7.6-7.6)	11.8 (8.8-12.6)	10.5 (0.3-34.0)
Age, median (range), years	72.0 (64-91)	77.0 (67-85)	71.5 (68-75)	78.0 (70-87)	73.5 (71-78)	70.0 (65-80)	68.0 (68-68)	76.0 (72-81)	75.0 (64-91)
Male sex, n (%)	6 (67)	5 (45)	1 (50)	6 (75)	3 (75)	7 (78)	1 (100)	3 (75)	32 (67)
AML type, n (%)									
De novo	5 (56)	11 (100)	2 (100)	6 (75)	2 (50)	6 (67)	1 (100)	3 (75)	36 (75)
Secondary	4 (44)	0	0	2 (25)	2 (50)	3 (33)	0	1 (25)	12 (25)
AML risk stratification, n (%)[a]									
Favorable	0	3 (27)	0	1 (13)	0	1 (11)	0	1 (25)	6 (13)
Intermediate	4 (44)	5 (45)	0	3 (38)	2 (50)	3 (33)	0	3 (75)	20 (42)
Adverse	5 (56)	3 (27)	2 (100)	3 (38)	2 (50)	4 (44)	1 (100)	0	20 (42)
Positive genetic abnormality, n (%)	7 (78)	9 (82)	2 (100)	7 (88)	3 (75)	5 (56)	1 (100)	2 (50)	36 (75)
−7 or del(7q)	1 (11)	2 (18)	0	2 (25)	1 (25)	2 (22)	0	0	8 (17)
−5 or del(5q)	2 (22)	2 (18)	0	1 (13)	0	1 (11)	1 (100)	0	7 (15)
NPM1	0	3 (27)	0	1 (13)	0	0	0	1 (25)	5 (10)
TP53 aneuploidy	1 (11)	1 (9)	0	2 (25)	0	1 (11)	0	0	5 (10)
−17/abn(17p); *TP53* abnormality	0	2 (18)	0	1 (13)	0	0	0	0	3 (6)
IDH1/IDH2-R172[b]	1 (11)	1 (9)	0	0	1 (25)	0	0	0	3 (6)
FLT3-ITD high AR	1 (11)	1 (9)	0	0	0	0	0	0	2 (4)
FLT3-ITD low AR	0	1 (9)	0	1 (13)	0	0	0	0	2 (4)
FLT3-TKD	0	0	0	0	1 (25)	0	0	0	1 (2)

[a] Missing data for 2 patients (n=1, 160 mg x 10 day cohort; n=1, 160 mg x 28 day cohort). [b] No patients had *IDH2*-R172 abnormality.
AR, allelic ratio; aza, azacitidine; ITD, internal tandem duplication; sonro, sonrotoclax; TKD, tyrosine kinase domain.

Table 2. Treatment Exposure in TN Unfit AML

	Sonro 40 mg × 10 d (n=9)	Sonro 80 mg × 10 d (n=11)	Sonro 80 mg × 14 d (n=2)	Sonro 160 mg × 10 d (n=8)	Sonro 160 mg × 14 d (n=4)	Sonro 160 mg × 28 d (n=9)	Sonro 320 mg × 14 d (n=1)	Sonro 320 mg × 21 d (n=4)	All TN AML (N=48)
	Aza								
No. of cycles, median (range)	4.0 (1.0-25.0)	15.0 (1.0-34.0)	2.0 (2.0-2.0)	8.5 (1.0-28.0)	1.0 (1.0-2.0)	5.0 (1.0-16.0)	7.0 (7.0-7.0)	8.5 (7.0-12.0)	7.0 (1.0-34.0)
Average cycle duration, median (range), days	32.0 (13.0-44.5)	31.1 (8.0-46.9)	22.8 (16.5-29.0)	34.4 (22.0-44.9)	25.0 (14.0-27.0)	35.1 (2.0-73.0)	32.9 (32.9-32.9)	32.4 (25.4-37.7)	31.8 (2.0-73.0)
Relative dose intensity (sonro), median (range), %	80.2 (42.6-105.9)	91.0 (38.8-100)	100 (100-100)	95.9 (21.6-109.4)	100 (96.1-100)	63.3 (29.5-100)	85.6 (85.6-85.6)	66.4 (39.3-94.0)	91.7 (21.6-109.4)
Relative dose intensity (aza), median (range), %	72.9 (39.4-101.2)	69.6 (37.2-100.4)	99.8 (98.5-101.1)	85.1 (57.2-100.2)	100.2 (99.9-101.0)	94.1 (44.3-100.2)	50.1 (50.1-50.1)	77.6 (50.5-87.4)	86.9 (37.2-101.2)

aza, azacitidine; sonro, sonrotoclax.

Safety

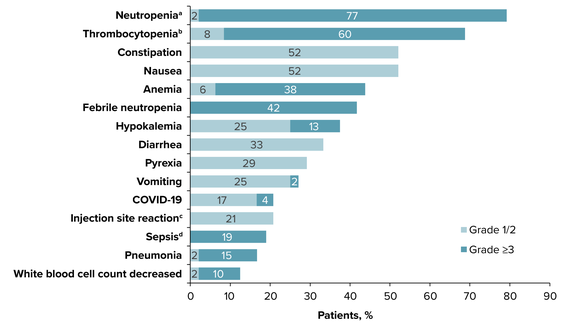
- An overall summary of TEAEs in patients with TN AML is shown in **Table 3**
- The most common any-grade TEAEs were neutropenia (including neutrophil count decreased), thrombocytopenia (including platelet count decreased), constipation, and nausea (**Figure 3**)
  - Neutropenia and thrombocytopenia were the most common grade ≥3 TEAEs and grade ≥3 infections and infestations occurred in 24 patients (50%)
- The most common TEAE class leading to treatment discontinuation was infections and infestations (azacitidine, n=5; sonrotoclax, n=5)
- The most common TEAE leading to dose reduction was neutropenia (n=9, sonrotoclax reduction; n=11, azacitidine reduction)
- Five patients had a TEAE leading to death, none were considered related to sonrotoclax or azacitidine treatment, and the 30-day mortality rate was 2%
  - Two TEAEs leading to death were considered related to disease (bronchopulmonary aspergillosis [80 mg x 10 day] and neutropenic sepsis [160 mg x 10 day])
  - Three TEAEs leading to death were not considered related to disease (pulmonary sepsis without preceding confirmed pneumonia [40 mg x 10 day], hospital acquired pneumonia [80 mg x 10 day], and metastatic squamous cell carcinoma [80 mg x 10 day])
- Three DLTs occurred in 2 patients in the azacitidine + sonrotoclax 80 mg x 10 day cohort (neutropenia [n=1; grade 4] and thrombocytopenia [n=2; grade 4])
- Laboratory TLS occurred in 1 patient in the azacitidine + sonrotoclax 160 mg x 10 day cohort (hyperuricemia and hyperphosphatemia; cycle 2) and resolved in 4 days with concomitant allopurinol

Table 3. TEAE Summary

Patients, n (%)	All TN AML (N=48)
Any TEAEs	48 (100)
Grade ≥3	44 (92)
Serious TEAEs	37 (77)
TEAEs leading to death[a]	5 (10)
TEAEs leading to discontinuation	
Aza	8 (17)
Sonro	8 (17)
TEAEs leading to reduction	
Aza	14 (29)
Sonro	12 (25)
TEAEs leading to interruption	
Aza	10 (21)
Sonro	14 (29)

[a] TEAEs leading to death were pneumonia, neutropenic sepsis, bronchopulmonary aspergillosis, pulmonary sepsis, and metastatic squamous cell carcinoma; none were considered related to aza or sonro.
aza, azacitidine; sonro, sonrotoclax.

Figure 3. TEAEs in ≥20% (All Grades) or ≥10% (Grade ≥3)



[a] Neutropenia includes the terms *neutropenia* and *neutrophil count decreased*. [b] Thrombocytopenia includes the terms *thrombocytopenia* and *platelet count decreased*. [c] All injection site reactions were related to azacitidine. [d] Sepsis is a grouped term excluding fungal sepsis.

Antileukemic Activity

- CR/CRh was achieved in 63% of patients by a median time to CR/CRh of 1.3 months (**Table 4**)
  - At a median follow-up of 19.8 months, the median duration of response was 15.1 months for CR
  - The median duration of response was 16.9 months for both CR/CRh and CR/CR with incomplete hematologic recovery (CRi, median follow-up 19.8 months)
- The ORR was 78% in patients with TN unfit AML (**Figure 4**)
- Minimal residual disease–negative status was achieved by 37% of all TN patients with unfit AML in the efficacy-evaluable population (**Figure 5**)

Table 4. Summary of Disease Responses[a]

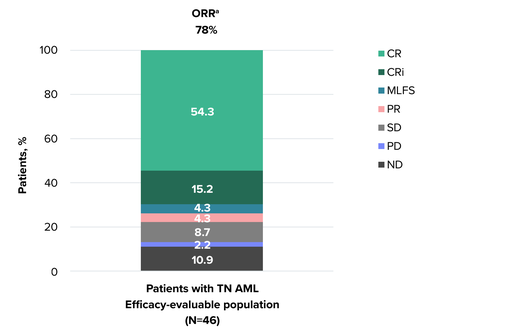
	Sonro 40 mg × 10 d (n=9)	Sonro 80 mg × 10 d (n=11)	Sonro 80 mg × 14 d (n=2)	Sonro 160 mg × 10 d (n=8)	Sonro 160 mg × 14 d (n=2)	Sonro 160 mg × 28 d (n=9)	Sonro 320 mg × 14 d (n=1)	Sonro 320 mg × 21 d (n=4)	All TN AML (N=46)
	Aza								
CR, n (%)	4 (44)	8 (73)	0	4 (50)	1 (50)	4 (44)	1 (100)	3 (75)	25 (54)
Time to CR, median (range), months	1.3 (1.3-1.8)	1.8 (0.9-6.5)	-	1.7 (1.0-4.0)	0.8 (0.8-0.8)	3.0 (1.1-7.9)	2.1 (2.1-2.1)	4.1 (2.1-11.1)	1.8 (0.8-11.1)
Duration of CR, median (95% CI), months[b]	NR (6.8-NE)	17.0 (0.6-NE)	-	NR (8.7-NE)	NR (NE-NE)	8.0 (4.4-NE)	NR (NE-NE)	3.7 (3.5-NE)	15.1 (6.8-NE)
CR/CRh, n (%)	5 (56)	8 (73)	0	5 (63)	1 (50)	5 (56)	1 (100)	4 (100)	29 (63)
Time to CR/CRh, median (range), months	1.3 (1.3-5.6)	1.4 (0.9-4.4)	-	1.2 (1.0-4.0)	0.8 (0.8-0.8)	1.2 (1.1-4.9)	2.1 (2.1-2.1)	4.1 (2.1-9.7)	1.3 (0.8-9.7)
Duration of CR/CRh, median (95% CI), months[b]	NR (6.8-NE)	17.9 (0.6-NE)	-	NR (8.7-NE)	NR (NE-NE)	8.7 (4.4-NE)	NR (NE-NE)	3.8 (3.5-NE)	16.9 (7.5-NE)
CR/CRi, n (%)	6 (67)	8 (73)	0	6 (75)	1 (50)	6 (67)	1 (100)	4 (100)	32 (70)
Time to CR/CRi, median (range), months	1.3 (1.1-5.6)	1.4 (0.9-4.4)	-	1.1 (1.0-4.0)	0.8 (0.8-0.8)	1.5 (1.1-4.9)	2.1 (2.1-2.1)	1.8 (1.7-2.1)	1.3 (0.8-5.6)
Duration of CR/CRi, median (95% CI), months[b]	NR (6.8-NE)	17.9 (0.6-NE)	-	NR (6.7-NE)	NR (NE-NE)	7.0 (4.0-NE)	NR (NE-NE)	NR (3.8-NE)	16.9 (6.8-NE)

[a] Responses were determined using the 2017 European LeukemiaNet criteria and partial hematology recovery criteria for AML. [b] Medians were estimated using the Kaplan-Meier method, with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
aza, azacitidine; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; NE, not estimable, NR, not reached; sonro, sonrotoclax.

CONCLUSIONS

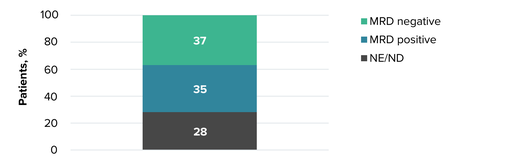
- Sonrotoclax + azacitidine combination treatment was generally well tolerated in patients with TN unfit AML
  - Across dose cohorts, 3 DLTs of grade 4 neutropenia (n=1) and grade 4 thrombocytopenia (n=2) occurred in 2 patients
- Sonrotoclax + azacitidine demonstrated antileukemic activity in TN unfit patients with AML in all dose cohorts
  - The ORR was 78%, of which CR/CRh was achieved in 63% of patients and CR in 54% of patients
- The study stopping criteria has not been met in any of the dose cohorts
- Safety expansion of x 14-day dosing is ongoing in 80 mg, 160 mg, and 320 mg cohorts to determine the recommended phase 2 dose

Figure 4. Response Rates



[a] ORR included CR, CRi, MLFS, and PR.
CR, complete response; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; ND, not done; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. MRD



MRD, minimal residual disease; ND, not done; NE, not evaluable.

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DISCLOSURES

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