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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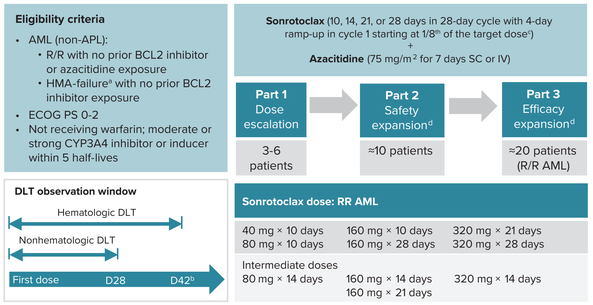
INTRODUCTION

- Acute myeloid leukemia (AML) is the most common acute form of leukemia in adults and has an aggressive disease course[1,2]
- Although treatment with the B-cell lymphoma 2 (BCL2) inhibitor venetoclax has improved outcomes in some patients with newly diagnosed AML,[3] venetoclax is not approved in relapsed/refractory (R/R) AML[4]
- 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[5]
- Here, we present the preliminary safety and antileukemic activity of sonrotoclax + azacitidine in R/R 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, myelodysplastic syndromes (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
- 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

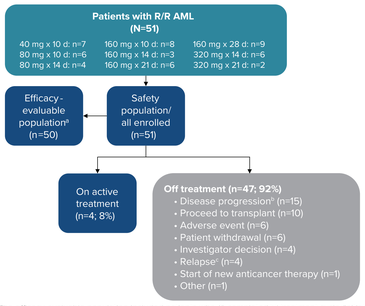


[a]HMA failure received ≥1 cycle of HMA and had PD or no PR or better hematologic improvement after 4 cycles of >75% of planned dose. [b] Or cycle 2 initiation. [c] As a precautionary measure for TLS monitoring, patients were hospitalized during the ramp-up period. [d] Safety monitoring committee reviews 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 51 patients with R/R AML were enrolled and had received sonrotoclax + azacitidine treatment and 4 (8%) remain on treatment (**Figure 2**)
- In all patients with R/R AML, the median age was 60 years and the median number of prior lines of therapy was 2 (**Table 1**)
- The median number of treatment cycles was 2, with the longest average cycle duration (median, 42.3 days) in the azacitidine + sonrotoclax 320 mg x 21 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 21 day cohort

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. [b] 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. [c] Hematologic relapse (after CR/CRi) defined as bone marrow blasts ≥5%, reappearance of blasts in the blood, or development of extramedullary disease.
CRi, CR with incomplete hematologic recovery; ELN, European LeukemiaNet.

Table 1. Baseline Patient Characteristics

	Sonro 40 mg × 10 d (n=7)	Sonro 80 mg × 10 d (n=6)	Sonro 80 mg × 14 d (n=4)	Sonro 160 mg × 10 d (n=8)	Sonro 160 mg × 14 d (n=3)	Sonro 160 mg × 21 d (n=6)	Sonro 160 mg × 28 d (n=9)	Sonro 320 mg × 14 d (n=6)	Sonro 320 mg × 21 d (n=2)	All R/R AML (N=51)
	Aza									
Study follow-up, median (range), months	15.4 (9.2-30.1)	19.9 (1.5-31.7)	0.9 (0.7-2.1)	6.8 (0.2-24.5)	1.7 (1.5-1.7)	5.8 (4.6-7.1)	4.9 (1.2-21.8)	3.8 (1.0-7.6)	7.4 (2.6-12.2)	5.8 (0.2-31.7)
Age, median (range), years	64.0 (36-80)	70.0 (54-78)	57.5 (52-70)	52.5 (36-71)	54.0 (27-67)	53.0 (42-66)	57.0 (29-69)	66.5 (44-74)	70.0 (67-73)	60.0 (27-80)
Male sex, n (%)	3 (43)	3 (50)	2 (50)	5 (63)	2 (67)	4 (67)	6 (67)	3 (50)	1 (50)	29 (57)
AML type, n (%)										
De novo	7 (100)	4 (67)	2 (50)	7 (88)	1 (33)	6 (100)	8 (89)	6 (100)	1 (50)	42 (82)
Secondary	0	2 (33)	2 (50)	1 (13)	2 (67)	0	1 (11)	0	1 (50)	9 (18)
HMA failure, n (%)	0	0	1 (25)	1 (13)	1 (33)	1 (17)	1 (11)	1 (17)	1 (50)	7 (14)
AML risk stratification, n (%)										
Favorable	1 (14)	1 (17)	0	1 (13)	0	0	2 (22)	0	0	5 (10)
Intermediate	3 (43)	1 (17)	2 (50)	4 (50)	0	2 (33)	2 (22)	0	0	14 (27)
Adverse	3 (43)	4 (67)	2 (50)	3 (38)	3 (100)	4 (67)	5 (56)	6 (100)	2 (100)	32 (63)
Positive genetic abnormality, n (%)	6 (86)	5 (83)	2 (50)	7 (88)	2 (67)	5 (83)	7 (78)	5 (83)	2 (100)	41 (80)
NPM1	2 (29)	1 (17)	0	2 (25)	0	0	3 (33)	1 (17)	0	9 (18)
TP53 aneuploidy	0	0	1 (25)	0	0	1 (17)	0	1 (17)	1 (50)	4 (8)
–17/abn(17p); *TP53* abnormality	1 (14)	1 (17)	0	0	0	0	0	0	0	2 (4)
–7 or del(7q)	1 (14)	0	0	2 (25)	0	1 (17)	2 (22)	0	0	6 (12)
IDH1	0	2 (33)	0	2 (25)	0	0	1 (11)	1 (17)	0	6 (12)
IDH2 R172	1 (14)	1 (17)	0	1 (13)	0	1 (17)	2 (22)	0	0	6 (12)
FLT3-ITD high AR	0	0	0	0	0	0	0	1 (17)	1 (50)	2 (4)
FLT3-ITD low AR	0	1 (17)	0	1 (13)	0	1 (17)	0	0	0	3 (6)
FLT3-TKD	0	0	1 (25)	0	0	0	1 (11)	0	0	2 (4)
–5 or del(5q)	0	1 (17)	0	1 (13)	0	1 (17)	0	0	0	3 (6)
Prior therapy										
Prior aza exposure, n (%)	0	0	1 (25)	0	1 (33)	1 (17)	1 (11)	2 (33)	1 (50)	7 (14)
No. of lines of prior systemic therapy, median (range)	1.0 (1-2)	1.0 (1-2)	1.5 (1-2)	2.0 (1-2)	2.0 (1-2)	2.0 (1-6)	1.0 (1-3)	2.0 (1-3)	1.5 (1-2)	2.0 (1-6)

AR, allelic ratio; aza, azacitidine; ITD, internal tandem duplication; sonro, sonrotoclax; TKD, tyrosine kinase domain.

Table 2. Treatment Exposure in R/R AML

	Sonro 40 mg × 10 d (n=7)	Sonro 80 mg × 10 d (n=6)	Sonro 80 mg × 14 d (n=4)	Sonro 160 mg × 10 d (n=8)	Sonro 160 mg × 14 d (n=3)	Sonro 160 mg × 21 d (n=6)	Sonro 160 mg × 28 d (n=9)	Sonro 320 mg × 14 d (n=6)	Sonro 320 mg × 21 d (n=2)	All R/R AML (N=51)
	Aza									
No. of cycles, median (range)	2.0 (2.0-15.0)	10.5 (1.0-28.0)	1.0 (1.0-1.0)	2.5 (1.0-20.0)	1.0 (1.0-2.0)	2.0 (1.0-7.0)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	3.5 (1.0-6.0)	2.0 (1.0-28.0)
Average cycle duration, median (range), days	34.5 (29.5-41.5)	32.7 (21.0-40.9)	26.5 (22.0-44.0)	35.0 (5.0-48.7)	34.0 (23.0-44.0)	36.8 (25.0-53.0)	35.0 (25.3-55.0)	40.7 (26.5-46.0)	42.3 (35.7-49.0)	35.0 (5.0-55.0)
Relative dose intensity (sonro), median (range), %	97.4 (26.0-100)	81.1 (57.0-112.7)	100 (100-100)	100 (33.9-100)	100 (90.9-100)	79.6 (54.9-100)	84.6 (22.0-156.0)	81.1 (47.2-100)	82.1 (64.3-100)	97.4 (22.0-156.0)
Relative dose intensity (aza), median (range), %	100 (52.3-100.3)	87.4 (45.8-101.0)	100.2 (99.8-101.5)	99.8 (73.0-101.1)	100 (85.2-100.0)	99.5 (64.9-103.4)	100 (69.9-100.9)	99.8 (60.5-100.3)	92.7 (84.3-101.1)	99.9 (45.8-103.4)

aza, azacitidine; sonro, sonrotoclax.

Safety

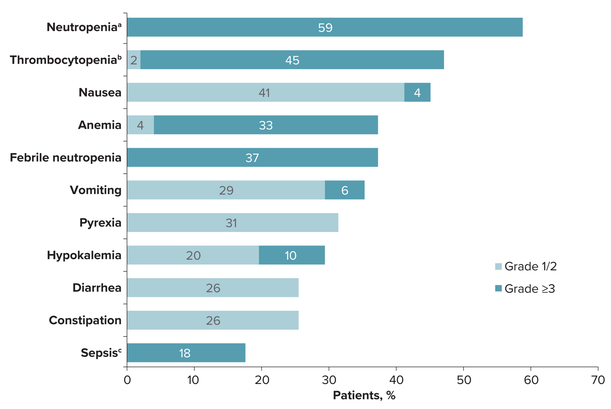
- An overall summary of TEAEs in patients with R/R AML is shown in **Table 3**
- The most common any-grade TEAEs were neutropenia (including neutrophil count decreased), thrombocytopenia (including platelet count decreased), and nausea (**Figure 3**)
  - Neutropenia was the most common grade ≥3 TEAE and grade ≥3 infections and infestations occurred in 24 patients (47%)
- The most common TEAE class leading to treatment discontinuation was infections and infestations (azacitidine, n=4; sonrotoclax, n=4)
- The most common TEAEs leading to dose reduction were neutropenia (sonrotoclax reduction, n=5) and neutrophil count decreased (azacitidine reduction, n=1)
- Six patients had a TEAE leading to death; the 30-day mortality rate was 2%
  - Two of these TEAEs were considered related to sonrotoclax, azacitidine, and disease (neutropenic sepsis [160 mg x 28 day], pneumonia [320 mg x 14 day])
  - Two TEAEs leading to death were related to PD (pulmonary mucormycosis [160 mg x 14 day], bone marrow failure [160 mg x 28 day])
  - The TEAEs of aorto-bronchial fistula (160 mg x 28 day) and Klebsiella sepsis (160 mg x 10 day) leading to death were not related to treatment or disease
- One DLT (grade 4 thrombocytopenia) occurred in the azacitidine + sonrotoclax 320 mg x 14 day cohort
- No cases of laboratory or clinical TLS were reported

Table 3. TEAE Summary

Patients, n (%)	All R/R AML (N=51)
Any TEAEs	50 (98)
Grade ≥3	45 (88)
Serious TEAEs	37 (73)
TEAEs leading to death[a]	6 (12)
TEAEs leading to discontinuation	
Aza	7 (14)
Sonro	7 (14)
TEAEs leading to reduction	
Aza	1 (2)
Sonro	7 (14)
TEAEs leading to interruption	
Aza	3 (6)
Sonro	5 (10)

[a] TEAEs leading to death were aorto-bronchial fistula, bone marrow failure, *Klebsiella* sepsis, neutropenic sepsis (related to aza and sonro), pneumonia (related to aza and sonro), and pulmonary mucormycosis.
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] Sepsis is a grouped term excluding fungal sepsis.

Antileukemic Activity

- CR/CRh was achieved in 42% of patients by a median time to CR/CRh of 1.9 months (**Table 4**)
  - The median duration of response was 13.1 months for CR (median follow-up, 20.8 months), CR/CRh (median follow-up, 3.5 months), and CR/CR with incomplete hematologic recovery (CRi; median follow-up, 3.5 months)
- The ORR was 54% in patients with R/R AML (**Figure 4**)

CONCLUSIONS

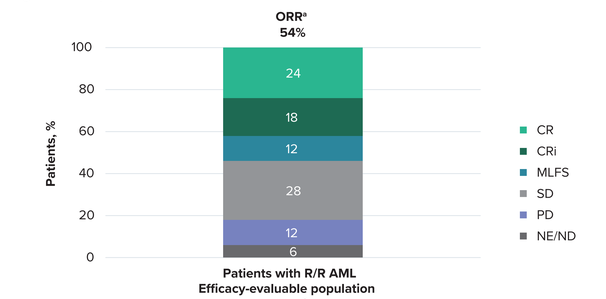
- Sonrotoclax + azacitidine combination treatment was generally well tolerated in patients with R/R AML without prior BCL2 inhibitor exposure
  - Across dose cohorts, 1 DLT of grade 4 thrombocytopenia occurred
- Sonrotoclax + azacitidine demonstrated antileukemic activity in patients with R/R AML in all dose cohorts
  - The ORR was 54%, of which CR was achieved by 24% and CR/CRh by 42%, and the transplant rate was 20%
- 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

Table 4. Summary of Disease Responses[a]

	Sonro 40 mg × 10 d (n=7)	Sonro 80 mg × 10 d (n=6)	Sonro 80 mg × 14 d (n=3)	Sonro 160 mg × 10 d (n=8)	Sonro 160 mg × 14 d (n=3)	Sonro 160 mg × 21 d (n=6)	Sonro 160 mg × 28 d (n=9)	Sonro 320 mg × 14 d (n=6)	Sonro 320 mg × 21 d (n=2)	All R/R AML (N=50)
	Aza									
CR, n (%)	2 (29)	3 (50)	1 (33)	2 (25)	0	2 (33)	2 (22)	0	0	12 (24)
Time to CR, median (range), months	3.2 (1.5-4.9)	4.1 (3.7-4.6)	0.8 (0.8-0.8)	3.2 (1.9-4.4)	-	1.4 (0.9-1.9)	1.3 (1.1-1.4)	-	-	1.9 (0.8-4.9)
Duration of CR, median (95% CI), months[b]	7.7 (2.3-NE)	18.0 (1.9-NE)	NR (NE-NE)	20.5 (NE-NE)	-	NR (NE-NE)	0.1 (NE-NE)	-	-	13.1 (0.1-20.5)
CR/CRh, n (%)	5 (71)	4 (67)	1 (33)	3 (38)	0	2 (33)	3 (33)	2 (33)	1 (50)	21 (42)
Time to CR/CRh, median (range), months	2.4 (1.2-3.5)	3.9 (1.1-4.6)	0.8 (0.8-0.8)	1.9 (1.0-1.9)	-	1.4 (0.9-1.9)	1.1 (0.8-1.4)	1.9 (1.3-2.4)	7.7 (7.7-7.7)	1.9 (0.8-7.7)
Duration of CR/CRh, median (95% CI), months[b]	8.6 (4.0-NE)	18.0 (1.9-NE)	NR (NE-NE)	20.5 (NE-NE)	-	NR (NE-NE)	NR (0.1-NE)	4.0 (0.1-NE)	NR (NE-NE)	13.1 (1.9-20.5)
CR/CRi, n (%)	4 (57)	4 (67)	1 (33)	3 (38)	0	2 (33)	3 (33)	3 (50)	1 (50)	21 (42)
Time to CR/CRi, median (range), months	3.0 (1.2-3.2)	3.0 (1.1-4.1)	0.8 (0.8-0.8)	1.0 (0.8-1.9)	-	1.4 (0.9-1.9)	1.1 (0.8-1.4)	1.2 (0.9-1.3)	7.7 (7.7-7.7)	1.3 (0.8-7.7)
Duration of CR/CRi, median (95% CI), months[b]	8.6 (4.0-NE)	18.0 (1.9-NE)	NR (NE-NE)	20.5 (NE-NE)	-	NR (NE-NE)	NR (0.1-NE)	4.0 (0.1-NE)	NR (NE-NE)	13.1 (1.9-20.5)

[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.

Figure 4. Response Rates



[a]ORR included CR, CRi, MLFS, and PR.
CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; ND, not done; NE, not evaluable.

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DISCLOSURES

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