

Updated Safety and Antileukemic Activity Data for Sonrotoclax (BGB-11417), a Potent and Selective BCL2 Inhibitor, in Patients With Relapsed/Refractory Acute Myeloid Leukemia

PF491

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CONCLUSIONS

- Sonrotoclax + azacitidine combination treatment was generally well tolerated and demonstrated antileukemic activity in patients with R/R AML without prior BCL2 inhibitor exposure, across all dose cohorts
 - One DLT of grade 4 thrombocytopenia occurred
 - The ORR was 60.3%; CR was achieved by 27.9% and CR/CRh by 42.6%
 - Overall, 23.5% of patients proceeded to transplant
- The safety stopping criteria have not been met in any of the dose cohorts
- Exploratory exposure-response analysis for the 14-d cohorts showed that antileukemic activity at exposures associated with the 320-mg dose was higher than exposures associated with 80 and 160 mg
- Follow-up evaluation of 14-d dosing cohorts is ongoing in 80-mg, 160-mg, and 320-mg cohorts to determine the recommended phase 2 dose
- Data for patients with treatment naive AML are presented in poster PF477

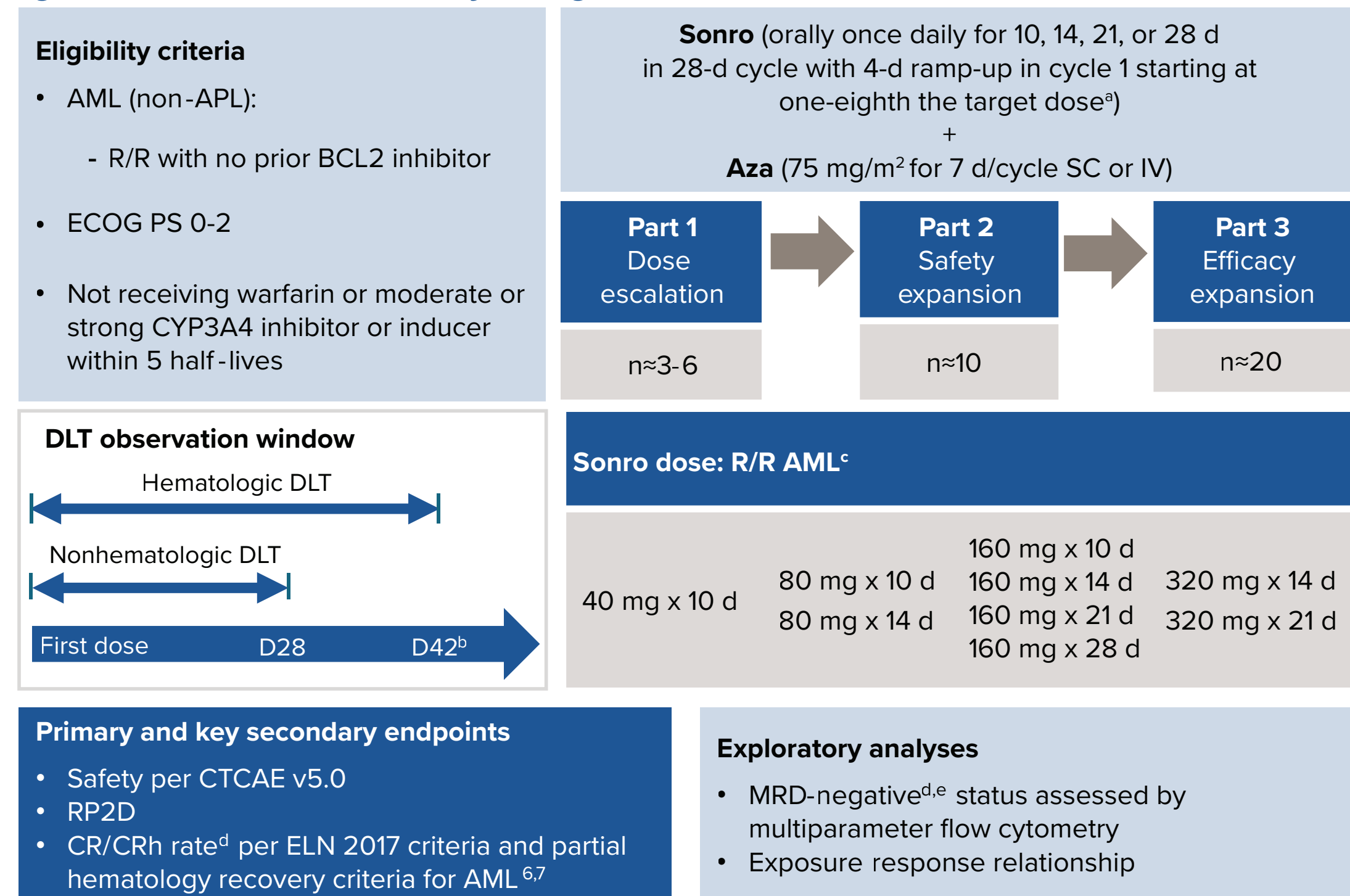
INTRODUCTION

- Acute myeloid leukemia (AML), the most common acute form of leukemia in adults, has an aggressive disease course^{1,2}
- Although treatment with venetoclax, a B-cell lymphoma 2 (BCL2) inhibitor, has improved outcomes in some patients with newly diagnosed AML,³ it is not approved in relapsed/refractory (R/R) AML⁴
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation⁵
- Updated safety and antileukemic activity data for sonrotoclax + azacitidine in R/R AML from the phase 1b part of the BGB-11417-103 study are presented

METHODS

- BGB-11417-103 (NCT04771130) is an ongoing, phase 1b/2, global, dose-finding and -expansion study evaluating the safety and antileukemic activity of sonrotoclax + azacitidine in patients with AML, myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasms (Figure 1)

Figure 1. BGB-11417-103 Study Design

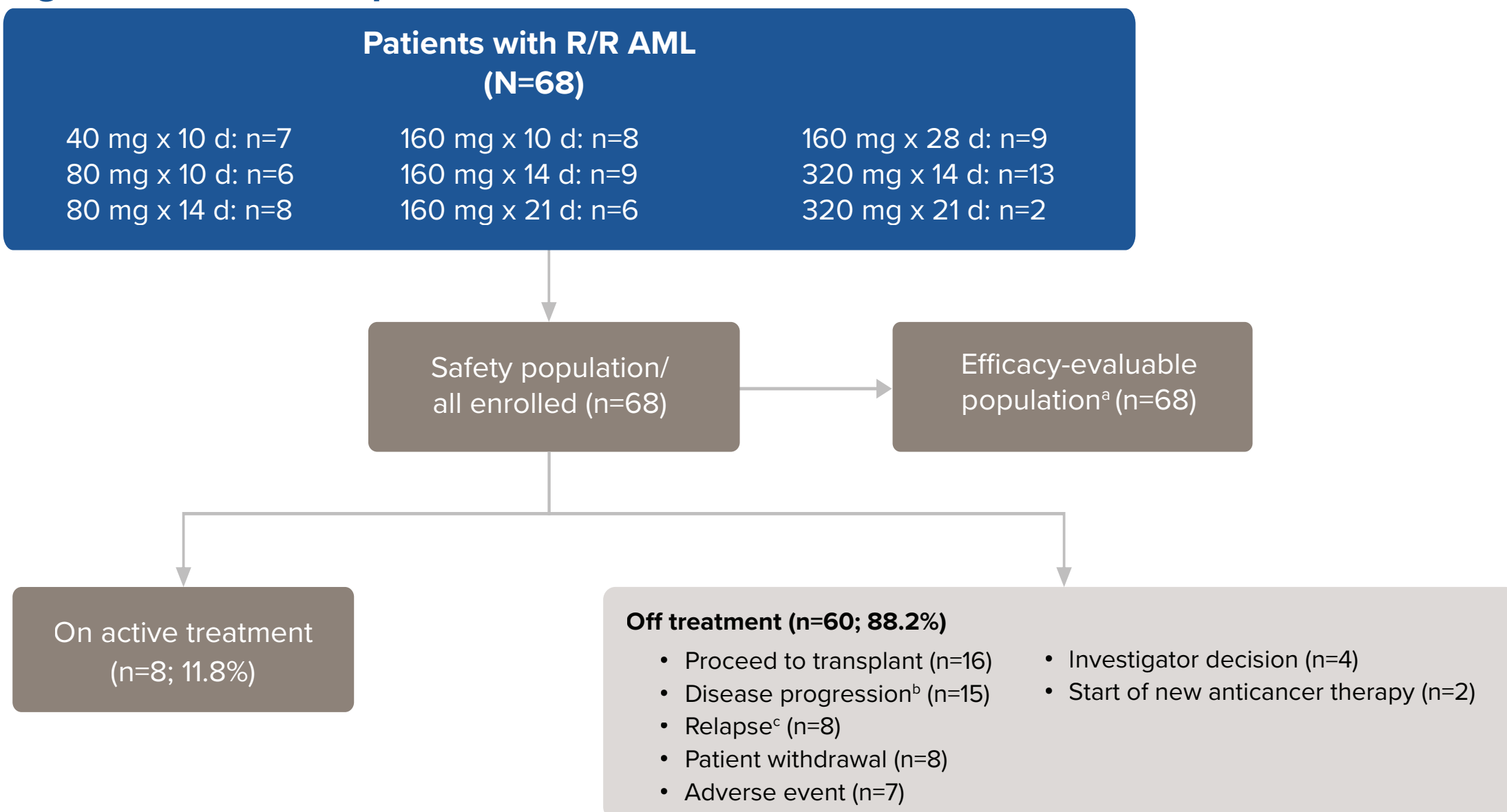


^aInitial 4-day ramp-up to mitigate potential risk of TLS. As a precautionary measure for TLS monitoring, patients were hospitalized during the ramp-up period. ^bOr C2 initiation. ^cDose reductions were done first by reducing the number of dosing days/cycles of sonro. Once 10-d dosing was reached, aza dosing was reduced and then sonro daily dose. ^dResponse and MRD status were assessed at end of C1 (C2 if remission not yet achieved) and then every three cycles until C13, then every six cycles. ^eMRD-negative was defined as ≤ 1 residual leukemic blasts per 1,000 leukocytes or 10^3 at any time on the study. ^fAbbreviations: APL, acute promyelocytic leukemia; aza, azacitidine; C, cycle; CYP3A4, cytochrome P450 3A4; d, day; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; IV, intravenous; MRD, minimal residual disease; RP2D, recommended phase 2 dose; SC, subcutaneous; sonro, sonrotoclax; TLS, tumor lysis syndrome.

RESULTS

- As of January 10, 2025, 68 patients with R/R AML were enrolled and treated with sonrotoclax + azacitidine; 8 (11.8%) remained on treatment (Figure 2)
- The median age was 60 years and the median number of prior lines of therapy was 1.0 (Table 1)
- The median number of study treatment cycles was 2; median average cycle length was 35.0 days (d)
- The median relative dose intensity of sonrotoclax was >80%, except in the 80-mg × 10-d cohort (74.9%)

Figure 2. Patient Disposition



Data cutoff: January 10, 2025. ^aPatients 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. ^bDefined as evidence of an increase in bone marrow blast percentage and/or in absolute blast counts in the blood, both per ELN 2017 response criteria. ^cHematologic relapse (after CR/CRh) defined as bone marrow blasts $\geq 5\%$, reappearance of blasts in the blood, or development of extramedullary disease. ^dAbbreviations: CR, CR with incomplete hematologic recovery; ELN, European LeukemiaNet.

Table 1. Baseline Patient Characteristics and Treatment Exposure in R/R AML

	Sonro dose + aza											Total (N=68)
	40 mg × 10 d (n=7)	80 mg × 10 d (n=6)	80 mg × 14 d (n=8)	160 mg × 10 d (n=9)	160 mg × 14 d (n=13)	160 mg × 21 d (n=6)	160 mg × 28 d (n=9)	320 mg × 14 d (n=13)	320 mg × 21 d (n=2)			
Study follow-up time, median (range), months	15.4 (9.2-39.5)	20.8 (1.5- 37.8)	5.0 (2.2-10.2)	6.8 (0.2-24.5)	5.5 (1.5-11.1)	6.8 (4.6-16.5)	4.9 (1.2-31.2)	5.9 (0.9-17.0)	12.1 (2.6-21.6)	6.2 (0.2-39.5)		
Age, median (range), years	64.0 (36-90)	70.0 (54-78)	57.5 (48-83)	52.5 (36-71)	53.0 (27-72)	53.0 (42-66)	57.0 (29-69)	64.0 (43-81)	70.0 (67-73)	60.0 (27-83)		
Male, n (%)	3 (42.9)	3 (50.0)	5 (62.5)	5 (62.5)	5 (55.6)	4 (66.7)	6 (66.7)	9 (69.2)	1 (50.0)	41 (60.3)		
AML type, n (%)												
De novo	7 (100)	4 (66.7)	7 (87.5)	7 (87.5)	5 (55.6)	6 (100)	8 (88.9)	12 (92.3)	1 (50.0)	57 (83.8)		
Secondary	0	2 (33.3)	1 (12.5)	1 (12.5)	4 (44.4)	0	1 (11.1)	1 (7.7)	1 (50.0)	11 (16.2)		
HMA failure, n (%) ^a	0	0	1 (12.5)	0	1 (11.1)	1 (16.7)	1 (11.1)	2 (15.4)	1 (50.0)	7 (10.3)		
ELN 2017 AML risk stratification, ^a n (%)												
Favorable	2 (28.6)	1 (16.7)	0	2 (25.0)	2 (22.2)	0	3 (33.3)	5 (38.5)	0	15 (22.1)		
Intermediate	1 (14.3)	1 (16.7)	4 (50.0)	2 (25.0)	3 (33.3)	2 (33.3)	1 (11.1)	1 (7.7)	0	15 (22.1)		
Adverse	4 (57.1)	4 (66.7)	4 (50.0)	4 (50.0)	4 (44.4)	4 (66.7)	5 (55.6)	7 (53.8)	2 (100)	38 (55.9)		
Positive genetic abnormality, n (%) ^b												
IDH1/IDH2	2 (28.6)	3 (50.0)	1 (12.5)	3 (37.5)	1 (11.1)	1 (16.7)	3 (33.3)	1 (7.7)	0	15 (22.1)		
FLT3	0	1 (16.7)	1 (12.5)	1 (12.5)	0	1 (16.7)	2 (22.2)	2 (15.4)	1 (50.0)	9 (13.2)		
NPM1	2 (28.6)	1 (16.7)	0	2 (25.0)	1 (11.1)	0	3 (33.3)	1 (7.7)	0	10 (14.7)		
TP53 aneuploidy or -170b/n(17p)	1 (14.3)	1 (16.7)	1 (12.5)	0	0	1 (16.7)	0	1 (7.7)	1 (50.0)	6 (8.8)		
Prior therapy												
Prior aza exposure, n (%)	0	1 (16.7)	3 (37.5)	0	2 (22.2)	1 (16.7)	1 (11.1)	3 (23.1)	1 (50.0)	12 (17.6)		
No. of lines of prior systemic therapy, median (range)	1.0 (1-2)	1.0 (1-2)	1.5 (1-5)	2.0 (1-2)	2.0 (1-4)	2.0 (1-6)	1.0 (1-3)	1.0 (1-3)	1.5 (1-2)	1.0 (1-6)		
Treatment exposure												
No. of cycles, median (range)	2.0 (2.0-15.0)	10.5 (1.0-36.0)	2.0 (1.0-8.0)	2.5 (1.0-20.0)	2.0 (1.0-5.0)	2.0 (1.0-7.0)	2.0 (1.0-4.0)	3.0 (1.0-12.0)	3.5 (1.0-6.0)	2.0 (1.0-36.0)		
Average cycle duration, median (range), days	35.0 (29.5-41.5)	33.3 (21.0-40.9)	34.8 (28.0-44.0)	35.0 (5.0-48.7)	33.2 (22.0-44.0)	36.8 (22.0-44.0)	36.8 (25.0-53.0)	35.0 (25.3-55.0)	42.3 (35.7-49.0)	35.0 (5.0-55.0)		
Relative sonro dose intensity, median (range), %	100.0 (76.5-100.0)	74.9 (57.0-112.7)	91.1 (47.9-100.0)	100.0 (83.9-100.0)	100.0 (79.4-103.9)	89.8 (54.9-100.0)	90.0 (54.9-100.0)	96.3 (50.7-116.8)	82.1 (64.3-101.1)	97.6 (22.0-156.0)		
Relative aza dose intensity, median (range), %	100.0 (52.3-100.3)	85.5 (45.8-101.0)	99.9 (69.5-101.5)	99.8 (73.0-101.1)	99.5 (79.2-100.8)	99.5 (64.9-103.4)	100.0 (69.9-100.9)	99.7 (52.5-109.1)	92.7 (84.3-101.1)	99.7 (45.8-109.1)		

^aHMA failure received ≥ 1 cycle of HMA and had PD or no PR or better hematologic improvement after four cycles of >75% of planned dose. ^bAs reported by investigator. ^cAbbreviations: aza, azacitidine; ELN, European LeukemiaNet; HMA, hypomethylating agent; PD, progressive disease; PR, partial response; sonro, sonrotoclax.

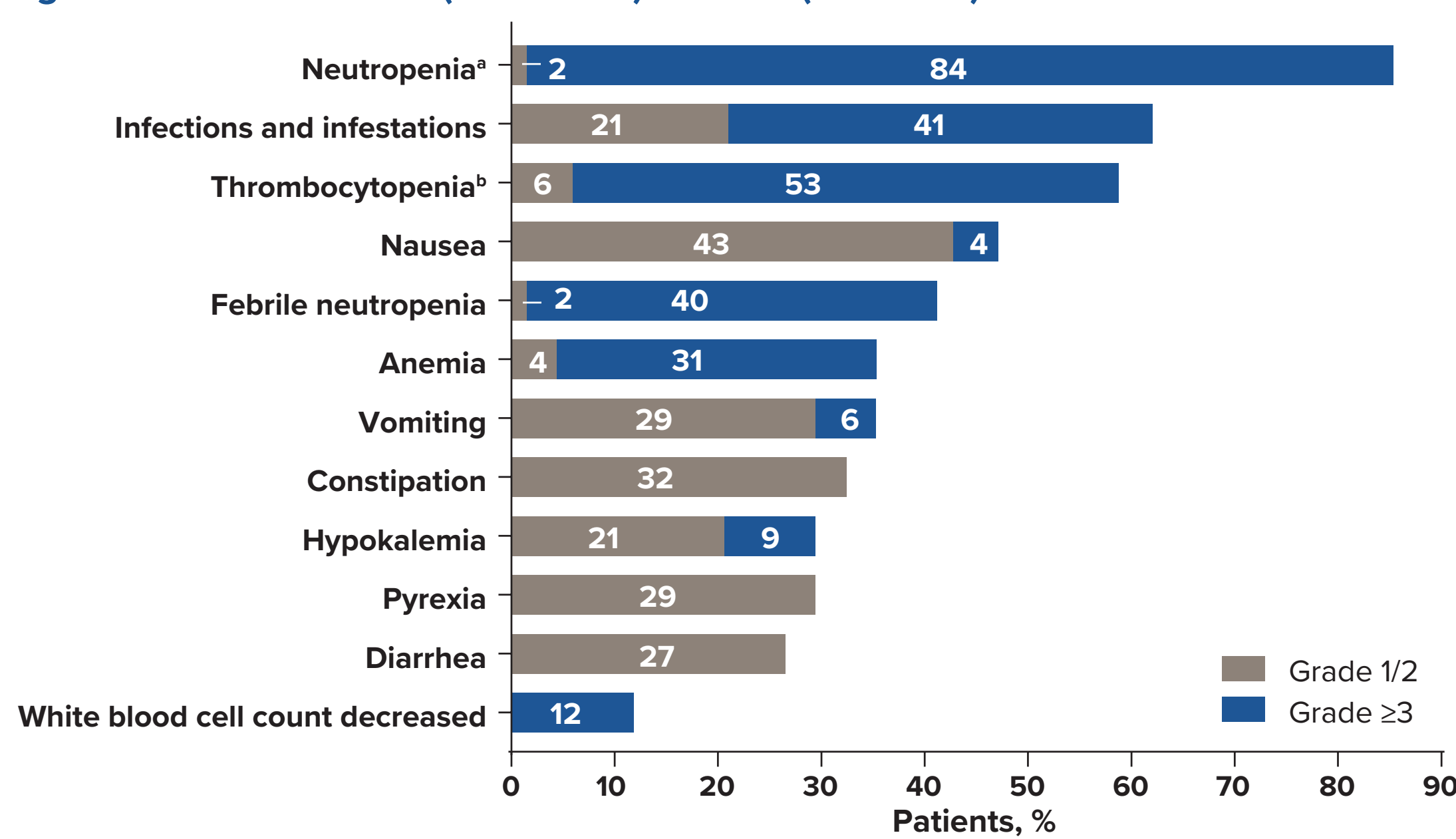
- Treatment-emergent adverse events (TEAEs) were similar in frequency and severity across doses (Table 2)
- The most common any-grade and grade ≥ 3 TEAEs were neutropenia, infections and infestations, and thrombocytopenia (Figure 3)
- No cases of laboratory or clinical tumor lysis syndrome were reported
- One dose-limiting toxicity (DLT), grade 4 thrombocytopenia, occurred with 320 mg × 14 d
- Six patients (8.8%) had a TEAE leading to death; 2 cases were treatment related (160 mg × 28 d, neutropenic sepsis; 320 mg × 14 d, pneumonia); the 30-d mortality rate was 1.5%
- Treatment discontinuation due to TEAEs occurred in 7 patients (10.3%)
 - The most common TEAE classes leading to discontinuation of sonrotoclax (n=4, 5.9%) or azacitidine (n=4, 5.9%) were infection and infestations
- TEAEs leading to dose reduction occurred in 8 patients (11.8%) and 2 patients (2.9%) with sonrotoclax and azacitidine, respectively
 - The most common TEAE class leading to dose reduction of sonrotoclax was neutropenia (n=7, 10.3%) and of azacitidine was neutropenia and thrombocytopenia (n=1 each, 1.5%)

Table 2. TEAE Summary in R/R AML

	Sonro dose + aza											Total (N=68)
	40 mg × 10 d (n=7)	80 mg × 10 d (n=6)	80 mg × 14 d (n=8)	160 mg × 10 d (n=9)	160 mg × 14 d (n=13)	160 mg × 21 d (n=6)	160 mg × 28 d (n=9)	320 mg × 14 d (n=13)	320 mg × 21 d (n=2)			
Any TEAEs	7 (100)	6 (100)	8 (100)	8 (100)	9 (100)	6 (100)	9 (100)	13 (100)	2 (100)	68 (100)		
Grade ≥ 3	7 (100)	5 (83.3)	7 (87.5)	7 (87.5)	8 (88.9)	5 (83.3)	9 (100)	13 (100)	2 (100)	63 (92.6)		
Neutropenia ^a	5 (71.4)	5 (83.3)	7 (87.5)	6 (75.0)	8 (88.9)	5 (83.3)	9 (100)	11 (84.6)	1 (50.0)	57 (83.8)		
Thrombocytopenia ^a	2 (28.6)	2 (33.3)	4 (50.0)	7 (87.5)	4 (44.4)	1 (16.7)	7 (77.8)	9 (69.2)	0	36 (52.9)		
Infection and infestation	4 (57.1)	4 (66.7)	0	5 (62.5)	6 (66.7)	1 (16.7)	2 (22.2)	4 (30.8)	2 (100)	28 (41.2)		
Serious TEAEs	5 (71.4)	4 (66.7)	4 (50.0)	7 (87.5)	8 (88.9)	4 (66.7)	7 (77.8)	8 (61.5)	2 (100)	49 (72.1)		
DLT, n/N (%)	0	0	0	0	0	0	0	1/12 (8.3) ^b	0	1/62 (1.6)		
Led to death ^c	0	0	0	1 (12.5)	1 (11.1)	0	3 (33.3)	1 (7.7)	0	6 (8.8)		
Led to discontinuation												
Aza	1 (14.3)	0	0	2 (25.0)	1 (11.1)	1 (16.7)	1 (11.1)	2 (15.4)	0	8 (11.8)		
Sonro	1 (14.3)	0	0	2 (25.0)	1 (11.1)	1 (16.7)	1 (11.1)	2 (15.4)	0	8 (11.8)		
Led to reduction												
Aza	0	1 (16.7)	0	0	0	0	0	1 (7.7)	0	2 (2.9)		
Sonro	0	2 (33.3)	1 (12.5)	1 (12.5)	0	1 (16.7)	1 (11.1)	1 (7.7)	1 (50.0)	8 (11.8)		
Led to interruption												
Aza	0	2 (33.3)	0	2 (25.0)	3 (33.3)	1 (16.7)	0	0	0	8 (11.8)		
Sonro	0	1 (16.7)	0	2 (25.0)	2 (22.2)	2 (33.3)	2 (22.2)	0	0	9 (13.2)		

^aNeutropenia includes the terms neutropenic, febrile neutropenia, neutrophil count decreased, and neutropenic sepsis. ^bThrombocytopenia includes the terms thrombocytopenia and platelet count decreased. ^cAchieved best response of CR/CRh and continued treatment with a dose (duration) reduction after count recovery. ^dAorto-bronchial fistula (160 mg × 28 d), bone marrow failure (160 mg × 28 d related to PD), Klebsiella sepsis (160 mg × 10 d, neutropenic sepsis [160 mg × 28 d, related to aza, sonro, and disease], pneumonia (320 mg × 14 d, related to aza, sonro, and disease), and pulmonary mucormycosis (160 mg × 14 d, related to PD). ^eAbbreviations: aza, azacitidine; CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; DLT, dose-limiting toxicity; PD, progressive disease; sonro, sonrotoclax.

Figure 3. TEAEs in $\geq 20\%$ (All Grades) or $\geq 10\%$ (Grade ≥ 3) of Patients With R/R AML



^aNeutropenia includes the terms neutropenic, febrile neutropenia, neutrophil count decreased, and neutropenic sepsis. ^bThrombocytopenia includes the terms thrombocytopenia and platelet count decreased.

^cAbbreviation: TEAE, treatment-emergent adverse event.

- With a median follow-up of 6.2 months (m), the overall response rate (ORR) in all patients was 60.3% (Figure 4A)
 - Complete response (CR)/CR with partial hematologic recovery (CRh) was achieved in 42.6% (95% CI, 30.7%-55.2%) of patients by a median time of 1.7 m; CR was achieved in 27.9% (95% CI, 17.7%-40.1%) of patients by a median of 1.9 m (Table 3 and Figure 4B)
 - In the cohorts with the longest follow-up (40, 80, and 160 mg × 10 d), 50%, 75% and 100% of patients who achieved CR/CRh, respectively, remained alive and progression free at 12 m since the first determination of response
- Overall, 23.5% of patients proceeded to transplant
- Minimal residual disease–negative status was achieved by 20.6% of patients (Figure 4C)

Table 3. Summary of Disease Responses in R/R AML^a

	Sonro dose + aza											
	40 mg × 10 d (n=7)	80 mg × 10 d (n=6)	80 mg × 14 d (n=8)	160 mg × 10 d (n=8)	160 mg × 14 d (n=9)	160 mg × 21 d (n=6)	160 mg × 28 d (n=9)	320 mg × 14 d (n=13)	320 mg × 21 d (n=2)	Total (N=68)		
CR, n (%)	2 (28.6)	3 (50.0)	2 (25.0)	2 (25.0)	1 (11.1)	2 (33.3)	2 (22.2)	5 (38.5)	0	19 (27.9)		
Time to CR, median (range), months	3.2 (1.5-4.9)	4.1 (3.7-4.6)	1.9 (1.7-2.1)	3.2 (1.9-4.4)	2.3 (2.3-2.3)	1.4 (0.9-1.9)	1.3 (1.1-1.4)	1.2 (0.8-5.1)	–	1.9 (0.8-5.1)		
By end of cycle 2, n (%)	1 (14.3)	0	2 (25.0)	1 (12.5)	1 (11.1)	2 (33.3)	2 (22.2)	4 (30.8)	0	13 (19.1)		
CR/CRh, n (%)	5 (71.4)	4 (66.7)	2 (25.0)	3 (37.5)	1 (11.1)	2 (33.3)	3 (33.3)	8 (61.5)	1 (50.0)	29 (42.6)		
Time to CR/CRh, median (range), months	2.4 (1.2-3.5)	3.9 (1.4-6)	1.9 (1.7-2.1)	1.9 (1.0-1.9)	1.4 (1.4-1.4)	1.4 (0.9-1.9)	1.1 (0.8-1.4)	1.3 (0.8-5.1)	7.7 (7.7-7.7)	1.7 (0.8-7.7)		
CR/CRI, n (%)	4 (57.1)	4 (66.7)	4 (50.0)	3 (37.5)	1 (11.1)	2 (33.3)	3 (33.3)	9 (69.2)	1 (50.0)	31 (45.6)		
Time to CR/CRI, median (range), months	2.0 (1.2-3.2)	3.0 (1.4-4)	1.0 (0.8-2.4)	1.0 (0.8-1.9)	1.4 (1.4-1.4)	1.4 (0.9-1.9)	1.1 (0.8-1.4)	1.2 (0.8-5.1)	7.7 (7.7-7.7)	1.7 (0.8-7.7)		
Proceeded to transplant, n (%)	3 (42.9)	1 (16.7)	2 (25.0)	2 (25.0)	3 (33.3)	2 (33.3)	2 (22.2)	1 (7.7)	0	16 (23.5)		
MRD negative, n (%)	2 (28.6)	1 (16.7)	0	1 (12.5)	1 (11.1)	2 (33.3)	1 (11.1)	5 (38.5)	1 (50.0)	14 (20.6)		
MRD nE/d, n (%)	2 (28.6)	1 (16.7)	3 (37.5)	2 (25.0)	5 (55.6)	2 (33.3)	7 (77.8)	3 (23.1)	1 (50.0)	26 (38.8)		