Vorläufige Sicherheit und antileukämische Aktivität von Sonrotoclax (BGB-11417), einem wirksamen und selektiven BCL2-inhibitor, bei therapienaiven Patienten mit Akuter Myeloischer Leukämie

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Presented at the Annual Meeting of the German, Austrian and Swiss Societies of Hematology and Medical Oncology 2024; October 11-14, 2024; Basel, Switzerland
Data originally presented at the EHA2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain. Abstract P538

Disclosures for Uwe Platzbecker

- **Honoraria**: Novartis, BMS, Janssen, AbbVie, Curis, Geron, Jazz, Akeso, Gilead, Servier
- **Consulting or advisory role**: AbbVie, BMS, Janssen, Novartis, GSK, Hemavant
- **Speakers bureau**: Novartis, BMS, Janssen, Jazz, Takeda, Sobi, Blueprint, AstraZeneca
- **Travel, accommodations, expenses**: AbbVie, Janssen

Introduction

- AML is the most common acute form of leukemia in adults and has an aggressive disease course[1,2]
- The BCL2 inhibitor venetoclax + azacitidine (aza) has improved outcomes in TN patients with AML unfit for intensive chemotherapy compared with aza alone[3]; however, relapse is common and prognosis is suboptimal[4,5]
- Sonrotoclax (sonro; 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, sonro has been well tolerated, with preliminary antitumor activity in B-cell malignancies, AML/MDS, and multiple myeloma[7-9]
- Here, we present the preliminary safety and antileukemic activity of sonro + aza in TN patients with unfit AML in BGB-11417-103, a phase 1b/2 study

AML, acute myeloid leukemia; BCL2, B-cell lymphoma 2; MDS, myelodysplastic syndromes; TN, treatment naive.

1. Shimony S, et al. *Am J Hematol*. 2023;98(3):502-526; 2. Yi M, et al. *J Hematol Oncol*. 2020;13(1):72; 3. DiNardo CD, et al. *N Engl J Med*. 2020;383(7):617-629;
4. Thol F, Ganser A. *Curr Treat Options Oncol*. 2020:21(8):66; 5. Greiner J, et al. *Int J Mol Sci*. 2022:23(6):3304; 6. Hu N, et al. AACR 2020. Abstract 3077; 7. Li C, et al. ASCO 2023. Abstract 7558;
8. Shortt J, et al. ASH 2022. Abstract 1443; 9. Quach H, et al. ASH 2023. Abstract 1011.

BGB-11417-103 (NCT04771130; EudraCT: 2021-003285-12) Study Design

- BGB-11417-103 is an ongoing, global, multicenter, dose-finding and -expansion study evaluating sonro ± aza in patients with AML, MDS, or MDS/MPN

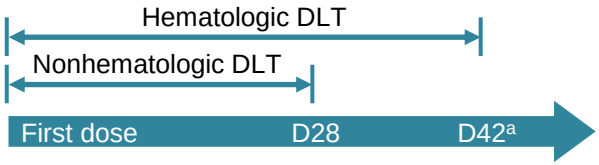
Eligibility criteria

- AML (non-APL):
  - TN unfit for intensive chemotherapy
  - No prior BCL2 inhibitor or aza exposure
- ECOG PS 0-2
- Not receiving warfarin; moderate or strong CYP3A4 inhibitor or inducer within 5 half-lives

Sonro (10, 14, 21, or 28 days in 28-day cycle with 4-day ramp-up in cycle 1 starting at 1/8th of the target dose[b])
+
Aza (75 mg/m^2 for 7 days SC or IV)

Part 1 Dose escalation	**Part 2** Safety expansion[c]	**Part 3** Efficacy expansion[c]
3-6 patients	≈10 patients	≈20 patients (TN AML)

DLT observation window

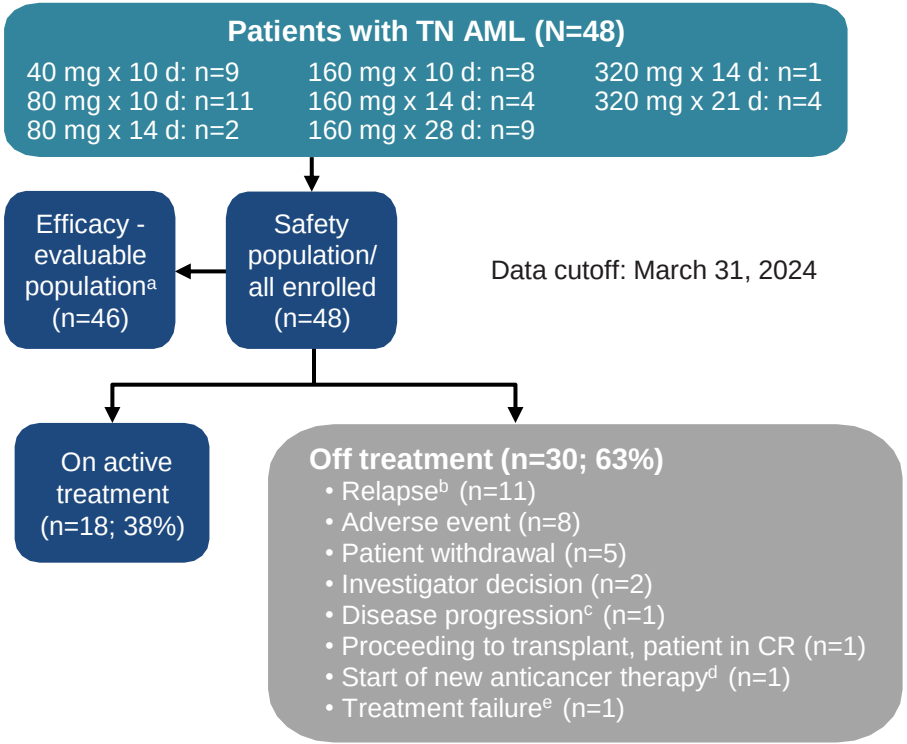


Sonro dose: TN AML		
40 mg x 10 days	160 mg x 10 days	320 mg x 21 days
80 mg x 10 days	160 mg x 28 days	320 mg x 28 days
Intermediate doses		
80 mg x 14 days	160 mg x 14 days	320 mg x 14 days

[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.
AML, acute myeloid leukemia; CYP3A4, cytochrome P450 3A4; HMA, hypomethylating agent; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; non-APL, nonacute promyelocytic leukemia.

Patient Disposition

- As of March 31, 2024, 48 patients with TN AML were enrolled and had received sonro + aza treatment
- Eighteen patients (38%) remain on treatment



[a] 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 (per ELN 2017). Two patients have yet to complete cycle 1 and were excluded. [b] Hematologic relapse (after CR/CRi) = BM blasts ≥5%, reappearance of blasts in blood, or development of extramedullary disease. [c] Evidence for an increase in BM blast percentage and/or increase in absolute blast counts in blood. [d] Patient switched therapy while in CRi. [e] No CR or CRi after 6 cycles of sonro + aza.
CRi, CR with incomplete hematologic recovery; ELN, European LeukemiaNet.

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)

[a] Missing data for 2 patients (n=1, 160 mg x 10-day cohort; n=1, 160 mg x 28-day cohort).

Baseline Patient Characteristics (cont.)

	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								
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[a]	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] No patients had *IDH2-R172* abnormality.
AR, allelic ratio; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

Overall TEAE Summary

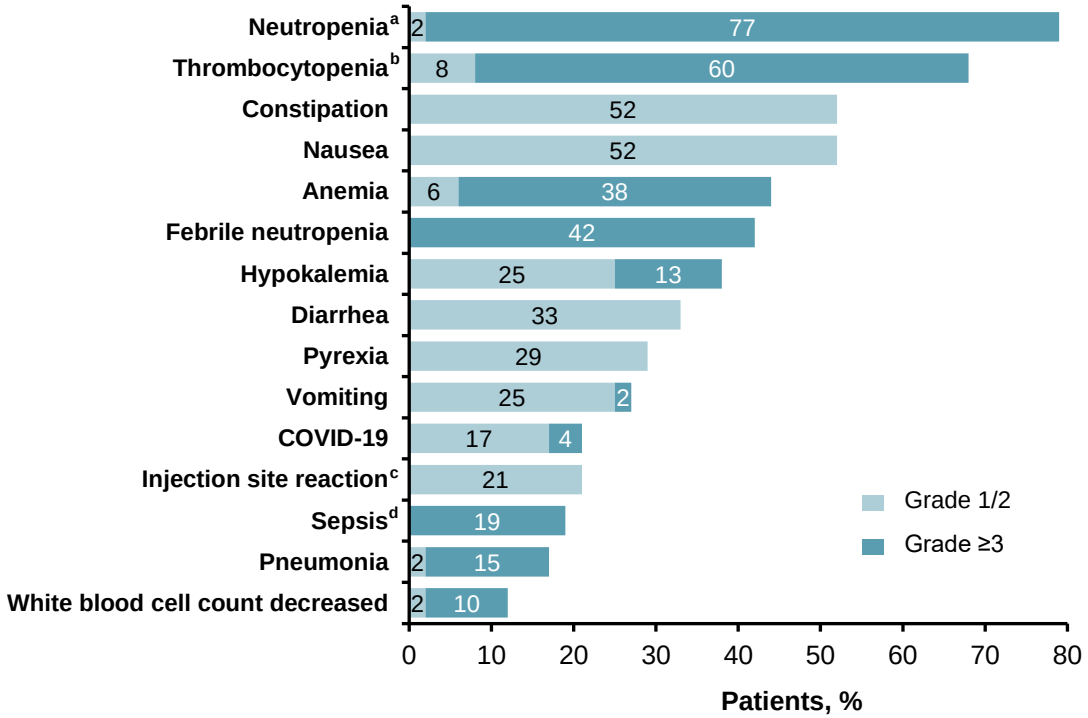
- Five patients had a TEAE leading to death, none related to sonro or aza treatment; the 30-day mortality rate was 2%
  - Two TEAEs leading to death, disease-related: bronchopulmonary aspergillosis (80 mg x 10 d); neutropenic sepsis (160 mg x 10 d)
  - Three TEAEs leading to death, not disease-related: pulmonary sepsis[a] (40 mg x 10 d); hospital acquired pneumonia (80 mg x 10 d); metastatic squamous cell carcinoma (80 mg x 10 d)
- Three DLTs in 2 patients (aza + sonro 80 mg x 10-d): grade 4 neutropenia (n=1) and grade 4 thrombocytopenia (n=2)
- Laboratory TLS in 1 patient (aza + sonro 160 mg x 10-d): had hyperuricemia and hyperphosphatemia in cycle 2; resolved in 4 d with concomitant allopurinol

Patients, n (%)	All TN AML (N=48)
Any TEAEs	48 (100)
Grade ≥3	44 (92)
Serious TEAEs	37 (77)
TEAEs leading to death	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] Without preceding confirmed pneumonia.
D, day.

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

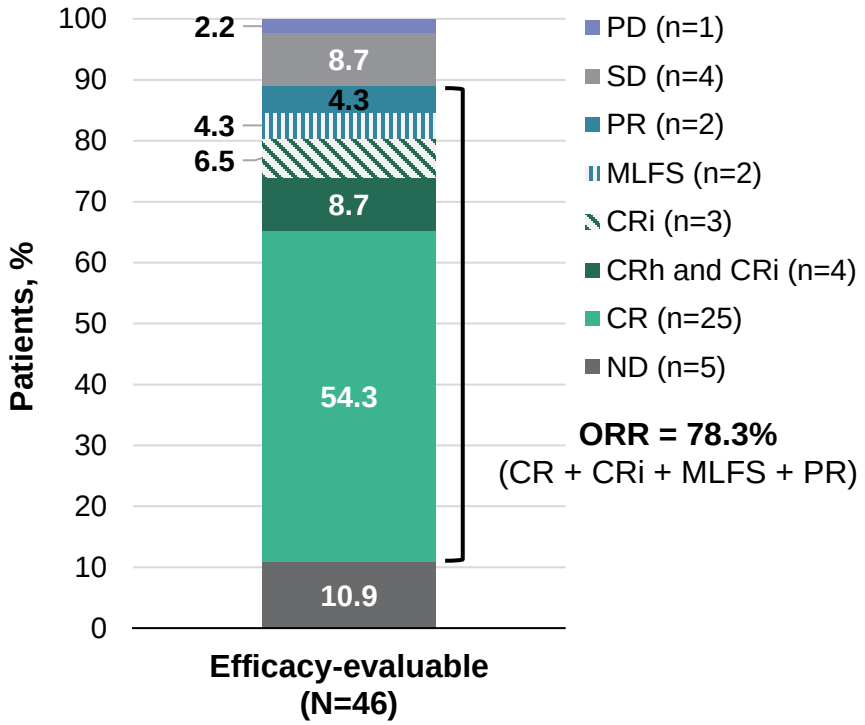
- Most common any-grade TEAEs: neutropenia,[a] thrombocytopenia,[b] constipation, and nausea
  - Most common grade ≥3 TEAEs: neutropenia and thrombocytopenia
  - Grade ≥3 infections and infestations occurred in 24 patients (50%)
- Most common TEAE class leading to treatment discontinuation: infections and infestations (aza, n=5; sonro, n=5)
- Most common TEAE leading to dose reduction: neutropenia (sonro reduction, n=9; aza reduction, n=11)



[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 aza. [d] Sepsis is a grouped term excluding fungal sepsis.

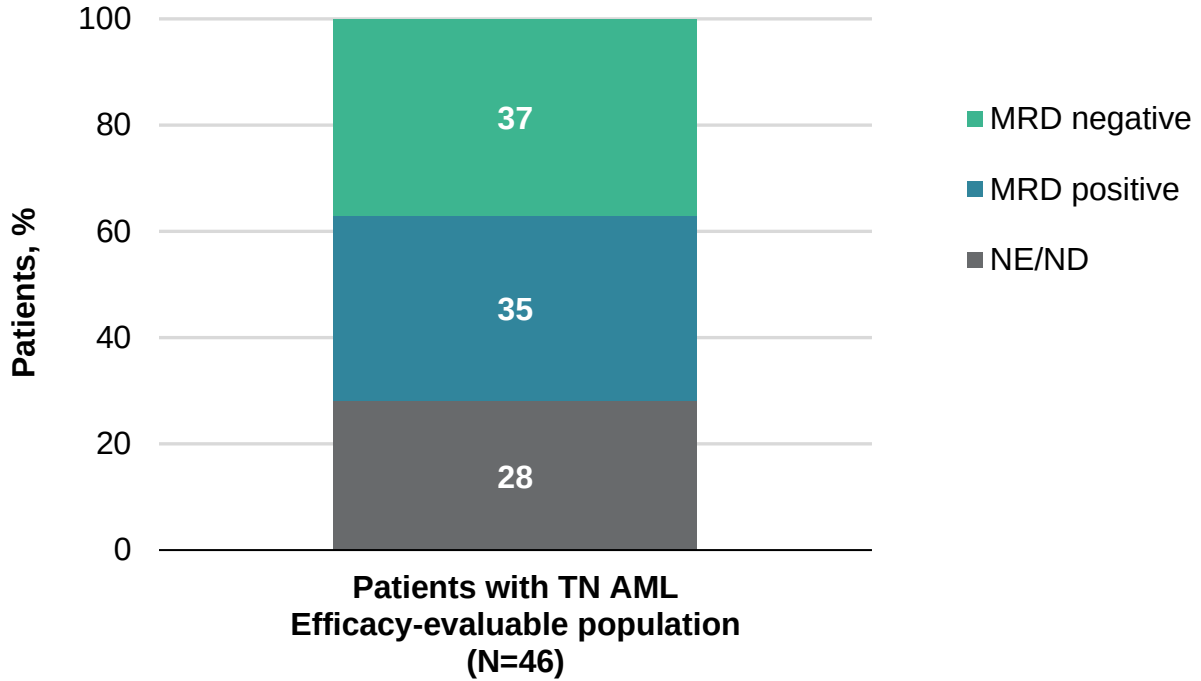
In patients with TN unfit AML, ORR was 78%

- CR/CRh rate: 63%
  Median time to CR/CRh, 1.3 months
- Median DOR for CR: 15.1 months
  Median follow-up, 19.8 months
- Median DOR for CR/CRh and CR/CRi: 16.9 months
  Median follow-up, 19.8 months



CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; DOR, duration of response; MLFS, morphologic leukemia-free state; ND, not done; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

MRD–negative status was achieved by 37% of patients with TN unfit AML



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

Conclusions

- Sonro + aza 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
- Sonro + aza 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

Acknowledgments

- The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers
- This study was sponsored by BeiGene, Ltd
- Medical writing was provided by Kendall Foote, PhD, of Nucleus Global, an Inizio company, and supported by BeiGene

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Backup Slides

Treatment Exposure in TN AML

- The median number of treatment cycles was 7, with the longest average cycle duration (median, 35.1 days) in the aza + sonro 160 mg x 28 day cohort

	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)

- The median dose intensity relative to the assigned dose of sonro was >80% except in the aza + sonro 160 mg x 28 day and 320 mg x 21 day cohorts

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 ELN 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.
CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; NE, not estimable, NR, not reached.