

Phase 1/2 Study of the All-Oral Combination of Revumenib (SNDX-5613) with Decitabine/Cedazuridine (ASTX727) and Venetoclax (SAVE) in Relapsed/Refractory AML

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Abstract

Background: Revumenib is an oral, selective inhibitor of the menin-KMT2A interaction, a critical dependency in *KMT2Ar*, *NUP98r*, and *NPM1mt* acute leukemias. Dual inhibition of menin and BCL2 shows synergistic activity in preclinical models.

Aim: To describe the safety and efficacy of the all-oral combination of revumenib, ASTX727, and venetoclax in children and adults with relapsed/refractory (R/R) AML (NCT05360160).

Methods: Patients (pts) aged ≥12 years with R/R AML or myeloid MPAL were enrolled. Phase 1 followed a 3+3 design. ASTX727 (35/100 mg) was given PO on days 1–5, venetoclax 400 mg PO on days 1–14, and revumenib 113 mg (DL0) or 163 mg (DL1) PO Q12h on days 1–28 with posaconazole or voriconazole prophylaxis. Revumenib monotherapy was resumed post-HSCT for 1-year of maintenance. A protocol amendment allowed holding revumenib after day 21 if day 14 bone marrow blasts were <5%. Measurable residual disease (MRD) analysis was done by multicolor flow cytometry (MFC, sen 10⁻⁴). Mutational analysis to assess resistance, and molecular MRD at 10⁻⁵ were performed.

Results: As of the data cutoff (Feb 2026), 42 pts with R/R AML were enrolled. The median age was 40 years (range, 12–82), including 5 adolescents (12%). Seventeen pts (40%) had *KMT2Ar*, 16 (38%) *NPM1mt*, and 9 (21%) *NUP98r*. Pts were heavily pretreated (median 2 prior lines, range 1–5); 60% had prior venetoclax, 50% prior hypomethylating agents, 32% prior HSCT, and 2 pts (5%) had prior menin inhibitor. The recommended phase 2 dose of revumenib was 163 mg PO Q12h with strong CYP3A4 inhibitors.

The most common all-grade adverse events were nausea (60%), vomiting (52%), QTc prolongation (50%), and hypokalemia (45%), mostly grade 1–2. Grade ≥3 events were most frequently febrile neutropenia (35%), thrombocytopenia (22%), lung infection (20%), and respiratory failure (15%). QTc prolongation grade ≥3 occurred in 2 pts (5%). Differentiation syndrome occurred in 4 pts (10%) [grade ≥3, in 2 pts (5%)], all resolved with steroids. There were no grade 5 treatment-related toxicities or early (60-day) mortality.

The overall response rate (CR+CRh+CRi+PR+MLFS) was 88% (37/42 pts), including 100% (17/17) in *KMT2Ar*, 75% (12/16) in *NPM1mt*, and 89% (8/9) in *NUP98r*. The CR/CRh rate was 60% (25 pts), with CR in 43% (18 pts), CRh in 17% (7 pts), CRi in 10% (4 pts), CRp in 2% (1 pt), MLFS in 14% (6 pts), and PR in 2% (1 pt). Median time to best response was 1 cycle (range, 1–3), and MRD negativity by MFC in responders was 64% (24/37), and 80% (20/25) in those with CR/CRh. Twenty pts (48%) proceeded to HSCT, with 71% (12/17), in *KMT2Ar*, 38% (6/16) in *NPM1mt* and 22% (2/9) in *NUP98r*.

With a median follow-up of 14 months, 18-mo overall survival (OS) was 43% (95% CI, 29–63) for all, with an 18-months OS of 47% (95% CI, 28–78) for *KMT2Ar*, 44% (95% CI, 17–100) for *NUP98r*, and 36% (95% CI, 18–76) for *NPM1mt*. Among pts achieving CR/CRh, 18-months OS was 61% (95% CI, 43–87), and 50% (95% CI, 32–77) remained in remission at 18 months. Median duration of response in pts with CR/CRh was not reached for *KMT2Ar*, 10 months (95% CI, 7.5–NR) for *NPM1mt*, and 5.9 months (95% CI, 4.1–NR) for *NUP98r* (Figure). Mutational analysis to assess resistance and molecular MRD assessments are ongoing, and results will be presented.

Conclusions: The all-oral combination of revumenib, venetoclax, and decitabine yields high remission rates in R/R AML with *KMT2Ar*, *NPM1mt*, or *NUP98r*, with durable responses in patients achieving deep remission.

Introduction

- Revumenib is an oral, selective inhibitor of the menin-KMT2A interaction, a critical dependency in *KMT2Ar*, *NUP98r*, and *NPM1mt* acute leukemias.
- Dual inhibition of menin and BCL2 shows synergistic activity in preclinical models.

Aim

- We sought to describe the safety and efficacy of the all-oral combination of revumenib, ASTX727, and venetoclax in children and adults with R/R AML (NCT05360160).

Methods

- Patients aged ≥12 years with R/R AML or myeloid MPAL were enrolled. Phase 1 used a 3+3 design.
- ASTX727 (35/100 mg) was given PO on days 1–5, venetoclax 400 mg PO on days 1–14, and revumenib 113 mg (DL0) or 163 mg (DL1) PO Q12h on days 1–28 with azole prophylaxis.
- Revumenib monotherapy was resumed post-HSCT for 1-year of maintenance.
- Per amendment, revumenib could be held after day 21 if day 14 marrow blasts were <5%.
- MRD analysis was assessed by multicolor flow cytometry (MFC, sen 10⁻⁴).
- Mutational analysis to assess resistance, and molecular MRD at 10⁻⁵ were performed.

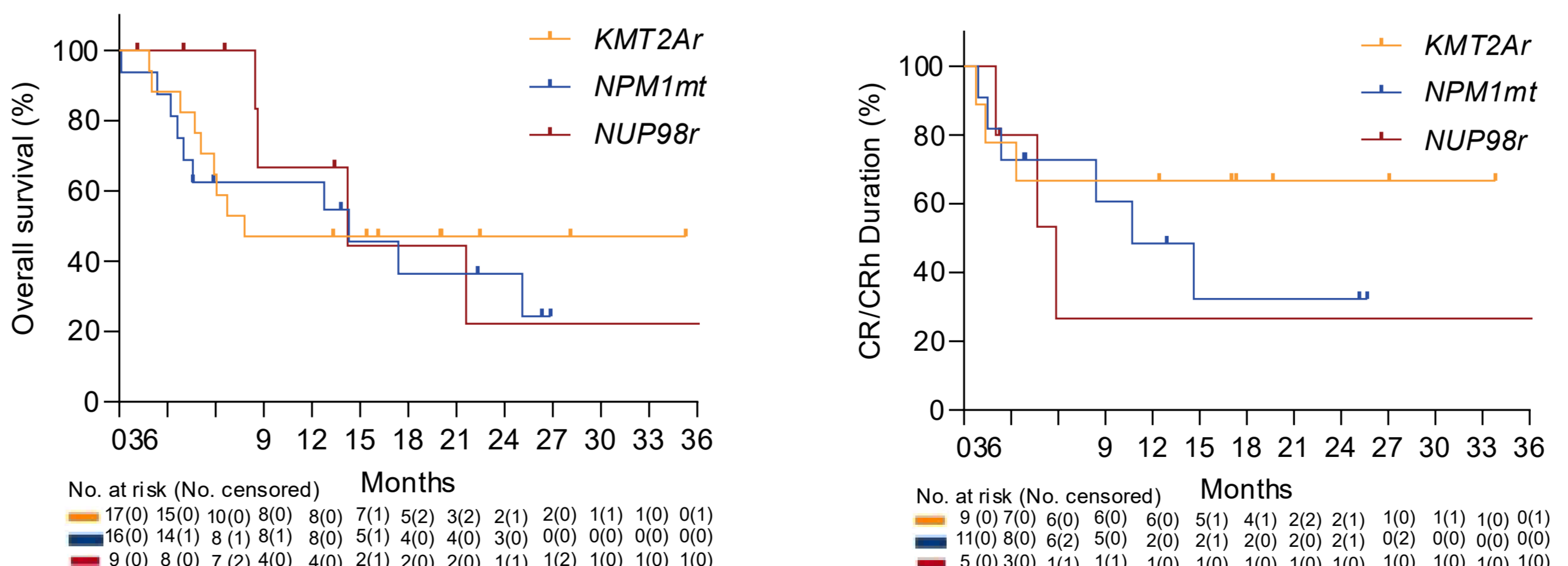
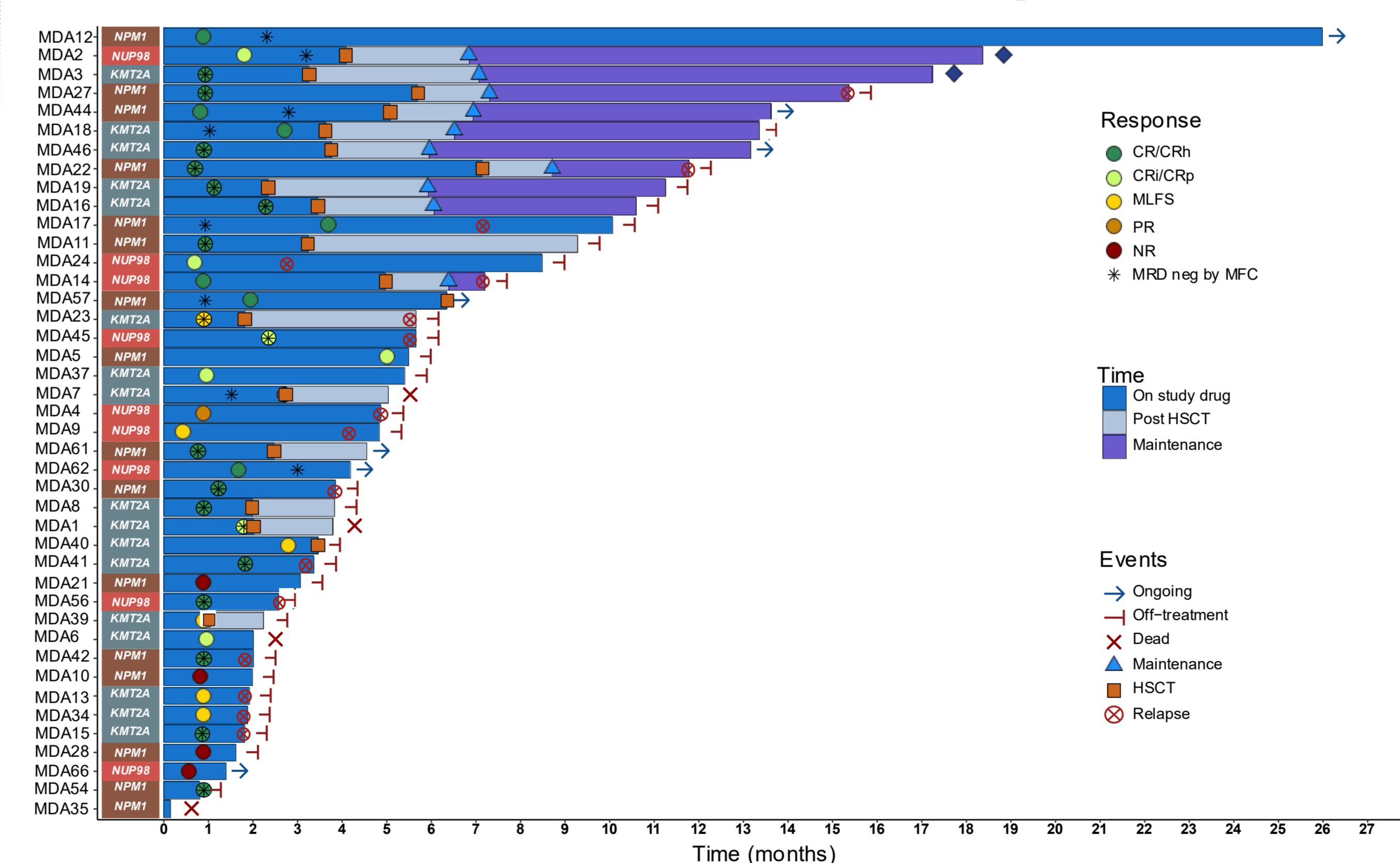
Safety

TEAEs, No. (%)	Any grade	Grade 3	Grade 4	Grade 5	≥ Grade 3
Febrile neutropenia	15 (36)	15 (36)	0 (0)	0 (0)	15 (36)
Lung infection	10 (24)	9 (21)	0 (0)	0 (0)	9 (21)
Platelet count decreased	9 (21)	3 (7)	6 (14)	0 (0)	9 (21)
Increased AST/ALT	30 (71)	7 (16)	2 (4)	0 (0)	9 (21)
Respiratory failure	6 (14)	0 (0)	6 (14)	0 (0)	6 (14)
Sinusitis	5 (12)	5 (12)	0 (0)	0 (0)	5 (12)
Sepsis	4 (10)	0 (0)	3 (7)	1 (2)	4 (10)
Neutrophil count decreased	4 (10)	1 (2)	3 (7)	0 (0)	4 (10)
Hypokalemia	18 (43)	3 (7)	0 (0)	0 (0)	3 (7)
Increased bilirubin	7 (17)	3 (7)	0 (0)	0 (0)	3 (7)
Acute kidney injury	3 (7)	2 (5)	1 (2)	0 (0)	3 (7)
Skin infection	3 (7)	3 (7)	0 (0)	0 (0)	3 (7)
QT prolongation	18 (43)	2 (5)	0 (0)	0 (0)	2 (5)
Pleural effusion	5 (12)	2 (5)	0 (0)	0 (0)	2 (5)
Differentiation syndrome	4 (10)	2 (5)	0 (0)	0 (0)	2 (5)
Anorexia	12 (29)	2 (5)	0 (0)	0 (0)	2 (5)
Hyperglycemia	2 (5)	2 (5)	0 (0)	0 (0)	2 (5)
Anemia	2 (5)	2 (5)	0 (0)	0 (0)	2 (5)
Vomiting	20 (48)	2 (5)	0 (0)	0 (0)	2 (5)
Diarrhea	12 (29)	2 (5)	0 (0)	0 (0)	2 (5)
Colitis	3 (7)	2 (5)	0 (0)	0 (0)	2 (5)
Pain in extremity	7 (17)	2 (5)	0 (0)	0 (0)	2 (5)
Syncope	2 (5)	2 (5)	0 (0)	0 (0)	2 (5)
Back pain	8 (19)	1 (2)	0 (0)	0 (0)	1 (2)
Catheter related infection	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)
Infective myositis	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)
Increased creatinine	7 (17)	1 (2)	0 (0)	0 (0)	1 (2)
Hyperuricemia	11 (26)	1 (2)	0 (0)	0 (0)	1 (2)
Acidosis	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)
Nausea	22 (52)	1 (2)	0 (0)	0 (0)	1 (2)
Anal fissure	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)
Soft tissue necrosis lower limb	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)
Encephalopathy	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)
Intracranial hemorrhage	1 (2)	0 (0)	1 (2)	0 (0)	1 (2)
Atrioventricular block complete	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)
Ventricular arrhythmia	1 (2)	0 (0)	1 (2)	0 (0)	1 (2)
Hypotension	3 (7)	1 (2)	0 (0)	0 (0)	1 (2)

Results

Characteristics	N=42
Median age, years [range]	40 [12-82]
Male, No. (%)	17 (40)
Female, No. (%)	25 (60)
Leukemia subtype, No. (%)	
AML	41 (98)
Myeloid MPAL	1 (2)
Therapy-related AML, No. (%)	6 (14)
Extramedullary disease, No. (%)	7 (17)
Genotype, No. (%)	
<i>KMT2Ar</i>	17 (40)
<i>NPM1mt</i>	16 (38)
<i>NUP98r</i>	9 (21)
Prior therapy, No. (%)	
Median no. of prior lines (range)	2 (1-5)
Prior venetoclax, No. (%)	22 (52)
Prior hypomethylating agent, No. (%)	21 (50)
Prior menin inhibitor, No. (%)	2 (5)
Prior HSCT, No. (%)	14 (33)

Survival and Duration of Response



Genotype	Median (95%CI)	6-months	12-months	18-months	24-months
<i>KMT2Ar</i>	7.7 (3.9, NR)	59 (40, 88)	47 (28, 78)	47 (28, 78)	47 (28, 78)
<i>NPM1mt</i>	14 (8.9, NR)	63 (43, 91)	63 (43, 91)	38 (18, 78)	38 (18, 78)
<i>NUP98r</i>	14 (8.5, NR)	100 (100, 100)	67 (38, 100)	44 (17, 100)	22 (4.1, 100)

Responses

Parameter	All patients (N=42)	<i>KMT2Ar</i> (N=17)	<i>NPM1mt</i> (N=16)	<i>NUP98r</i> (N=9)
ORR, No. (%)	37 (88)	17 (100)	12 (75)	8 (89)
95% CI	75-95	82-100	51-90	57-98
Median time to best response, (range), months	1.1 (0.4-5)	1.2 (0.5-2.9)	0.9 (0.7-5)	0.9 (0.4-2.3)
CR/CRh rate, No. (%)	25 (60)	9 (53)	11 (65)	5 (60)
Median time to first CR/CRh, (range), months	1.0 (0.7-2.9)	1.7 (0.9-2.9)	0.9 (0.7-1.9)	1.1 (0.7-1.7)
CRc rate, No. (%)	30 (71)	12 (71)	12 (75)	6 (67)
95% CI	56-83	47-87	51-90	35-88
Best response, No. (%)				
CR	18 (43)	7 (41)	9 (56)	2 (22)
CRh	7 (17)	2 (12)	2 (13)	3 (33)
CRi	4 (10)	3 (18)	1 (6)	0 (0)
CRp	1 (2)	0 (0)	0 (0)	1 (11)
PR	1 (2)	0 (0)	0 (0)	1 (11)
MLFS	6 (14)	5 (29)	0 (0)	1 (11)
No response	4 (10)	0 (0)	3 (19)	1 (11)
Died	1 (2)	0 (0)	1 (6)	0 (0)
Cycle 1 D14 bone marrow blasts <5%, No. (%)	22/31 (71)	10/14 (71)	8/10 (80)	4/7 (57)
MRD neg by MFC (10-4) in responders, No./Evaluable (%)	25/37 (68)	11/17 (65)	10/12 (83)	4/8 (50)
At end of cycle 1	18/37 (49)	8/17 (47)	9/12 (75)	1/8 (13)
Within CR/CRh	20/25 (80)	8/9 (89)	9/11 (82)	3/5 (60)
Within CRc	24/30 (80)	10/12 (83)	10/12 (83)	4/6 (67)
Median time to MRD neg by MFC (range), months	0.9 (0.7-7.1)	0.9 (0.8-1.8)	0.9 (0.7-7.1)	2 (0.9-3.2)
Proceeded to HSCT, No. (%)	19 (45)	11 (65)	6 (38)	2 (22)

Conclusion

- The all-oral combination of revumenib, venetoclax, and decitabine yields high remission rates in R/R AML with *KMT2Ar*, *NPM1mt*, or *NUP98r*, with durable responses in patients achieving deep remission.

Journal of Clinical Oncology®

The All-Oral Combination of Revumenib, Decitabine and Venetoclax for Relapsed or Refractory Acute Myeloid Leukemia (SAVE)

https://ascopubs.org/doi/10.1200/JCO.2026.011589

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