

Clinical Activity of Revumenib in Patients With Relapsed/Refractory *NUP98*-Rearranged Acute Leukemias

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INTRODUCTION

- The menin-*KMT2A* interaction is critical for leukemogenesis in *NPM1*-mutated (*NPM1m*), *KMT2A*-rearranged (*KMT2Ar*), and *NUP98*-rearranged (*NUP98r*) acute leukemias¹⁻⁴
 - Preclinical data demonstrate that leukemias driven by *NUP98r* activate proleukemogenic transcription factors via the menin-*KMT2A* interaction, which results in sensitivity to menin inhibition⁴
- Acute myeloid leukemia (AML) with *NUP98r* is a recognized subtype by World Health Organization 2022 criteria,⁵ with a global incidence of 2.5%-5% in adults and 7.2%-10.8% in pediatric and young adult patients⁶⁻⁹; however, rates are likely underestimated due to limited routine use of comprehensive fusion-detection methods and may vary by testing modality
- In pediatric and adult populations, the 1-year event-free survival rate in patients with *NUP98r* AML versus those with European LeukemiaNet favorable risk was 59% versus 86%, respectively, which decreased to 27% versus 78% at 5 years¹⁰
- Revumenib, a first-in-class, oral, potent, and selective inhibitor of the menin-*KMT2A* interaction, is used for the treatment of relapsed/refractory (R/R) AML harboring an *NPM1* mutation or R/R acute leukemia with a *KMT2A* translocation in adult and pediatric patients 1 year and older, but efficacy data in patients with *NUP98r* acute leukemia have been limited^{11,12}

OBJECTIVE

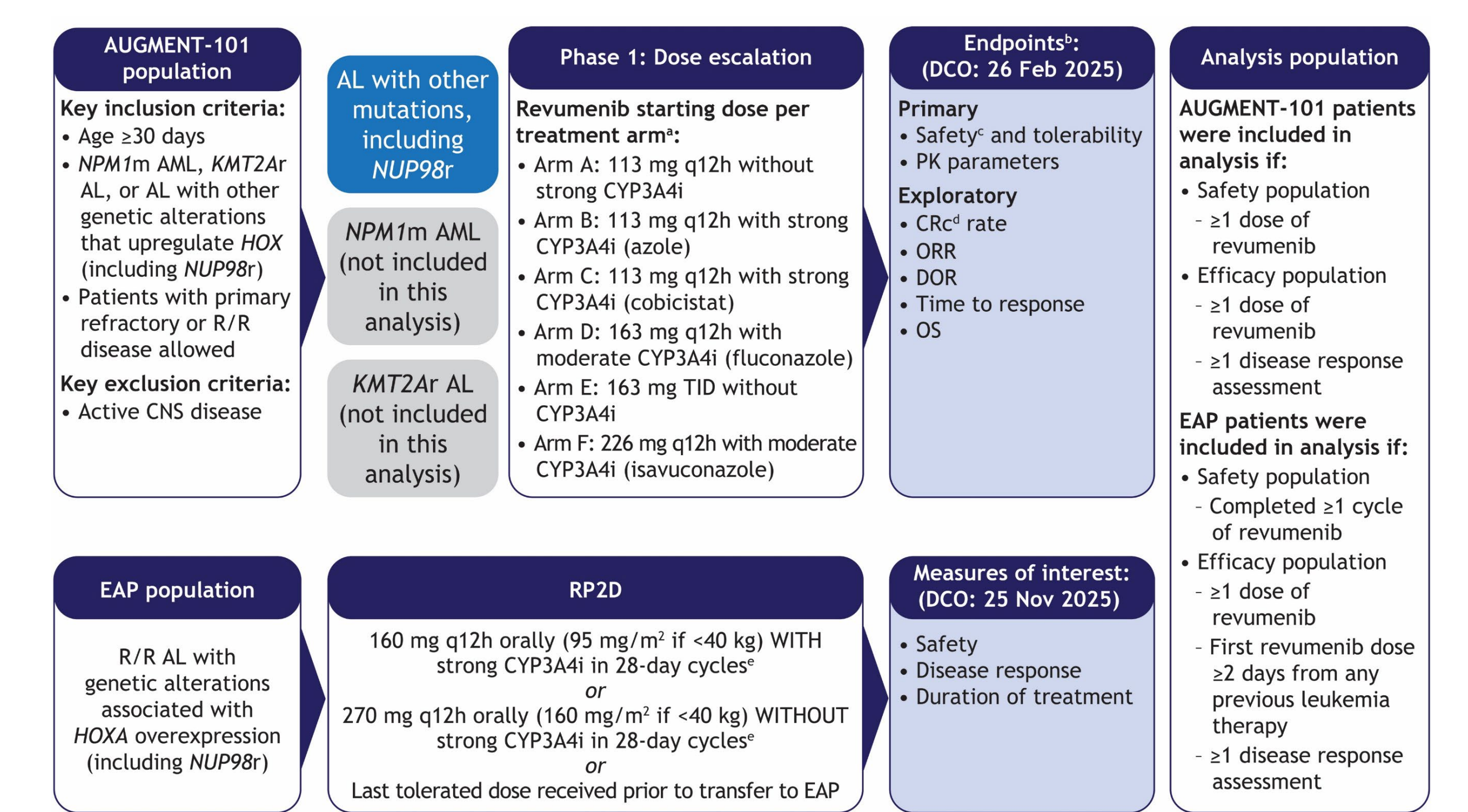
- To describe the safety and preliminary efficacy of revumenib monotherapy in patients with R/R *NUP98r* acute leukemia who were treated in the phase 1 portion of the AUGMENT-101 trial (NCT04065399) and an expanded access program (EAP; NCT05918913)

METHODS

Study design

- AUGMENT-101 is an ongoing phase 1/2, open-label, dose-escalation and -expansion study of revumenib in R/R acute leukemia with genetic alterations associated with *HOXA* overexpression, including *NPM1m*, *KMT2Ar*, or *NUP98r* (Figure 1)
 - All patients with *NUP98r* were enrolled in the phase 1 portion, and the revumenib dose was based on the arm in which patients were enrolled
 - Patients were included in the efficacy population if they had ≥1 disease-response assessment
- Revumenib was also available via an EAP, which allowed enrollment of any patient with a R/R acute leukemia with genetic alterations associated with *HOXA* overexpression (Figure 1)
 - Patients in the EAP received the recommended phase 2 dose (RP2D; 160 mg [95 mg/m² if <40 kg] with or 270 mg [160 mg/m² if <40 kg] without a strong CYP3A4 inhibitor [CYP3A4i]) every 12 hours (q12h) in 28-day cycles, or they received the last tolerated dose on other revumenib trials prior to transfer to the EAP
 - Disease response assessments were performed until composite complete remission (CRc) was reached; no further response data were required for collection
- Responses were investigator assessed in both studies

Figure 1. AUGMENT-101 and EAP study design



RESULTS

Patients

- Overall, 26 patients were included in the safety population, 23 (88%) of whom had AML (Table 1)
- Baseline characteristics were similar between the AUGMENT-101 and EAP populations and patients were similarly pretreated (median of 3 prior lines of therapy), with frequent prior exposure to venetoclax and/or hematopoietic stem cell transplant (HSCT)
- Patients from AUGMENT-101 received various dose levels, including 113 mg q12h with cobicitast (n = 2), 163 mg q12h with cobicitast (n = 1), 276 mg q12h with cobicitast (n = 1), 163 mg q12h without strong CYP3A4i (n = 1), and 163 mg 3 times daily without a strong CYP3A4i (n = 1); patients from the EAP received the RP2D or received the last tolerated dose prior to transfer to the EAP
- Median (range) duration of treatment was 11.8 weeks (1.7-48.0); patients received a median (range) of 3 cycles (1-12) of revumenib

Table 1. Demographic and baseline characteristics

	AUGMENT-101 (n = 6) ^a	EAP (n = 20) ^b	Total (N = 26) ^c
Age, median (range), y	18.0 (14.0-79.0)	19.0 (1.8-68.0)	18.0 (1.8-79.0)
Age group, n (%)			
<18 y	3 (50)	10 (50)	13 (50)
18-65 y	2 (33)	9 (45)	11 (42)
≥65 y	1 (17)	1 (5)	2 (8)
Female, n (%)	2 (33)	11 (55)	13 (50)
Race, n (%)			
White	6 (100)	12 (60)	18 (69)
Non-White	0	7 (35)	7 (27)
Unknown	0	1 (5)	1 (4)
Leukemia type, n (%)			
AML	5 (83)	18 (90)	23 (88)
ALL	0	1 (5)	1 (4)
MPAL	0	1 (5)	1 (4)
Other ^d	1 (17)	0	1 (4)
<i>NUP98</i> fusion partner, n (%)			
<i>NUP98</i> :: <i>NSD1</i>	3 (50)	13 (65)	16 (62)
<i>NUP98</i> :: <i>KDMSA</i>	0	2 (10)	2 (8)
<i>NUP98</i> ::other	3 (50)	4 (20)	7 (27)
Unknown	0	1 (5)	1 (4)
Co-mutations, n (%)			
<i>FLT3</i> -ITD	3 (50)	4 (20)	7 (27)
<i>FLT3</i> -TKD	0	1 (5)	1 (4)
<i>FLT3</i> not available ^e	0	4 (20)	4 (15)
<i>TP53</i>	0	2 (10)	2 (8)
<i>TP53</i> not available/missing ^f	1 (17)	9 (45)	10 (38)
<i>RAS</i>	0	3 (15)	3 (12)
<i>RAS</i> not available/missing ^f	1 (17)	12 (60)	13 (50)
No. of prior lines of therapy, median (range)	3 (1-5)	3 (1-7)	3 (1-7)
Prior therapy, n (%)			
Venetoclax	4 (67)	16 (80)	20 (77)
<i>FLT3</i> inhibitor	3 (50)	9 (45)	12 (46)
HSCT	4 (67)	9 (45)	13 (50)

^aDCO; 26 February 2025. ^bDCO; 25 November 2025. ^cSafety population, defined as patients with baseline *NUP98* rearrangement who received ≥1 dose of revumenib.

^dRecorded in the patient's chart as "MDS." ^eNot ITD or TKD mutant, nor wild type. ^fInformation not present in the patient record.

ALL, acute lymphoblastic leukemia; DCO, data cutoff; EAP, expanded access program; ITD, internal tandem duplication; MDS, myelodysplastic syndrome; MPAL, mixed-phenotype acute leukemia; TKD, tyrosine kinase domain.

Efficacy

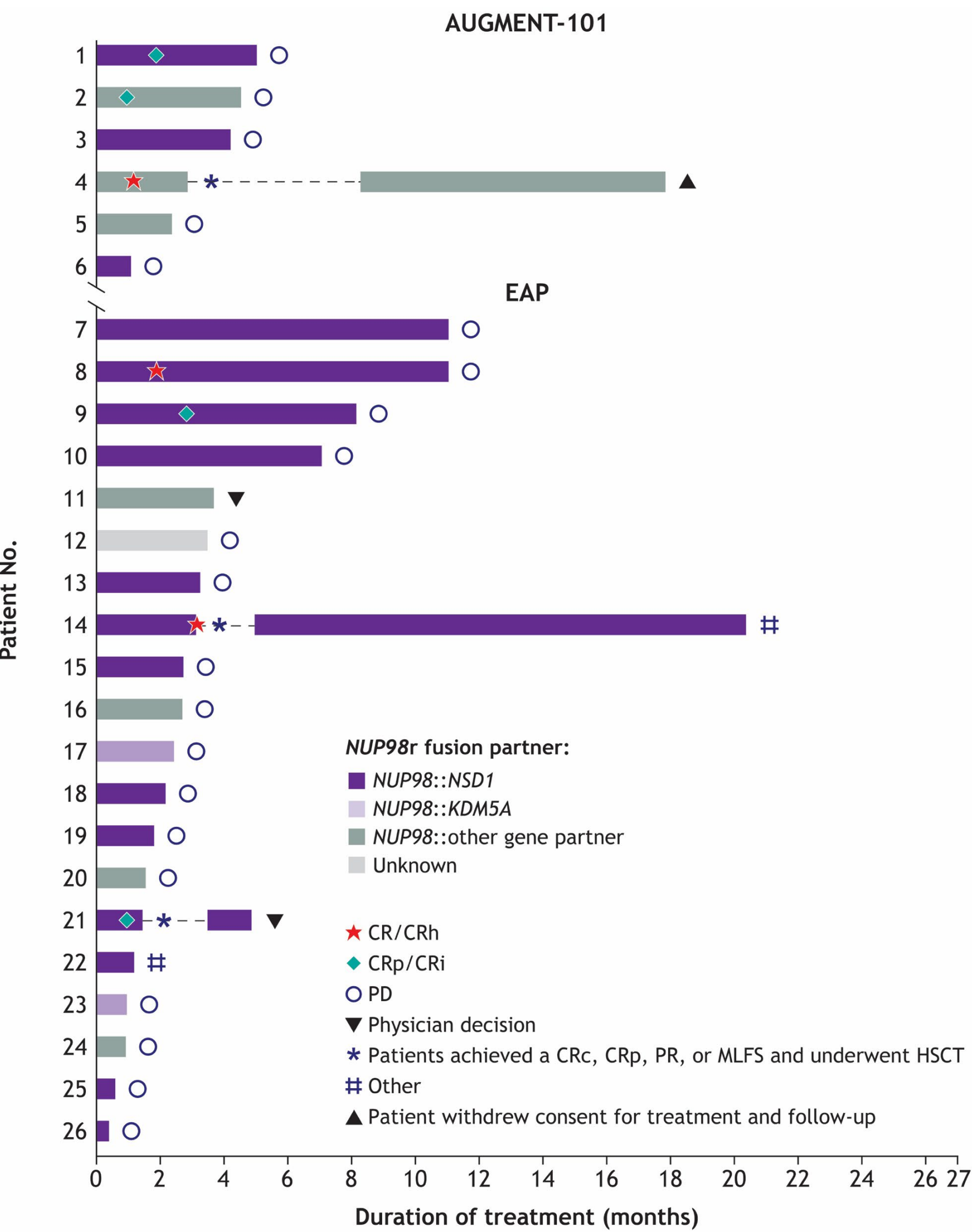
- CRc was achieved in 7/25 (28.0%) patients in the efficacy population, with a median duration of response of 6.7 months (95% confidence interval, 0.5-not reached; Table 2)
- One of 6 patients with CRc achieved measurable residual disease negativity (assessed by flow cytometry)
- Three of 7 (42.9%) responders proceeded to HSCT while in remission and all received post-HSCT maintenance with revumenib (Figure 2)
- Three patients without documented response remained on revumenib for >4 months

Table 2. Efficacy

	AUGMENT-101 (n = 6)	EAP ^a (n = 19)	Total (N = 25)
ORR, n (%) ^b	3 (50.0)	4 (21.1)	7 (28.0)
95% CI ^c	11.8-88.2	6.1-45.6	12.1-49.4
Best overall response, n (%)			
CR	0	2 (10.5)	2 (8.0)
CRh	1 (16.7)	0	1 (4.0)
CRi	1 (16.7)	1 (5.3)	2 (8.0)
CRp	1 (16.7)	1 (5.3)	2 (8.0)
MLFS	0	0	0
PR	0	0	0
PD/relapse	1 (16.7)	5 (26.3)	6 (24.0)
No response	2 (33.3)	10 (52.6)	12 (48.0)
CRc rate, n (%) ^d	3 (50.0)	4 (21.1)	7 (28.0)
95% CI ^c	11.8-88.2	6.1-45.6	12.1-49.4
Duration of CRc, mo ^{e,f}			
Median (95% CI ^c)	NR (2.8-NR)	6.7 (0.5-NR)	6.7 (0.5-NR)
Time to first CRc, mo ^f			
Median (range)	1.2 (0.95-1.87)	2.4 (0.95-3.15)	1.9 (0.95-3.15)
CR + CRh rate, n (%)	1 (16.7)	2 (10.5)	3 (12.0)
95% CI ^c	0.4-64.1	1.3-33.1	2.5-31.2
MRD-negative status, n/N (%) ^g			
CRc	1/3 (33.3)	0	1/6 (16.7)
CR + CRh	1/1 (100)	0	1/2 (50.0)

^aOne patient did not meet the response-evaluable criteria and was excluded from the efficacy population. ^bCRc = MLFS. ^cExact 95% CIs of response rate are 2-sided and calculated using the Clopper-Pearson method. ^dCR = CRh + CRi + CRp. ^eKaplan-Meier method was used and 2-sided 95% CI calculated based on the Greenwood method. ^fDuration of response and time to response calculated for responders (those achieving CRc, n = 7) in the efficacy population. ^gMRD-negative status percentage based on number of responders with MRD status available; assessment performed by flow cytometry. CR, complete remission; CRc, composite CR; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; EAP, expanded access program; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NR, not reached; ORR, overall response rate (CRc + MLFS + PR); PD, progressive disease; PR, partial remission.

Figure 2. Duration of revumenib monotherapy in patients with R/R *NUP98r* acute leukemia (safety population)



Duration of post-HSCT revumenib treatment is shown after the dashed line. Patient 13 (treated on the EAP) did not meet the response-evaluable criteria and was excluded from the efficacy population. CR, complete remission; CRc, composite CR; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; EAP, expanded access program; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial remission.

Safety

- Treatment-emergent adverse events (TEAEs) occurred in 23/26 (88%) patients in the safety population; the most common were febrile neutropenia (31%) and nausea (23%)
- Grade ≥3 TEAEs occurred in 18 (69%) patients (Table 3); the most common were febrile neutropenia (23%) and pneumonia, anemia, decreased neutrophil count, and decreased white blood cell count (19% each)
- Thrombocytopenia or platelet count decrease occurred in 4 (15%) patients (all grade ≥3)
- QTcF prolongation and differentiation syndrome only occurred in EAP patients, were infrequent, and did not lead to revumenib discontinuation (grade ≥3 events occurred in 2 [8%] and 1 [4%] patients, respectively)

Table 3. Summary of AEs

Parameter, n (%)	AUGMENT-101 (n = 6)	EAP (n = 20)	Total (N = 26)
Grade ≥3 TEAE	4 (67)	14 (70)	18 (69)
Grade ≥3 TRAE	2 (33)	9 (45)	11 (42)
SAE	4 (67)	13 (65)	17 (65)
Related	1 (17)	5 (25)	6 (23)
TEAEs leading to dose modification	2 (33)	8 (40)	10 (38)
Reduction	0	3 (15)	3 (12)
Interruption	2 (33)	5 (25)	7 (27)
TEAEs leading to revumenib discontinuation	0	0	0
TEAEs leading to dose modification	1 (17)	7 (35)	8 (31)
Reduction	0	2 (10)	2 (8)
Interruption	1 (17)	5 (25)	6 (23)
TEAEs leading to revumenib discontinuation	0	0	0
TEAE or TRAE leading to death	0	0	0

AE, adverse event; EAP, expanded access program; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

CONCLUSIONS

- Revumenib monotherapy induced CRc in 28% of patients with R/R *NUP98r* acute leukemia, with responses detected after 1-3 cycles and lasting a median of nearly 7 months
- Some patients received prolonged revumenib monotherapy (>4 months) without achieving a documented response or experiencing overt progression, which further highlights the clinical benefit in this population with few effective treatment options
- A substantial proportion of patients who achieved a documented response subsequently proceeded to HSCT, suggesting that revumenib monotherapy may serve as an effective bridge to transplant
- The safety profile of revumenib was predictable and manageable, with no new safety signals identified
- These findings suggest revumenib is tolerable and can provide clinical benefit to patients with R/R *NUP98r* acute leukemia, a high-risk, historically hard-to-treat population

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