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# 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 (*NPM1*m), *KMT2A*-rearranged (*KMT2A*r), and *NUP98*-rearranged (*NUP98*r) acute leukemias[1-4]
  - Preclinical data demonstrate that leukemias driven by *NUP98*r activate proleukemogenic transcription factors via the menin-KMT2A interaction, which results in sensitivity to menin inhibition[4]
- Acute myeloid leukemia (AML) with *NUP98*r 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 patients[6-9]; 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 *NUP98*r AML versus those with European LeukemiaNet favorable risk was 59% versus 86%, respectively, which decreased to 27% versus 78% at 5 years[10]
- 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 *NUP98*r acute leukemia have been limited[11,12]

## OBJECTIVE

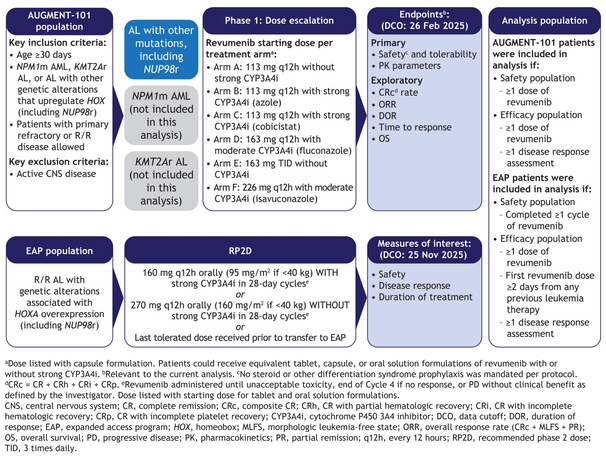
- To describe the safety and preliminary efficacy of revumenib monotherapy in patients with R/R *NUP98*r acute leukemia who were treated in the phase 1 portion of the AUGMENT-101 trial (NCT04065399) and an expanded access program (EAP; NCT05918913)

## 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 *NPM1*m, *KMT2A*r, or *NUP98*r (**Figure 1**)
  - All patients with *NUP98*r 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/m$^2$ if <40 kg] with or 270 mg [160 mg/m$^2$ 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**




[a]Dose listed with capsule formulation. Patients could receive equivalent tablet, capsule, or oral solution formulations of revumenib with or without strong CYP3A4i. [b]Relevant to the current analysis. [c]No steroid or other differentiation syndrome prophylaxis was mandated per protocol. [d]CRc = CR + CRh + CRi + CRp. [e]Revumenib administered until unacceptable toxicity, end of Cycle 4 if no response, or PD without clinical benefit as defined by the investigator. Dose listed with starting dose for tablet and oral solution formulations.
CNS, central nervous system; CR, complete remission; CRc, composite CR; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; DCO, data cutoff; DOR, duration of response; EAP, expanded access program; *HOX*, homeobox; MLFS, morphologic leukemia-free state; ORR, overall response rate (CRc + MLFS + PR); OS, overall survival; PD, progressive disease; PK, pharmacokinetics; PR, partial remission; q12h, every 12 hours; RP2D, recommended phase 2 dose; TID, 3 times daily.

## 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 cobicistat (n = 2), 163 mg q12h with cobicistat (n = 1), 276 mg q12h with cobicistat (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) |
| ***NUP98* fusion partner, n (%)** | | | |
| *NUP98*::*NSD1* | 3 (50) | 13 (65) | 16 (62) |
| *NUP98*::*KDM5A* | 0 | 2 (10) | 2 (8) |
| *NUP98*::other | 3 (50) | 4 (20) | 7 (27) |
| Unknown | 0 | 1 (5) | 1 (4) |
| **Co-mutations, n (%)** | | | |
| *FLT3*-ITD | 3 (50) | 4 (20) | 7 (27) |
| *FLT3*-TKD | 0 | 1 (5) | 1 (4) |
| *FLT3* not available[e] | 0 | 4 (20) | 4 (15) |
| *TP53* | 0 | 2 (10) | 2 (8) |
| *TP53* not available/missing[f] | 1 (17) | 9 (45) | 10 (38) |
| *RAS* | 0 | 3 (15) | 3 (12) |
| *RAS* 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) |
| FLT3 inhibitor | 3 (50) | 9 (45) | 12 (46) |
| HSCT | 4 (67) | 9 (45) | 13 (50) |

[a]DCO: 26 February 2025. [b]DCO: 25 November 2025. [c]Safety population, defined as patients with baseline *NUP98* rearrangement who received ≥1 dose of revumenib. [d]Recorded in the patient's chart as "MDS." [e]Not ITD or TKD mutant, nor wild type. [f]Information 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

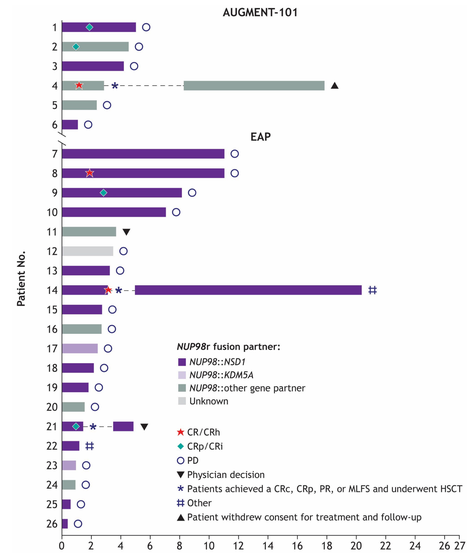
- CRc was achieved in 7/25 (28.0%) patients in the efficacy population, with a median duration of response of 6.7 months (95% confidence interval, 0.5-not reached; **Table 2**)
  - One of 6 patients with CRc achieved measurable residual disease negativity (assessed by flow cytometry)
- Three of 7 (42.9%) 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) |

[a]One patient did not meet the response-evaluable criteria and was excluded from the efficacy population. [b]CRc + MLFS. [c]Exact 95% CIs of response rate are 2 sided and calculated using the Clopper-Pearson method. [d]CR + CRh + CRi + CRp. [e]Kaplan-Meier method was used and 2-sided 95% CI calculated based on the Greenwood method. [f]Duration of response and time to response calculated for responders (those achieving CRc, n = 7) in the efficacy population. [g]MRD-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 *NUP98*r 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 |
| **TRAEs leading to dose modification** | 1 (17) | 7 (35) | 8 (31) |
| Reduction | 0 | 2 (10) | 2 (8) |
| Interruption | 1 (17) | 5 (25) | 6 (23) |
| **TRAEs 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 *NUP98*r 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 *NUP98*r acute leukemia, a high-risk, historically hard-to-treat population

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