AML-110

Revumenib for Patients With Relapsed or Refractory (R/R) Nucleophosmin 1–Mutated (*NPM1*m) Acute Myeloid Leukemia (AML): Updated Results From the Phase 2 AUGMENT-101 Study

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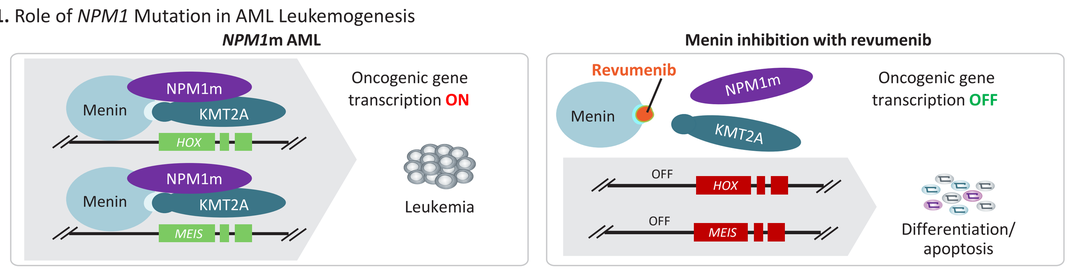
INTRODUCTION

- Nucleophosmin 1 (*NPM1*) mutation is a critical driver mutation, present in ≈30% of adults with acute myeloid leukemia (AML) at initial diagnosis[1-3]
- In *NPM1*-mutated (*NPM1*m) AML, leukemogenesis is driven by the interaction between menin and wild-type lysine methyltransferase 2A (KMT2A)[4]
- The prognosis for patients with relapsed or refractory (R/R) *NPM1*m AML is poor, and there are no approved targeted therapies[1,5]
- Revumenib, a first-in-class, potent, selective menin inhibitor, disrupts menin-KMT2A interactions (**Figure 1**) and has demonstrated activity in patients with *NPM1*m AML in the:
  - Phase 1 portion of AUGMENT-101 (NCT04065399)[3,6]
  - Phase 2 primary efficacy population of AUGMENT-101 (n=64)[7]

AIM

- Here we report updated results for the entire efficacy-evaluable population (n=77) in the phase 2 AUGMENT-101 R/R *NPM1*m AML cohort

Figure 1. Role of *NPM1* Mutation in AML Leukemogenesis



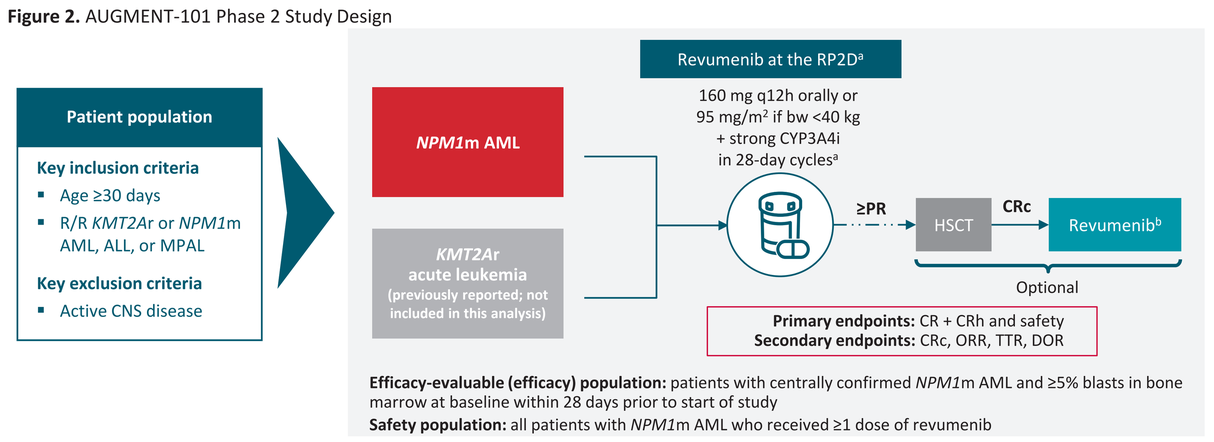
AML, acute myeloid leukemia; HOX, homeobox; KMT2A, lysine methyltransferase 2A; MEIS, Meis homeobox; NPM1m, nucleophosmin 1 mutated.

METHODS

STUDY DESIGN

- The study design is shown in **Figure 2**; the methods have been previously published[7]

Figure 2. AUGMENT-101 Phase 2 Study Design



Efficacy-evaluable (efficacy) population: patients with centrally confirmed *NPM1*m AML and ≥5% blasts in bone marrow at baseline within 28 days prior to start of study
Safety population: all patients with *NPM1*m AML who received ≥1 dose of revumenib

[a]Revumenib administered until unacceptable toxicity, the end of cycle 4 if no response, or progressive disease without clinical benefit as defined by the investigator.
[b]Maintenance therapy with revumenib after allogeneic HSCT was allowed per protocol amendment for eligible patients, with maintenance treatment continued until disease progression or unacceptable toxicity.
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; bw, body weight; CNS, central nervous system; CR, complete remission; CRc, composite CR (CR + CRh + CRp + Cri); CRh, CR with partial hematologic recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; DOR, duration of response; HSCT, hematopoietic stem cell transplant; KMT2Ar, lysine methyltransferase 2A rearranged; MPAL, mixed-phenotype acute leukemia; NPM1m, nucleophosmin 1 mutated; ORR, overall response rate (CRc + MLFS + PR); PR, partial remission; q12h, every 12 hours; RP2D, recommended phase 2 dose; R/R, relapsed or refractory; TTR, time to response.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- As of September 18, 2024, 84 patients with *NPM1*m AML had received ≥1 recommended phase 2 dose (RP2D) of revumenib and were included in the safety population (**Table 1**)
  - Of these patients, 77 met the criteria for inclusion in the efficacy population
- Patients were older, with almost half the population >65 years
- Patients were heavily pretreated, with 35% having received ≥3 prior lines of therapy (**Table 2**)

Table 1. Demographics and Baseline Characteristics

Parameter		Efficacy population (n=77)[a]	Safety population (N=84)[b]
Age	Median (range), y	63 (11-84)	63 (11-84)
	<18 y, n (%)	1 (1.3)	1 (1.2)
	≥18 to <65 y, n (%)	38 (49.4)	42 (50.0)
	≥65 y, n (%)	38 (49.4)	41 (48.8)
Female, n (%)		45 (58.4)	50 (59.5)
Race, n (%)	White	43 (55.8)	48 (57.1)
	Non-White	15 (19.5)	16 (19.0)
	Unknown[c]	19 (24.7)	20 (23.8)
Disease status at baseline, n (%)	Primary refractory	5 (6.5)	7 (8.3)
	Relapsed refractory	38 (49.4)	41 (48.8)
	Early untreated relapse[d]	22 (28.6)	23 (27.4)
	Late untreated relapse[e]	12 (15.6)	13 (15.5)

[a]All patients who received ≥1 dose of revumenib and had centrally confirmed *NPM1*m AML and ≥5% blasts in bone marrow at baseline within 28 days prior to start of study. [b]All patients with *NPM1*m AML who received ≥1 dose of revumenib. [c]Includes missing. [d]Early untreated relapse defined as relapse <1 year from prior remission.
[e]Late untreated relapse defined as relapse ≥1 year from prior remission.
AML, acute myeloid leukemia; NPM1m, nucleophosmin 1 mutated; R/R, relapsed or refractory.

Table 2. Baseline Mutation Status and Treatment History

Parameter, n (%)		Efficacy population (n=77)[a]	Safety population (N=84)[b]
Co-mutations[c]	*FLT3*-ITD	23 (29.9)	26 (31.0)
	FLT3-TKD	6 (7.8)	6 (7.1)
	RAS	3 (3.9)	3 (3.6)
	TP53	4 (5.2)	4 (4.8)
	IDH1	11 (14.3)	11 (13.1)
	IDH2	10 (13.0)	10 (11.9)
No. of prior lines of therapy	Median (range)	2 (1-7)	2 (1-7)
	≥3	27 (35.1)	29 (34.5)
	≥4	15 (19.5)	16 (19.0)
Prior therapies	Venetoclax	57 (74.0)	62 (73.8)
	HSCT	18 (23.4)	20 (23.8)
	>1 prior HSCT	6 (7.8)	8 (9.5)
	FLT3 inhibitor	31 (40.3)	32 (38.1)
	IDH1 inhibitor	5 (6.5)	5 (6.0)
	IDH2 inhibitor	5 (6.5)	5 (6.0)

[a]All patients who received ≥1 dose of revumenib and had centrally confirmed *NPM1*m AML and ≥5% blasts in bone marrow at baseline within 28 days prior to start of study. [b]All patients with *NPM1*m AML who received ≥1 dose of revumenib. [c]Co-mutation testing was conducted locally at the discretion of the investigator.
AML, acute myeloid leukemia; FLT3, fms related receptor tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; IDH, isocitrate dehydrogenase; ITD, internal tandem duplication; NPM1m, nucleophosmin 1 mutated; R/R, relapsed or refractory; TKD, tyrosine kinase domain; TP53, tumor protein p53.

EFFICACY

- Within the efficacy population, a complete remission (CR) + CR with partial hematologic recovery (CRh) response (primary outcome) was achieved in 26.0% of patients (**Table 3**)
  - Almost half of patients experienced a morphological response, with an overall response rate (ORR) of 48.1%
- Rates of CR + CRh were similar across subgroups, including those based on prior treatment experience, although the study was not powered to make comparisons between subgroups (**Figure 3**)
- Median time to first CR/CRh was 2.8 months (range, 0.9-8.8 months) (**Figure 4, Table 4**)
  - Median duration of CR/CRh was 4.7 months (95% CI, 2.1-8.2 months)
- Median overall survival (OS) was 4.8 months (95% CI, 3.4-8.4 months) (**Figure 5**)
- In a subpopulation analysis, median OS in:
  - CR + CRh responders (n=20) was 23.3 months (95% CI, 7.2 months-not reached [NR])
  - ORR responders (n=37) was 23.3 months (95% CI, 8.4 months-NR)

PATIENTS WHO PROCEEDED TO HSCT

- Five patients underwent hematopoietic stem cell transplant (HSCT)
  - Of these, 4 patients were in CR or CRh and 1 was in morphological leukemia-free state
- Of the patients who underwent HSCT, 3 resumed revumenib as maintenance treatment
  - Median time from HSCT to resuming revumenib was 42 days (range, 41-72 days) (**Figure 4**)

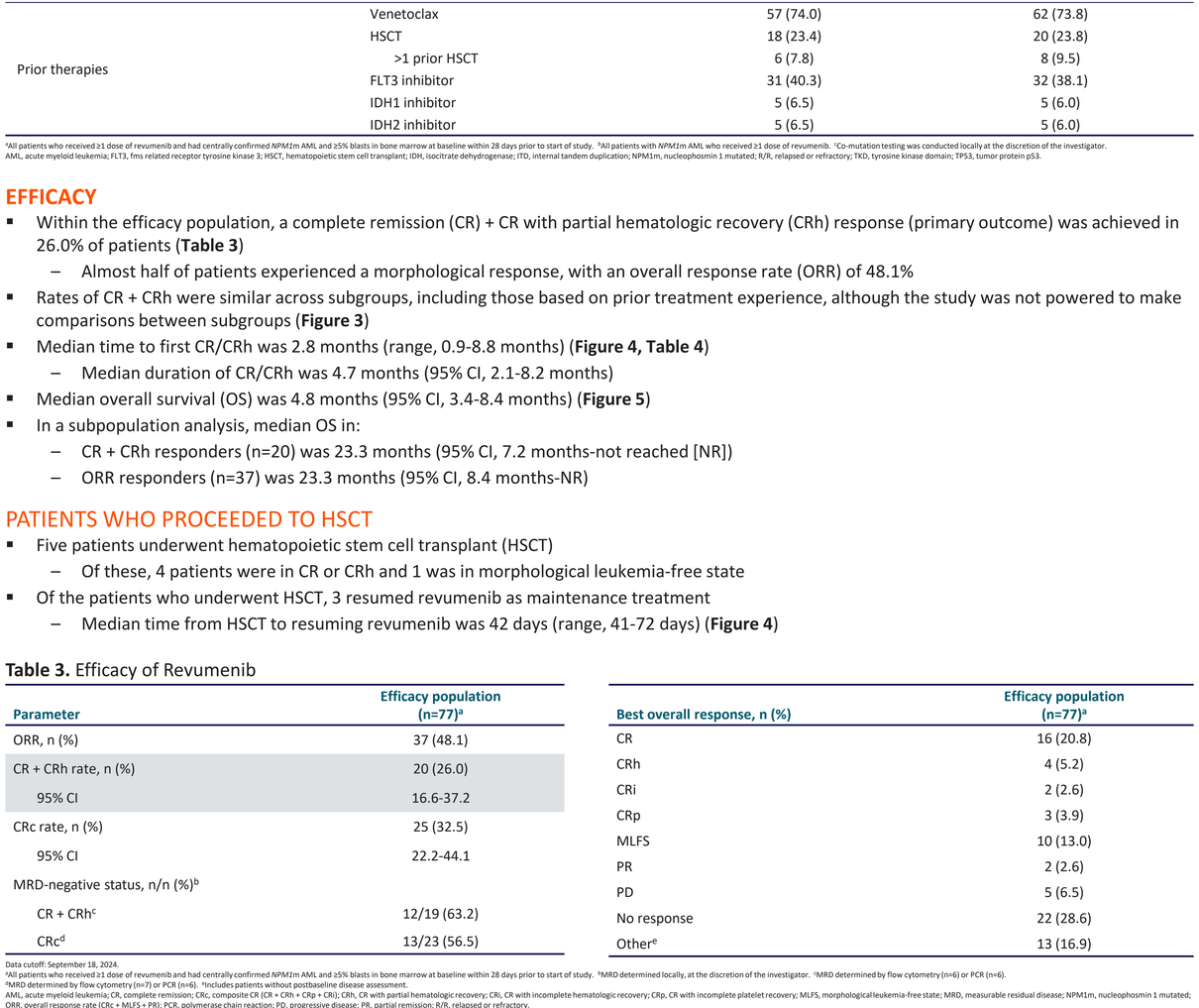
Table 3. Efficacy of Revumenib

Parameter	Efficacy population (n=77)[a]
ORR, n (%)	37 (48.1)
CR + CRh rate, n (%)	20 (26.0)
95% CI	16.6-37.2
CRc rate, n (%)	25 (32.5)
95% CI	22.2-44.1
MRD-negative status, n/n (%)[b]	
CR + CRh[c]	12/19 (63.2)
CRc[d]	13/23 (56.5)

Best overall response, n (%)	Efficacy population (n=77)[a]
CR	16 (20.8)
CRh	4 (5.2)
CRi	2 (2.6)
CRp	3 (3.9)
MLFS	10 (13.0)
PR	2 (2.6)
PD	5 (6.5)
No response	22 (28.6)
Other[e]	13 (16.9)

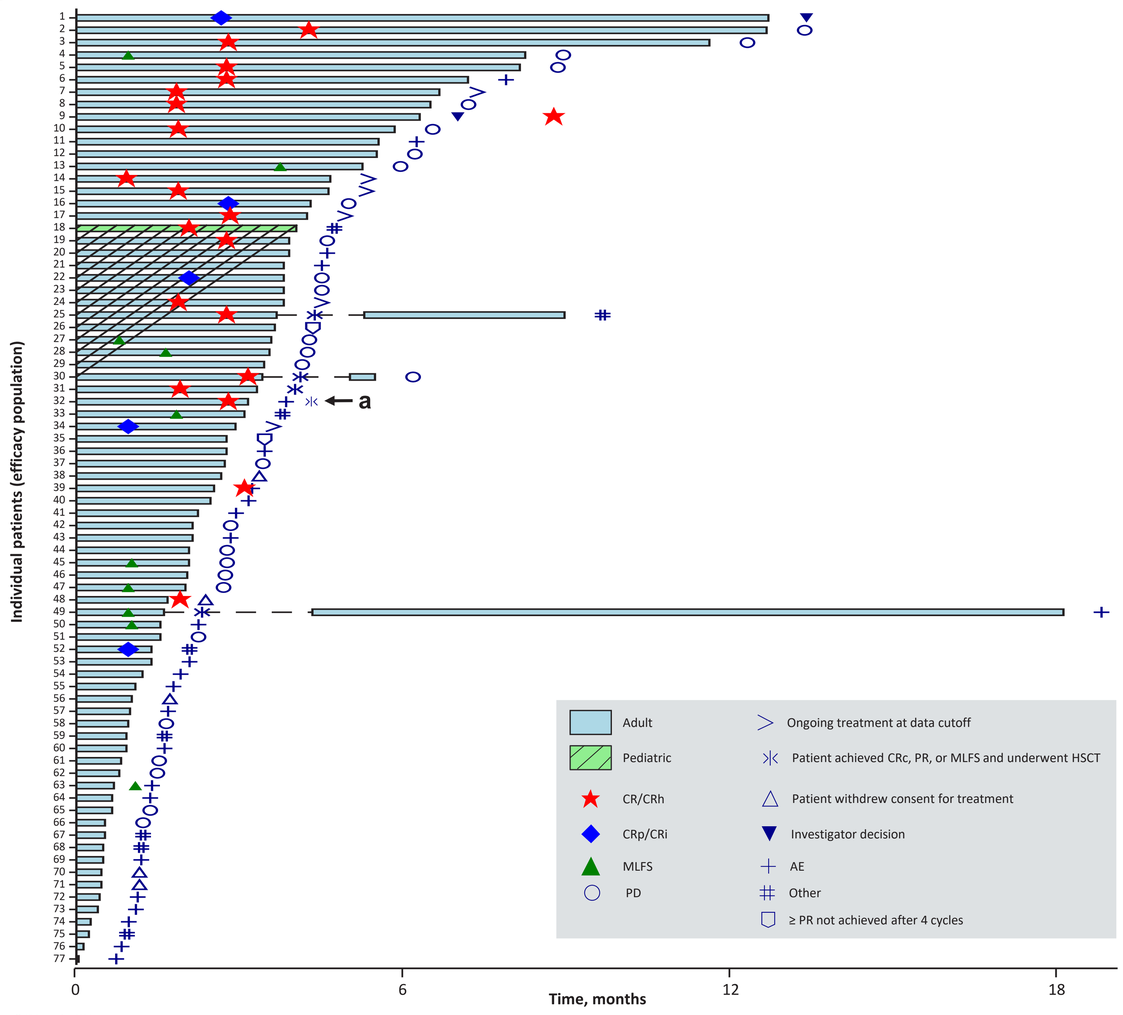
Data cutoff: September 18, 2024.
[a]All patients who received ≥1 dose of revumenib and had centrally confirmed *NPM1*m AML and ≥5% blasts in bone marrow at baseline within 28 days prior to start of study. [b]MRD determined locally, at the discretion of the investigator. [c]MRD determined by flow cytometry (n=6) or PCR (n=6).
[d]MRD determined by flow cytometry (n=7) or PCR (n=6). [e]Includes patients without postbaseline disease assessment.
AML, acute myeloid leukemia; CR, complete remission; CRc, composite CR (CR + CRh + CRp + CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, measurable residual disease; NPM1m, nucleophosmin 1 mutated; ORR, overall response rate (CRc + MLFS + PR); PCR, polymerase chain reaction; PD, progressive disease; PR, partial remission; R/R, relapsed or refractory.

Figure 3. Subgroup Analyses



Data cutoff: September 18, 2024.
AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; FLT3, fms related receptor tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; IDH, isocitrate dehydrogenase; NPM1m, nucleophosmin 1 mutated; R/R, relapsed or refractory.

Figure 4. Duration of Treatment



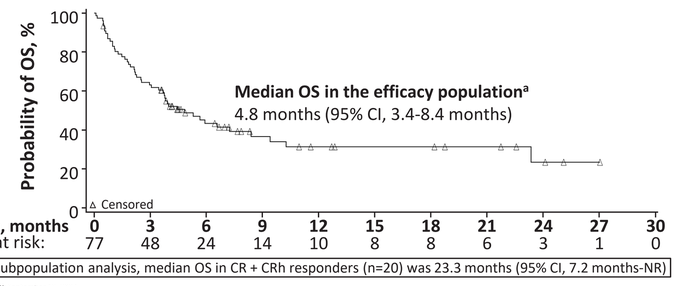
Data cutoff: 18 September 2024.
[a]Five patients proceeded to HSCT while in remission during the study, including this patient who was taken off study due to AE but subsequently proceeded to HSCT 6 weeks later while still in remission without any intervening antileukemia therapy.
AE, adverse event; CR, complete remission; CRc, composite CR (CR + CRh + CRp + CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial remission.

Table 4. Time to Events

Parameter	Months
Time to first ORR (n=37), median (range)	1.8 (0.8-4.6)
Time to first CR/CRh (n=20), median (range)	2.8 (0.9-8.8)
Duration of CR/CRh, median (95% CI)	4.7 (2.1-8.2)
Time to MRD negativity for patients with CR + CRh (n=12), median (range)[a]	2.8 (1.8-4.7)

Data cutoff: September 18, 2024.
[a]MRD assessment was not required as part of the study. MRD determined by flow cytometry (n=6) or PCR (n=6).
CR, complete remission; CRc, composite CR (CR + CRh + CRp + CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, measurable residual disease; ORR, overall response rate (CRc + MLFS + PR); PCR, polymerase chain reaction; PR, partial remission.

Figure 5. Overall Survival



In a subpopulation analysis, median OS in CR + CRh responders (n=20) was 23.3 months (95% CI, 7.2 months-NR)

Data cutoff: September 18, 2024.
[a]All patients who received ≥1 dose of revumenib and had centrally confirmed *NPM1*m AML and ≥5% blasts in bone marrow at baseline within 28 days prior to start of study.
AML, acute myeloid leukemia; NPM1m, nucleophosmin 1 mutated; OS; overall survival; R/R, relapsed or refractory.

SAFETY

- In the safety population, discontinuation due to treatment-related adverse events (TRAE) occurred in <5% of patients (**Table 5**)
- The safety profile was consistent with prior reports (**Table 5**)[7,8]
- Differentiation syndrome (a class effect of menin inhibitors) and corrected QT interval (QTc) prolongation were manageable, with few associated discontinuations and no deaths (**Table 6**)

Table 5. Safety of Revumenib

Overall incidence, n (%)	Safety population (N=84)[a] TEAEs	TRAEs
Any grade	83 (98.8)	66 (78.6)
Grade ≥3	77 (91.7)	50 (59.5)
Serious AE	64 (76.2)	31 (36.9)
AEs leading to:		
Dose reduction	10 (11.9)	10 (11.9)
Dose interruption	56 (66.7)	42 (50.0)
Treatment discontinuation	25 (29.8)	4 (4.8)[b]
Death	21 (25.0)	1 (1.2)[c]

Any-grade TEAEs in ≥20% of patients, n (%)	Safety population (N=84)[a]
QTc prolongation	36 (42.9)
Vomiting	31 (36.9)
Febrile neutropenia	29 (34.5)
Hypokalemia	27 (32.1)
Nausea	24 (28.6)
Anemia	23 (27.4)
Diarrhea	23 (27.4)
Fatigue	20 (23.8)
Pyrexia	20 (23.8)
Epistaxis	18 (21.4)
Peripheral edema	18 (21.4)

Grade ≥3 TEAEs in ≥10% of patients, n (%)	Safety population (N=84)[a]
Febrile neutropenia	28 (33.3)
Anemia	21 (25.0)
QTc prolongation	19 (22.6)
Decreased platelet count	14 (16.7)
Sepsis	13 (15.5)
Pneumonia	12 (14.3)
Thrombocytopenia	12 (14.3)
Differentiation syndrome	11 (13.1)
Decreased WBC count	10 (11.9)
Decreased neutrophil count	9 (10.7)

Data cutoff: September 18, 2024.
[a]All patients who received ≥1 dose of revumenib. [b]Reasons for treatment discontinuation: cardiac arrest, differentiation syndrome, osteomyelitis, QTc prolonged + syncope (n=1 each). [c]Reason for treatment death classified as cardiac arrest; however, the investigator reported 2 possible causes of death: intracranial hemorrhage (patient had profound thrombocytopenia since baseline [platelet counts of 6 to 13 × 10^9/L]) and arrhythmia; an autopsy was not performed.
AE, adverse event; AML, acute myeloid leukemia; NPM1m, nucleophosmin 1 mutated; QTc, corrected QT interval; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WBC, white blood cell.

Table 6. Differentiation Syndrome and QTc Prolongation

Differentiation syndrome	Safety population (N=84)[a]
All grade, n (%)	16 (19.0)[b]
Grade ≥3, n (%)[c]	11 (13.1)
Time to initial onset, median (range), days	10 (4-34)
Duration, median (range), days	14.5 (3-57)
Associated treatment changes, n (%)	
Dose interruptions	7 (8.3)
Dose reductions	0
Discontinuations	1 (1.2)

QTc prolongation	Safety population (N=84)[a]
All grade, n (%)	36 (42.9)
Grade ≥3, n (%)[c]	19 (22.6)
Time to initial onset, median (range), days	8 (1-84)
Duration, median (range), days	4 (1-14)
Associated treatment changes, n (%)	
Dose interruptions	18 (21.4)
Dose reductions	8 (9.5)
Discontinuations	1 (1.2)

Data cutoff: September 18, 2024.
[a]All patients with *NPM1*m AML who received ≥1 dose of revumenib. [b]Steroids were used to treat differentiation syndrome in 100% of cases, and hydroxyurea was used in 31.3% of those cases. [c]Based on the maximum grade experienced by each patient.
AML, acute myeloid leukemia; NPM1m, nucleophosmin 1 mutated; QTc, corrected QT interval; R/R, relapsed or refractory.

CONCLUSIONS

- **Revumenib demonstrated clinically meaningful responses in this heavily pretreated, older population with R/R *NPM1*m AML with a CR + CRh rate of 26%, and nearly half of patients achieved a morphological response with an ORR of 48%**
- **The safety profile remains consistent with previous reports, and <5% of patients discontinued due to a TRAE**
- **These findings support continued investigation of revumenib as a treatment for *NPM1*m AML in earlier lines of therapy and in combination with standard of care**
- **Clinical studies of revumenib in combination with azacitidine + venetoclax (EVOLVE-2 [HOVON-177; NCT06652438]) or intensive chemotherapy (SNDX-5613-0708 [NCT06226571; EU-CT 2024-514531-18-00]) are ongoing**

See the recently published manuscript of the primary efficacy population (n=64):
Arellano ML, et al. Menin inhibition with revumenib for *NPM1*-mutated (*NPM1*m) relapsed or refractory acute myeloid leukemia: AUGMENT-101
Blood. 2025. doi: 10.1182/blood.2025028357; Published online May 7, 2025.

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