AML - 773

Efficacy of Revumenib in Acute Myeloid Leukemia Harboring *NPM1*-Mutated Co-Mutations: Post Hoc Analysis of AUGMENT-101

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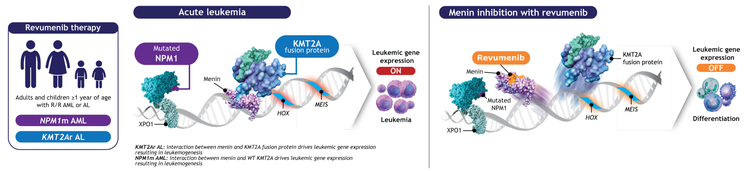
INTRODUCTION

- Nucleophosmin-1 mutations (*NPM1*m) are key drivers of leukemogenesis, occurring in ~30% of newly diagnosed and 12% of relapsed/refractory (R/R) adult acute myeloid leukemia (AML) cases[1-3]
- *NPM1*m AML is molecularly complex; newly diagnosed patients have a median of 4 co-mutations (range, 0-11),[4,5] with a similar proportion of co-mutations observed at relapse[3]
  - Co-mutations in *DNMT3A*, *FLT3*, *WT1*, and *IDH1* are associated with poor prognosis[4,6-8] and higher relapse rates,[7,9,10] while the impact of *IDH2* is variable[8,9]
- Revumenib, a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction (**Figure 1**), is used for the treatment of 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[11,12]
- In a post hoc analysis from AUGMENT-101 (NCT04065399) evaluating revumenib monotherapy in patients with R/R *NPM1*m AML (data cutoff: 18 September 2024),[13] the efficacy population (N = 77) demonstrated an overall response rate (ORR) of 48.1%, a complete remission (CR) + CR with partial hematologic recovery (CRh) rate of 26.0%, a composite CR rate of 32.5%, and a measurable residual disease (MRD)–negativity rate of 63.2% among CR + CRh responders with available MRD status

Figure 1. Revumenib mechanism of action



KMT2Ar AL: interaction between menin and KMT2A fusion protein drives leukemic gene expression resulting in leukemogenesis
NPM1m AML: interaction between menin and WT KMT2A drives leukemic gene expression resulting in leukemogenesis

HOX, homeobox; *MEIS*, Meis homeobox.

OBJECTIVE

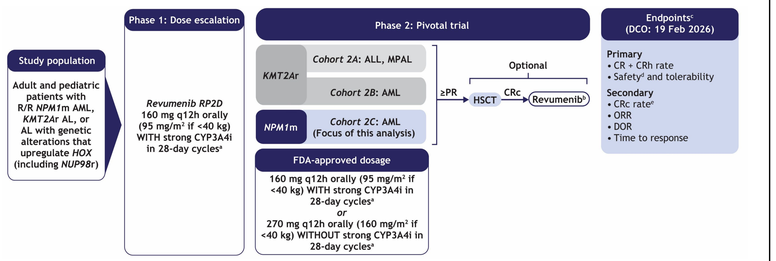
- To further characterize the efficacy of revumenib monotherapy in patients with R/R AML harboring *NPM1*m co-mutations that are potentially prognostic of adverse outcomes

METHODS

Study design

- AUGMENT-101 is an ongoing phase 1/2, open-label, dose-escalation and -expansion study of revumenib in pediatric and adult patients with R/R *NPM1*m, *KMT2A*-rearranged, or *NUP98*r-rearranged acute leukemia (**Figure 2**)
- This current analysis of AUGMENT-101 includes adult patients with centrally confirmed *NPM1*m and available next-generation sequencing results for co-mutations (N = 54)
- *NPM1*m co-mutations were grouped and defined as follows (co-mutation subgroups are not mutually exclusive):
  - *FLT3* mutations (*DNMT3A* + *FLT3*, and *FLT3*), which include both internal tandem duplications and tyrosine kinase domain mutations; subtype was not specified
  - *IDH1/2* mutations (*DNMT3A* + *IDH1*/2, and *IDH1*/2)
  - *FLT3* + *IDH1*/2 mutations
  - Other mutations (common secondary AML co-mutations [*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2*], spliceosome co-mutations [*SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*], *TET2*, *TP53*, *NRAS*, and *KRAS*)
- Outcomes based on *NPM1*m co-mutations are descriptive and not powered for statistical comparisons

Figure 2. AUGMENT-101 study design



[a]Revumenib administered until unacceptable toxicity, end of Cycle 4 if no response, or PD without clinical benefit as defined by the investigator; no steroid or other differentiation syndrome prophylaxis was mandated per protocol. Patients could receive tablet, capsule, or oral solution formulations of revumenib with or without a strong CYP3A4i. Figure shows starting dose for tablet and oral solution formulations; capsule formulation dosage was 163 mg or 276 mg q12h with or without strong CYP3A4i, respectively. [b]Maintenance therapy with revumenib after HSCT was allowed per protocol amendment for eligible patients, with treatment continued until PD or unacceptable toxicity. [c]Relevant to the current analysis. [d]No steroid or other differentiation syndrome prophylaxis was mandated per protocol. [e]CRc = CR + CRh + CRp + CRi.
ALL, acute lymphoblastic leukemia; 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; *HOX*, homeobox; MPAL, mixed-phenotype acute leukemia; ORR, overall response rate; PD, progressive disease; PR, partial remission; q12h, every 12 hours; R*P2D*, recommended phase 2 dose.

RESULTS

Patients

- This analysis included 54 adults with centrally confirmed *NPM1*m and next-generation sequencing results (**Table 1**)
- Overall, the median (range) age was 65.0 years (19-84); 59% were White, 57% were female, and the median (range) number of co-mutations was 3 (1-8)
- Patients were heavily pretreated, with a median (range) of 2 (1-7) prior lines of therapy
  - 74% had prior venetoclax, 26% had prior hematopoietic stem cell transplant, 48% had prior FLT3 inhibitors, and 4% and 6% had prior IDH1 and IDH2 inhibitors, respectively

Table 1. Demographic and baseline characteristics by co-mutation subgroup

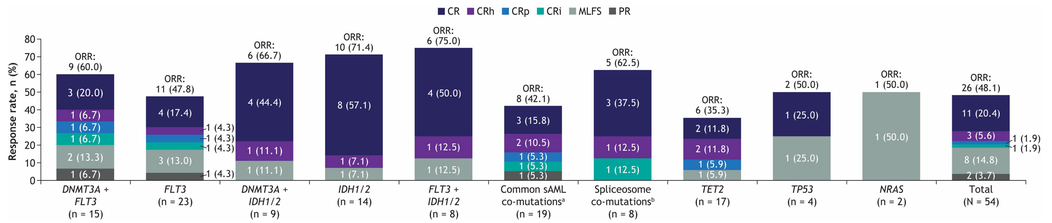
	FLT3 mutations		*IDH1/2* mutations		*FLT3* + *IDH1/2*	Other mutations					Total (N = 54)
	DNMT3A + *FLT3* (n = 15)	*FLT3* (n = 23)	*DNMT3A* + *IDH1/2* (n = 9)	*IDH1/2* (n = 14)	*FLT3* + *IDH1/2* (n = 8)	Common sAML co-mutations[a] (n = 19)	Spliceosome co-mutations[b] (n = 8)	*TET2* (n = 17)	*TP53* (n = 4)	*NRAS* (n = 2)	*KRAS* (n = 1)	
Age, median (range), y	68.0 (44-80)	65.0 (21-80)	65.0 (51-80)	66.5 (40-80)	68.5 (59-80)	63.0 (44-76)	69.0 (55-75)	75.0 (34-84)	58.0 (48-80)	68.5 (57-80)	77.0 (77-77)	65.0 (19-84)
Female, n (%)	8 (53)	12 (52)	5 (56)	6 (43)	3 (38)	9 (47)	3 (38)	12 (71)	3 (75)	1 (50)	1 (100)	31 (57)
Race, n (%)												
White	9 (60)	17 (74)	6 (67)	10 (71)	5 (63)	14 (74)	6 (75)	12 (71)	2 (50)	1 (50)	1 (100)	32 (59)
Non-White[c]	1 (7)	1 (4)	1 (11)	2 (14)	1 (13)	1 (5)	0	4 (24)	1 (25)	0	0	8 (15)
Other[d]	5 (33)	5 (22)	2 (22)	2 (14)	2 (25)	4 (21)	2 (25)	1 (6)	1 (25)	1 (50)	0	14 (26)
Number of co-mutations, median (range)	4 (3-8)	4 (2-8)	3 (3-5)	4 (1-6)	4 (3-5)	4 (2-8)	4 (2-6)	3 (1-7)	4 (3-6)	5 (3-6)	3 (3-3)	3 (1-8)
Number of prior lines of therapy, median (range)	2 (1-7)	2 (1-7)	3 (1-7)	3 (1-7)	4 (1-7)	2 (1-7)	2 (1-5)	2 (1-7)	2 (1-5)	4 (2-5)	1 (1-1)	2 (1-7)
Prior therapy, n (%)												
Venetoclax	11 (73)	18 (78)	7 (78)	9 (64)	6 (75)	15 (79)	5 (63)	14 (82)	3 (75)	2 (100)	1 (100)	40 (74)
HSCT	3 (20)	7 (30)	2 (22)	4 (29)	1 (13)	6 (32)	2 (25)	4 (24)	1 (25)	1 (50)	0	14 (26)
FLT3i	10 (67)	14 (61)	7 (78)	9 (64)	5 (63)	7 (37)	2 (25)	6 (35)	1 (25)	1 (50)	0	26 (48)
IDH1i	1 (7)	1 (4)	1 (11)	2 (14)	1 (13)	1 (5)	1 (13)	0	1 (25)	1 (50)	0	2 (4)
IDH2i	1 (7)	2 (9)	1 (11)	3 (21)	2 (25)	2 (11)	2 (25)	1 (6)	0	0	0	3 (6)

[a]Includes *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2*. [b]Includes *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*. [c]Black or African American and Asian. [d]Includes "other," "multiple," "unknown," and "missing."
i, inhibitor; sAML, secondary AML.

Efficacy

- Best overall response to revumenib monotherapy, as of 19 February 2026 and stratified by co-mutation subgroup, is shown in **Figure 3**
  - ORR was highest in patients with *FLT3* + *IDH1/2* (6/8; 75.0%), *IDH1/2* (10/14; 71.4%), and *DNMT3A* + *IDH1/2* (6/9; 66.7%) co-mutations
- Accordingly, CR + CRh rates were also highest in patients with *FLT3* + *IDH1/2* (5/8; 62.5%), *IDH1/2* (9/14; 64.3%), and *DNMT3A* + *IDH1/2* (5/9; 55.6%) co-mutations (**Table 2**)
  - Most patients who achieved CR + CRh and had MRD status available also achieved MRD negativity

Figure 3. Best overall response to revumenib monotherapy in patients with R/R *NPM1*m AML, stratified by co-mutation subgroup



Each stacked segment represents the response rate (percentage of all patients in the subgroup) for the indicated response category. No patients with *KRAS* co-mutation (n = 1) achieved a response (ORR = 0).
[a]Includes *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2*. [b]Includes *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*.
CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial remission; sAML, secondary AML.

Table 2. Response rates and MRD-negativity rates in patients with R/R *NPM1*m AML, stratified by co-mutation subgroup

	FLT3 mutations		*IDH1/2* mutations		*FLT3* + *IDH1/2*	Other mutations					Total (N = 54)
	DNMT3A + *FLT3* (n = 15)	*FLT3* (n = 23)	*DNMT3A* + *IDH1/2* (n = 9)	*IDH1/2* (n = 14)	*FLT3* + *IDH1/2* (n = 8)	Common sAML co-mutations[a] (n = 19)	Spliceosome co-mutations[b] (n = 8)	*TET2* (n = 17)	*TP53* (n = 4)	*NRAS* (n = 2)	*KRAS* (n = 1)	
CR + CRh rate, n (%)	4 (26.7)	5 (21.7)	5 (55.6)	9 (64.3)	5 (62.5)	5 (26.3)	4 (50.0)	4 (23.5)	1 (25.0)	0	0	14 (25.9)
95% CI	7.8-55.1	7.5-43.7	21.2-86.3	35.1-87.2	24.5-91.5	9.1-51.2	15.7-84.3	6.8-49.9	0.6-80.6	0-84.2	0-97.5	15.0-39.7
MRD-negativity rate, n/N[c,d] (%)	4/4 (100)	5/5 (100)	5/5 (100)	8/9 (88.9)	5/5 (100)	3/5 (60.0)	3/4 (75.0)	3/4 (75.0)	0/1 (0)	0/0	0/0	9/14 (64.3)
CRc rate, n (%)	6 (40.0)	7 (30.4)	5 (55.6)	9 (64.3)	5 (62.5)	7 (36.8)	5 (62.5)	5 (29.4)	1 (25.0)	0	0	16 (29.6)
95% CI	16.3-67.7	13.2-52.9	21.2-86.3	35.1-87.2	24.5-91.5	16.3-61.6	24.5-91.5	10.3-56.0	0.6-80.6	0-84.2	0-97.5	18.0-43.6
MRD-negativity rate, n/N[c,d] (%)	5/5 (100)	6/6 (100)	5/5 (100)	8/9 (88.9)	5/5 (100)	4/6 (66.7)	4/5 (80.0)	3/4 (75.0)	0/1 (0)	0/0	0/0	10/15 (66.7)

[a]Includes *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2*. [b]Includes *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*. [c]MRD negativity was assessed locally by flow cytometry or PCR and defined as an MRD-negative assessment (no blasts detected above the assay limit of detection) at any visit on or after the first response and up to the start of new antileukemic therapy. [d]From responders with MRD status available.
CR, complete remission; CRc, composite CR; CRh, CR with partial hematologic recovery; sAML, secondary AML.

Safety

- The 3 most frequent treatment-emergent adverse events were QTcF prolongation, febrile neutropenia, and vomiting (n = 21 each; **Table 3**)
- Grade ≥3 differentiation syndrome (DS) occurred in 8/54 (15%) patients; this was consistent with prior reports[12,13]
- No patients experienced grade 5 DS or QTcF prolongation
- Treatment-related adverse events leading to discontinuation were infrequent

Table 3. Summary of TEAEs (≥25% any grade) and TRAEs

	Total (N = 54)	
	Any grade	Grade ≥3
TEAE, n (%)	53 (98)	51 (94)
QTcF prolongation	21 (39)	11 (20)
Febrile neutropenia	21 (39)	20 (37)
Vomiting	21 (39)	3 (6)
Anemia	18 (33)	16 (30)
Diarrhea	16 (30)	4 (7)
Hypokalemia	16 (30)	4 (7)
Fatigue	15 (28)	3 (6)
Nausea	15 (28)	5 (9)
TRAE, n (%)	41 (76)	31 (57)
TEAEs leading to dose modifications, n (%)	37 (69)	
Interruption	35 (65)	
Reduction	7 (13)	
TEAEs leading to revumenib discontinuation, n (%)	20 (37)	
TRAEs leading to dose modifications, n (%)	30 (56)	
Interruption	27 (50)	
Reduction	7 (13)	
TRAEs leading to revumenib discontinuation, n (%)	3 (6)[a]	

[a]Three patients had 4 TRAEs leading to discontinuation (osteomyelitis, QTcF prolongation, syncope, and differentiation syndrome).
TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

CONCLUSIONS

- Revumenib demonstrated deep, clinically meaningful responses in patients with high-risk co-mutation profiles across the broad and heterogeneous R/R *NPM1*m AML population, including those associated with adverse outcomes
- The safety profile of revumenib in patients included in this analysis is consistent with the overall population in AUGMENT-101[13]
- Overall, these findings continue to support revumenib as a treatment option for R/R *NPM1*m AML regardless of co-mutation profile

REFERENCES

1. Falini B, et al. *N Engl J Med*. 2005;352(3):254-266.
2. Ranieri R, et al. *Leukemia*. 2022;36(10):2351-2367.
3. Issa GC, et al. *Blood Adv*. 2023;7(6):933-942.
4. Cocciardi S, et al. *Hemasphere*. 2025;9(1):e70060.
5. Lachowiez CA, et al. *Blood Adv*. 2020;4(7):1311-1320.
6. Atluri H, et al. *Blood*. 2025;142(suppl 1):959.
7. Bezerra MF, et al. *Blood*. 2020;135(11):870-875.
8. Dunlap JB, et al. *Am J Hematol*. 2019;94(8):913-920.
9. Hernandez-Sanchez A, et al. *Leukemia*. 2026;40(2):418-428.
10. Sharma N, Liesveld JL. *Cancers (Basel)*. 2023;15(4):1177.
11. Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.
12. Arellano ML, et al. *Blood*. 2025;146(9):1065-1077.
13. Arellano ML, et al. Presented at: 30th Congress of the European Hematology Association (EHA); 12-15 June 2025; Milan, Italy. Poster PS1467.

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