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

PF514

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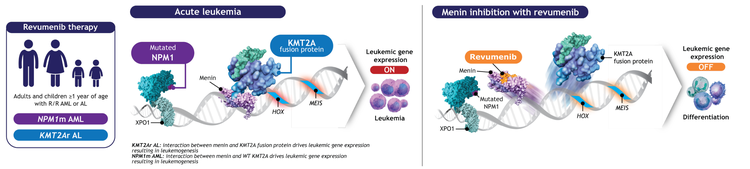
## INTRODUCTION

- 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**




*HOX*, homeobox; *MEIS*, Meis homeobox.

## OBJECTIVE

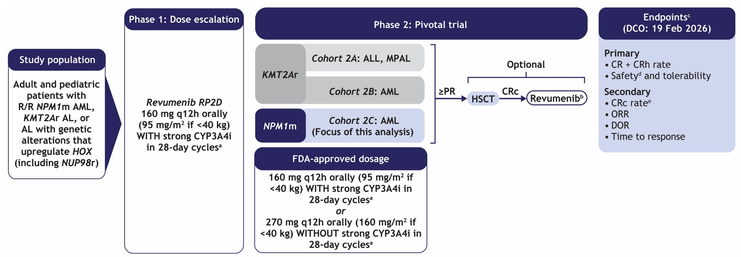
- To further characterize the efficacy of revumenib monotherapy in patients with R/R AML harboring *NPM1*m co-mutations that are potentially prognostic of adverse outcomes

## 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; RP2D, 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**

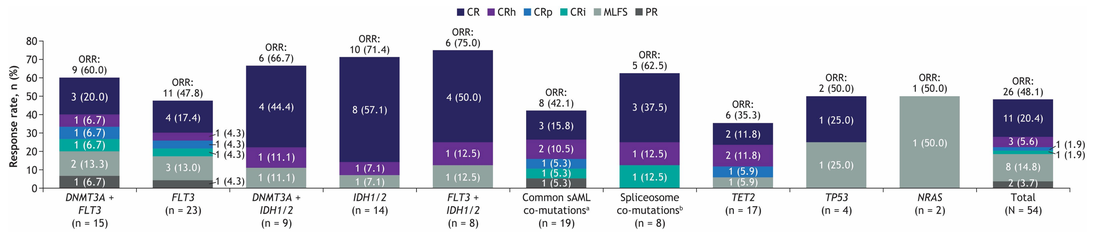
| | *FLT3* mutations | | *IDH1/2* mutations | | *FLT3* + *IDH1/2* | Other mutations | | | | | Total (N = 54) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *DNMT3A* + *FLT3* (n = 15) | *FLT3* (n = 23) | *DNMT3A* + *IDH1/2* (n = 9) | *IDH1/2* (n = 14) | *FLT3* + *IDH1/2* (n = 8) | Common sAML 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

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### ACKNOWLEDGMENTS

AUGMENT-101 is sponsored by Syndax Pharmaceuticals, Inc. Medical writing and editorial assistance were provided by Alex Dimitri, PhD, of Lumanity Communications Inc., and were funded by Syndax Pharmaceuticals, Inc.

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