Revumenib for Patients With Relapsed or Refractory Nucleophosmin 1-Mutated (*NPM1*m) Acute Myeloid Leukemia (AML): Outcomes by Prior Treatment in the Phase 2 AUGMENT-101 Study

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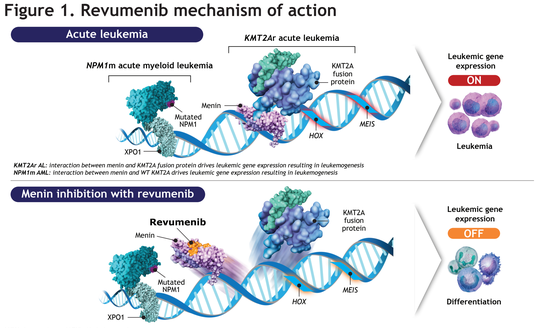
INTRODUCTION

- *NPM1* mutations are key drivers of leukemogenesis, primarily in AML[1,2]
- *NPM1*-mutated (*NPM1*m) AML occurs in ~30% of newly diagnosed and 12% of relapsed/refractory (R/R) adult cases, with ~50% of patients experiencing progressive disease or death after frontline treatment[1-3]
- Data show decreasing complete remission (CR) rates with each line of high-intensity therapy, from 48% at first salvage to 30% and 11% with each subsequent therapy[3]
- Current standard of care varies based on patient and disease characteristics,[4] but prognosis for patients with R/R *NPM1*m AML remains poor (16% survival rate at 1 year), highlighting the need for novel treatments[3]
- Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction that disrupts multiple key drivers of leukemogenesis (*KMT2A*r and *NPM1*m[5]; **Figure 1**)
  - Revumenib is the only menin inhibitor approved for R/R AL harboring a *KMT2A* translocation or an *NPM1* mutation in adult and pediatric patients (≥1 year) in the United States, based on AUGMENT-101 trial data[6]

Figure 1. Revumenib mechanism of action



HOX, homeobox; *MEIS*, Meis homeobox.

OBJECTIVE

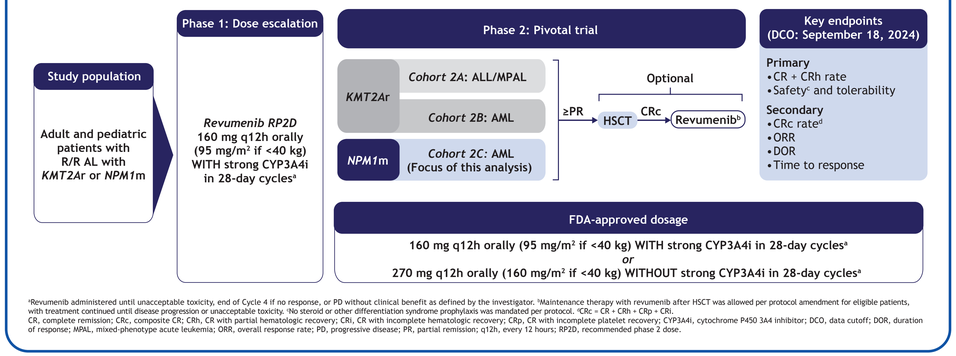
- To further characterize the efficacy and safety of revumenib monotherapy in patients with R/R *NPM1*m AML based on prior treatment

METHODS

Study design

- AUGMENT-101 (NCT04065399) is an ongoing phase 1/2, open-label, dose-escalation and -expansion study of revumenib in R/R *KMT2A*r and *NPM1*m AL (**Figure 2**)
- The current analysis of outcomes based on prior treatment is descriptive and is 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. [b]Maintenance therapy with revumenib after HSCT was allowed per protocol amendment for eligible patients, with treatment continued until disease progression or unacceptable toxicity. [c]No steroid or other differentiation syndrome prophylaxis was mandated per protocol. [d]CRc = CR + CRh + CRp + CRi.
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; 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

- As of September 18, 2024, 84 patients were included in the safety population and 77 were included in the efficacy population (**Table 1**)
- Patients were heavily pretreated, with a median (range) of 2 (1-7) prior lines of therapy; 35.1% of patients received ≥3 prior lines of therapy in the efficacy population
- Median (range) duration of follow-up was 3.9 (0.1-29.9) months for both the safety and efficacy populations
  - Median (range) duration of treatment was 10.2 (0-55.0) weeks and 11.0 (0-55.0) weeks, respectively
  - At data cutoff, 6 (7.8%) patients in the efficacy population and 7 (8.3%) patients in the safety population were still on treatment

Table 1. Demographic and baseline characteristics, mutation status, and prior treatment history[7]

	Efficacy population[a] (N = 77)	Safety population[b] (N = 84)
Age, median (range), y	63 (11-84)	63 (11-84)
Age group, n (%)		
<18 y	1 (1.3)	1 (1.2)
18 to <65 y	38 (49.4)	42 (50.0)
≥65 y	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)
Comutations, n (%)[f]		
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, n (%)	27 (35.1)	29 (34.5)
≥4, n (%)	15 (19.5)	16 (19.0)
Prior therapy, n (%)		
Venetoclax	57 (74.0)	62 (73.8)
HSCT	18 (23.4)	20 (23.8)
>1 prior HSCT	6 (7.8)	8 (9.5)
FLT3i	31 (40.3)	32 (38.1)
IDH1i	5 (6.5)	5 (6.0)
IDH2i	5 (6.5)	5 (6.0)

[a]Patients with centrally confirmed *NPM1*m AML who had ≥5% baseline bone marrow blasts within 28 days prior to start of study treatment. [b]All enrolled patients who received ≥1 dose of revumenib during the study. [c]Includes "missing." [d]Relapse <1 year from prior remission. [e]Relapse ≥1 year from prior remission. [f]Among patients with test results available; comutation testing was conducted locally at the discretion of the investigator.
ITD, internal tandem duplication; *RAS*, rat sarcoma; TKD, tyrosine kinase domain.

Efficacy

- In the efficacy population (N = 77), CR + CR with partial hematologic recovery (CRh) response (primary outcome) was achieved in 26.0% of patients (**Table 2**)
  - The CR + CRh rate was generally consistent across subgroups (**Figure 3**)
- Among CR + CRh responders in the efficacy population, median duration of CR + CRh was 4.7 months (95% confidence interval, 2.1-8.2; **Table 2**)
  - Median duration of CR + CRh by prior treatment was similar to that of the overall population
- Among patients who achieved CR + CRh and had measurable residual disease (MRD) status available, MRD-negativity rate was 63.2% (12/19) and median (range) time to MRD negativity was 2.8 (1.8-4.7) months

Safety

- Safety data from the safety population (N = 84) were reported previously; 66 (78.6%) patients experienced a treatment-related adverse event (TRAE); TRAEs led to treatment discontinuation in 4 (4.8%) patients and death in 1 (1.2%)[4]
- Rates of patients who experienced differentiation syndrome (DS), a class effect of menin inhibitors, were low without any patients receiving DS prophylaxis, consistent across subgroups (15.0%-28.1%), and manageable with steroid ± hydroxyurea treatment per protocol guidance
  - Events occurred early (median [range] time to initial onset, 10 [4-34] days), and median time to resolution was 14.5 (3-57) days
  - Across subgroups, 9.7%-21.9% of patients experienced grade ≥3 DS events
  - No dose reductions were required; 1 patient discontinued treatment due to DS, and no deaths due to DS were reported
- Fridericia's corrected QT interval (QTcF) prolongation events were predictable, manageable per protocol guidance, and occurred early, with similar time to onset (median [range], 8 [1-84] days) and duration (median [range] time to resolution, 4 [1-14] days) across subgroups
  - Rates of patients who experienced QTcF prolongation ranged from 20.0%-80.0% due to small sample sizes for prior IDH1i and IDH2i subgroups
  - Across subgroups, 9.4%-24.2% of patients experienced grade ≥3 QTcF prolongation events
  - One patient discontinued treatment due to QTcF prolongation

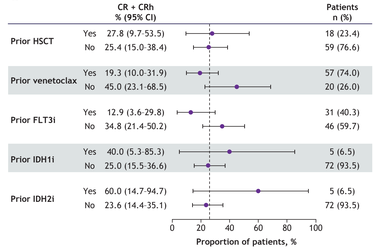
Table 2. Efficacy and time to events

	Efficacy population (N = 77)					
Parameter	**Overall (N = 77)**	**Prior HSCT (n = 18)**	**Prior venetoclax (n = 57)**	**Prior FLT3i (n = 31)**	**Prior IDH1i (n = 5)**	**Prior IDH2i (n = 5)**
CR + CRh rate, n (%) 95% CI	20 (26.0) 16.6-37.2	5 (27.8) 9.7-53.5	11 (19.3) 10.0-31.9	4 (12.9) 3.6-29.8	2 (40.0) 5.3-85.3	3 (60.0) 14.7-94.7
Duration of CR + CRh,[a,b] mo Median (95% CI)	4.7 (2.1-8.2)	5.6 (1.8-NR)	3.9 (1.0-8.2)	4.3 (0.9-NR)	3.9 (NR-NR)	8.2 (NR-NR)
Time to CR + CRh,[a,b] mo Median (range)	2.8 (0.9-8.8)	1.9 (1.8-2.8)	2.8 (1.8-4.3)	1.9 (1.8-1.9)	1.4 (0.9-1.9)	4.3 (2.8-8.8)
MRD negativity,[b,c] n[d]/N[e] (%)	12/19 (63.2)	3/5 (60.0)	7/11 (63.6)	4/4 (100)	2/2 (100)	2/3 (66.7)
Time to MRD negativity,[b,c] mo Median (range)	2.8 (1.8-4.7)	2.1 (1.8-3.7)	2.1 (1.8-4.7)	1.9 (1.8-2.8)	3.7 (2.8-4.7)	3.1 (1.9-4.3)

[a]For CR + CRh responders in the efficacy population. [b]Analyzed among CR + CRh responders. [c]MRD determined locally at the discretion of the investigator; MRD assessment was not required as part of the study. [d]MRD negativity determined by flow cytometry or PCR: overall (flow cytometry: n = 6; PCR: n = 6); prior HSCT (flow cytometry: n = 3); prior venetoclax (flow cytometry: n = 5; PCR: n = 2); prior FLT3i (flow cytometry: n = 2; PCR: n = 2); prior IDH1i (PCR: n = 2); prior IDH2i (flow cytometry: n = 1; PCR: n = 1). [e]N is the number of CR + CRh responders with MRD status available.
CR, complete remission; CRh, CR with partial hematologic recovery; NR, not reached.

- Both the venetoclax-exposed and FLT3i-exposed subgroups were more heavily pretreated than the overall population (**Table 1**), which may account for their numerically lower responses (**Figure 3**)
  - Of patients in the venetoclax-exposed subgroup, 43.9% had ≥3 lines of therapy and 26.3% had ≥4 lines of therapy
  - Of patients in the FLT3i-exposed subgroup, 45.2% had ≥3 lines of therapy and 32.3% had ≥4 lines of therapy; additionally 64.5% had relapsed refractory disease

Figure 3. CR + CRh rates[7]



CR, complete remission;
CRh, CR with partial hematologic recovery.

CONCLUSIONS

- These findings from AUGMENT-101 continue to support revumenib as a preferred treatment option for patients with *NPM1*m AML regardless of prior treatment
- Revumenib monotherapy demonstrated efficacy in R/R *NPM1*m AML across prior treatment subgroups, with some variability observed among more heavily pretreated populations, such as those with prior exposure to FLT3i or venetoclax
- Well-characterized AEs, such as DS, a class effect of menin inhibitors, and the majority of QTcF prolongation events occurred within the first treatment cycle, were manageable per protocol guidance, and were consistent across subgroups
  - Grade ≥3 DS rates were low and similar across subgroups, with no protocol-mandated prophylaxis

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