AML-111

Updated Results and Longer Follow-Up From the AUGMENT-101 Phase 2 Study of Revumenib in Patients With Relapsed or Refractory (R/R) *KMT2A*r Acute Leukemia

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INTRODUCTION

- Revumenib, an oral, small-molecule menin inhibitor that disrupts the menin–lysine methyltransferase 2A (KMT2A) interaction, is being investigated in adult and pediatric patients with relapsed or refractory (R/R) *KMT2A*-rearranged (*KMT2A*r) and nucleophosmin 1–mutated (*NPM1*m) acute leukemias in the AUGMENT-101 study (NCT04065399)[1,2]
- On November 15, 2024, the US Food and Drug Administration approved Revuforj (revumenib) for the treatment of R/R acute leukemia with a *KMT2A* translocation in patients aged ≥1 year[3]

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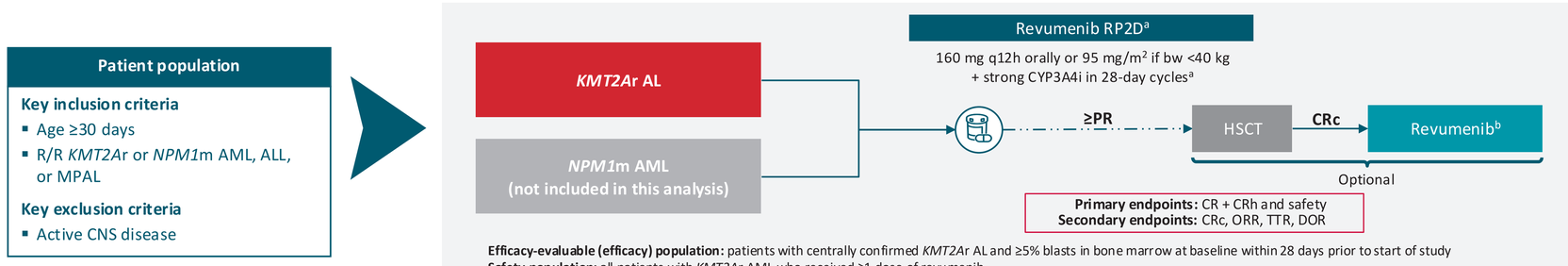
- Here we provide an update on the phase 2 portion of patients with *KMT2A*r acute leukemia after the previously reported interim analysis[2]

METHODS

STUDY DESIGN

- This was a prespecified updated analysis (data cutoff: February 29, 2024) of the ongoing AUGMENT-101 phase 2 study of revumenib in patients with R/R *KMT2A*r acute leukemia (**Figure 1**)

Figure 1. AUGMENT-101 Phase 2 Study Design[2]



[a]Revumenib administered until unacceptable toxicity, 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.
AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; bw, body weight; CNS, central nervous system; CR, complete remission; CRc, composite CR; 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; PR, partial response; 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 February 29, 2024, 116 patients received ≥1 dose of revumenib at a recommended phase 2 dose of 163 mg (or 95 mg/m^2 if body weight <40 kg) and were included in the *KMT2A*r safety population (**Table 1**)
- At the time of data cutoff, 97 patients had sufficient follow-up to be evaluable for efficacy

Table 1. Demographics and Baseline Characteristics

Parameter	Efficacy population (n=97)[a]	Safety population (N=116)[b]
Age, median (range), y	37.0 (0.6-75.0)	35.5 (0.6-75.0)
<18 y, n (%)	20 (20.6)	28 (24.1)
≥18 to <65 y, n (%)	65 (67.0)	74 (63.8)
≥65 y, n (%)	12 (12.4)	14 (12.1)
Female, n (%)	55 (56.7)	67 (57.8)
Race, n (%)		
White	69 (71.1)	80 (69.0)
Non-White	16 (16.5)	18 (15.5)
Unknown	12 (12.4)	18 (15.5)
Leukemia type, n (%)		
AML	78 (80.4)	95 (81.9)
ALL	13 (13.4)	15 (12.9)
MPAL/other	6 (6.2)	6 (5.2)
Co-mutations, n (%)[c]		
FLT3-ITD	5 (5.2)	7 (6.0)
FLT3-TKD	2 (2.1)	3 (2.6)
RAS	12 (12.4)	12 (10.3)
TP53	5 (5.2)	5 (4.3)
Primary refractory, n (%)	19 (19.6)	20 (17.2)
No. of prior lines of therapy, median (range)	2 (1-11)	2 (1-11)
≥3, n (%)	41 (42.3)	51 (44.0)
Prior venetoclax, n (%)	62 (63.9)	73 (62.9)
Prior HSCT, n (%)	46 (47.4)	59 (50.9)

Data cutoff: February 29, 2024.
[a]All patients who received ≥1 dose of revumenib and had centrally confirmed *KMT2A*r AL and ≥5% blasts in bone marrow at baseline.
[b]All patients with *KMT2A*r AL who received ≥1 dose of revumenib.
[c]In patients who had co-mutation status reported.
AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FLT3, fms related receptor tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication; KMT2Ar, lysine methyltransferase 2A rearranged; MPAL; mixed-phenotype acute leukemia; RAS, rat sarcoma virus; TKD, tyrosine kinase domain; TP53, tumor protein P53.

EFFICACY

- Response rates were consistent with those reported in the interim analysis[2] (**Table 2**)
- Median duration of response (DOR) of complete remission (CR) + CR with partial hematologic recovery (CRh) was 6.4 months (95% CI, 1.9 months-not reached [NR]) in the 22 responders
  - 8 patients continue to remain in follow-up without relapse or death
- For the 13 patients who achieved CR + CRh in the interim analysis (data cutoff: July 24, 2023), median DOR of CR + CRh at this updated analysis (data cutoff: February 29, 2024) was 13.0 months (95% CI, 3.4 months-NR)
- Responses were observed across all major subgroups (**Figure 2**) and across the majority of *KMT2A* translocations (**Table 3**)
- Duration of treatment for the 62 efficacy-evaluable patients with a response is shown in **Figure 3**
- Time to first response, median (range):
  - Overall response rate (n=62): 1.0 month (0.9-3.1 months)
  - CR + CRh (n=22): 2.0 months (0.9-4.6 months)
    - Adult responders (n=51): 1.9 months (0.9-4.6 months)
    - Pediatric responders (n=11): 2.5 months (1.0-3.9 months)
- Of the 62 responders, 21 (34%) proceeded to HSCT

Table 2. Efficacy of Revumenib

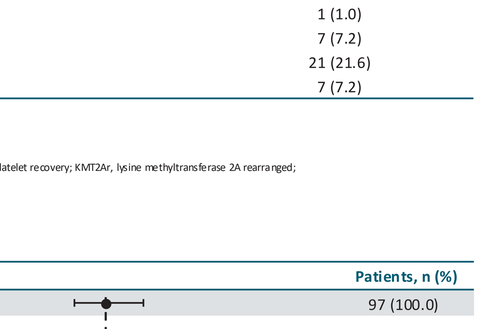
Parameter	Efficacy population (n=97)[a]
ORR, n (%)	62 (63.9)
CR + CRh rate, n (%)	22 (22.7)
95% CI	14.8-32.3
CRc rate, n (%)	41 (42.3)
95% CI	32.3-52.7
Negative MRD status, n/N (%)[b]	
CR + CRh	11/18 (61.1)
CRc	21/36 (58.3)

Best overall response, n (%)	Efficacy population (n=97)[a]
CR	15 (15.5)
CRh	7 (7.2)
CRi	2 (2.1)
CRp	17 (17.5)
MLFS	20 (20.6)
PR	1 (1.0)
PD	7 (7.2)
No response	21 (21.6)
Other[c]	7 (7.2)

Data cutoff: February 29, 2024.
[a]All patients who received ≥1 dose of revumenib and had centrally confirmed *KMT2A*r acute leukemia and ≥5% blasts in bone marrow at baseline.
[b]MRD testing done locally; not all patients had MRD status reported.
[c]Includes patients without postbaseline disease assessment.
CR, complete remission; CRc, composite CR; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; KMT2Ar, lysine methyltransferase 2A rearranged; MLFS, morphological leukemia-free state; MRD, measurable residual disease; ORR, overall response rate; PD, progressive disease; PR, partial remission.

Figure 2. Subgroup Analyses

	CR + CRh rate (95% CI)	Patients, n (%)
Overall	22.7 (14.8-32.3)	97 (100.0)
Age group		
<18 y	25.0 (8.7-49.1)	20 (20.6)
≥18 to <65 y	18.5 (9.9-30.0)	65 (67.0)
≥65 y	41.7 (15.2-72.3)	12 (12.4)
Sex		
Female	21.8 (11.8-35.0)	55 (56.7)
Male	23.8 (12.1-39.5)	42 (43.3)
Race		
White	23.2 (13.9-34.9)	69 (71.1)
Non-White	18.8 (4.0-45.6)	16 (16.5)
Unknown	25.0 (5.5-57.2)	12 (12.4)
Histology		
AML	23.1 (14.3-34.0)	78 (80.4)
ALL	23.1 (5.0-53.8)	13 (13.4)
Acute leukemia of ambiguous lineage	16.7 (0.4-64.1)	6 (6.2)
Prior HSCT		
Yes	26.1 (14.3-41.1)	46 (47.4)
No	19.6 (9.8-33.1)	51 (52.6)
Primary refractory		
Yes	31.6 (12.6-56.6)	19 (19.6)
No	20.5 (12.2-31.2)	78 (80.4)
No. of prior lines of therapy		
1	32.1 (15.9-52.4)	28 (28.9)
2	21.4 (8.3-41.0)	28 (28.9)
≥3	17.1 (7.2-32.1)	41 (42.3)
Prior venetoclax		
Yes	16.1 (8.0-27.7)	62 (63.9)
No	34.3 (19.1-52.2)	35 (36.1)



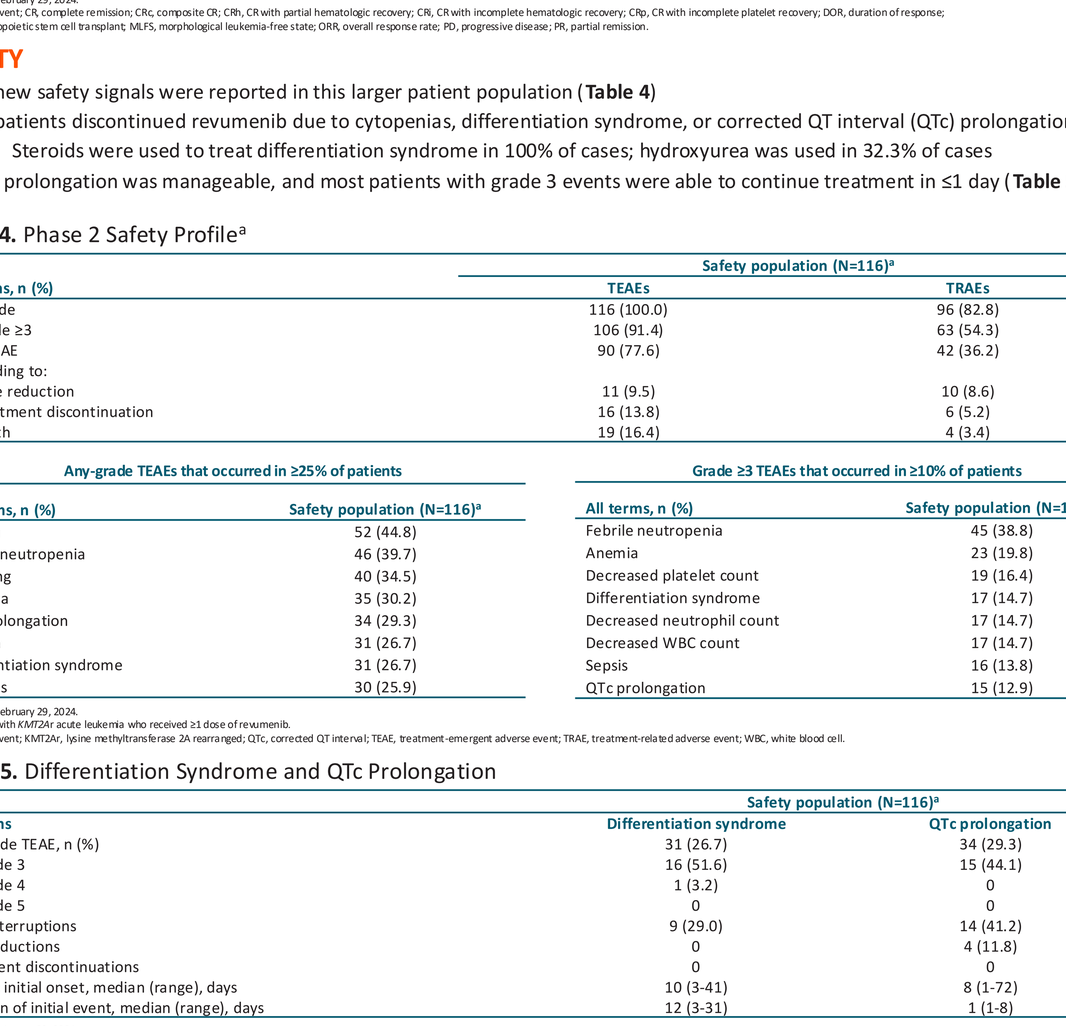
Data cutoff: February 29, 2024.
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; HSCT, hematopoietic stem cell transplant.

Table 3. Responses Seen Across the Majority of *KMT2A* Translocations

	Summary of ORR		Summary of CR + CRh rate	
***KMT2A* translocation**	**n/N[a]**	**ORR (95% CI)**	**n/N**	**CR + CRh rate (95% CI)**
t(9;11)	20/23	87.0 (66.4-97.2)	5/23	21.7 (7.5-43.7)
t(11;19)	9/18	50.0 (26.0-74.0)	2/18	11.1 (1.4-34.7)
t(10;11)	6/11	54.5 (23.4-83.3)	2/11	18.2 (2.3-51.8)
t(6;11)	8/10	80.0 (44.4-97.5)	3/10	30.0 (6.7-65.2)
t(4;11)	7/11	63.6 (30.8-89.1)	3/11	27.3 (6.0-61.0)
t(1;11)	0/2	0.0 (0.0-84.2)	0/2	0.0 (0.0-84.2)
Other translocations[b]	3/4	75.0 (19.4-99.4)	1/4	25.0 (0.6-80.6)
Unknown *KMT2A* fusion partner	9/18	50.0 (26.0-74.0)	6/18	33.3 (13.3-59.0)

Data cutoff: February 29, 2024.
[a]N is the total number of patients with the specified *KMT2A* rearrangement/translocation.
[b]Two patients had t(11;22), 1 had t(11;16), and 1 had t(11;14;19).
CR, complete remission; CRh, CR with partial hematologic recovery; KMT2A, lysine methyltransferase 2A; ORR, overall response rate.

Figure 3. Duration of Treatment



Data cutoff: February 29, 2024.
AE, adverse event; CR, complete remission; CRc, composite CR; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; DOR, duration of response; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; ORR, overall response rate; PD, progressive disease; PR, partial remission.

SAFETY

- No new safety signals were reported in this larger patient population (**Table 4**)
- No patients discontinued revumenib due to cytopenias, differentiation syndrome, or corrected QT interval (QTc) prolongation
  - Steroids were used to treat differentiation syndrome in 100% of cases; hydroxyurea was used in 32.3% of cases
- QTc prolongation was manageable, and most patients with grade 3 events were able to continue treatment in ≤1 day (**Table 5**)

Table 4. Phase 2 Safety Profile[a]

	Safety population (N=116)[a]	
All terms, n (%)	**TEAEs**	**TRAEs**
Any grade	116 (100.0)	96 (82.8)
Grade ≥3	106 (91.4)	63 (54.3)
Serious AE	90 (77.6)	42 (36.2)
AEs leading to:		
Dose reduction	11 (9.5)	10 (8.6)
Treatment discontinuation	16 (13.8)	6 (5.2)
Death	19 (16.4)	4 (3.4)

Any-grade TEAEs that occurred in ≥25% of patients		Grade ≥3 TEAEs that occurred in ≥10% of patients	
All terms, n (%)	**Safety population (N=116)[a]**	**All terms, n (%)**	**Safety population (N=116)[a]**
Nausea	52 (44.8)	Febrile neutropenia	45 (38.8)
Febrile neutropenia	46 (39.7)	Anemia	23 (19.8)
Vomiting	40 (34.5)	Decreased platelet count	19 (16.4)
Diarrhea	35 (30.2)	Differentiation syndrome	17 (14.7)
QTc prolongation	34 (29.3)	Decreased neutrophil count	17 (14.7)
Anemia	31 (26.7)	Decreased WBC count	17 (14.7)
Differentiation syndrome	31 (26.7)	Sepsis	16 (13.8)
Epistaxis	30 (25.9)	QTc prolongation	15 (12.9)

Data cutoff: February 29, 2024.
[a]All patients with *KMT2A*r acute leukemia who received ≥1 dose of revumenib.
AE, adverse event; KMT2Ar, lysine methyltransferase 2A rearranged; QTc, corrected QT interval; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WBC, white blood cell.

Table 5. Differentiation Syndrome and QTc Prolongation

	Safety population (N=116)[a]	
All terms	**Differentiation syndrome**	**QTc prolongation**
Any grade TEAE, n (%)	31 (26.7)	34 (29.3)
Grade 3	16 (51.6)	15 (44.1)
Grade 4	1 (3.2)	0
Grade 5	0	0
Dose interruptions	9 (29.0)	14 (41.2)
Dose reductions	0	4 (11.8)
Treatment discontinuations	0	0
Time to initial onset, median (range), days	10 (3-41)	8 (1-72)
Duration of initial event, median (range), days	12 (3-31)	1 (1-8)

Data cutoff: February 29, 2024.
[a]All patients with *KMT2A*r acute leukemia who received ≥1 dose of revumenib.
KMT2Ar, lysine methyltransferase 2A rearranged; QTc, corrected QT interval; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- **In this updated phase 2 analysis, revumenib continued to consistently provide clinically meaningful responses in heavily pretreated patients with R/R *KMT2A*r acute leukemias, including high rates of measurable residual disease negativity and ability to proceed to HSCT**
- **The safety profile of revumenib was manageable; no patients discontinued treatment due to differentiation syndrome or QTc prolongation**
- **This trial represents the largest evaluation of a targeted therapy for patients with R/R *KMT2A*r acute leukemias to date, including the largest pediatric menin inhibitor cohort**
- **The independent *NPM1*m AML cohort results will be presented in future publications**
- **Revumenib is the first approved menin inhibitor and first approved treatment for *KMT2A*r acute leukemia**

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