Revumenib Monotherapy in Patients With Relapsed/Refractory *KMT2Ar* Acute Leukemia: Efficacy and Safety Results From the AUGMENT-101 Phase 1/2 Study

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INTRODUCTION

- Revumenib, a small-molecule inhibitor of the menin–histone-lysine N-methyltransferase 2A (KMT2A) interaction, is being investigated in adult and pediatric patients with relapsed/refractory (R/R) *KMT2A*-rearranged (*KMT2Ar*) and nucleophosmin 1–mutated (*NPM1m*) acute leukemias in the phase 1/2 AUGMENT-101 study (NCT04065399)[1]
- In the phase 1 study, patients were assigned to 1 of 6 dose-escalation cohorts designed to identify a recommended phase 2 dose (RP2D) for concomitant administration of a cytochrome P450 3A4 inhibitor (CYP3A4i; moderate or strong) or no CYP3A4i
- RP2D was determined based on review of pharmacokinetics, clinical activity, safety, and tolerability data
- An initial analysis of the phase 1 study has been reported[1]
  - Revumenib resulted in deep, durable responses in heavily pretreated R/R acute leukemias; 37.5% of responders proceeded to hematopoietic stem cell transplant (HSCT)
  - Grade ≥3 treatment-related adverse events (TRAEs) were reported in 16.2% of patients; asymptomatic prolongation of the QT interval was the only dose-limiting toxicity identified
- Here we provide an update of >1-year additional experience of patients with R/R *KMT2Ar* acute leukemia in the phase 1 portion of the AUGMENT-101 study, which has completed enrollment, and report topline efficacy and safety results from the phase 2 portion of the study

METHODS

- The phase 1/2 study used a highly innovative trial design enabling an early phase pivotal study for both adult and pediatric, with *KMT2Ar* acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and mixed-phenotype acute leukemia (MPAL). The study also includes a separate *NPM1m* AML cohort
- Phase 1 methods have been previously published[1]
- The pivotal phase 2 portion of the study was initiated after identification of an RP2D of 163 mg (or 95 mg/m^2 if body weight <40 kg) every 12 hours (q12h) with a strong CYP3A4i in 28-day cycles until unacceptable toxicity or lack of at least morphological leukemia-free state (MLFS) by end of cycle 4
  - Phase 2 study enrolled patients in 2 subgroups: those with R/R *KMT2Ar* acute leukemia (including AML, ALL, MPAL) and patients with R/R *NPM1m* AML
  - Phase 2 primary objectives were the assessment of the complete remission (CR)+CR with partial hematologic recovery (CRh) rate and evaluation of safety and tolerability of revumenib
  - A planned interim analysis (IA) of adult and pediatric patients with *KMT2Ar* acute leukemia was conducted with data cutoff in July 2023, and topline data are reported here
  - The efficacy population for the IA (n=57) included all phase 2 patients who had centrally confirmed *KMT2Ar* acute leukemia, had ≥5% blasts in bone marrow at baseline, had received ≥1 dose of study drug, and had started treatment at the same time as or before the 38th adult AML efficacy-evaluable patient
    - The analysis was conducted when 57 patients (adult and pediatric) had completed 6 months of follow-up or discontinued therapy
  - Enrollment of R/R *NPM1m* AML in cohort 2C is ongoing, and data for this cohort are not included in this analysis

RESULTS

PHASE 1

EFFICACY

- As of July 24, 2023, 132 patients aged 0.8 to 82.0 years with R/R acute leukemia were enrolled in the phase 1 study and included in the overall population
- Among 77 patients with R/R *KMT2Ar* acute leukemia treated with revumenib in the 6 dose-escalation cohorts, CR+CRh rate was 31.2% (24/77) and overall response rate (ORR; ie, composite CR [CRc]+MLFS+partial remission) was 64.9% (50/77), with 38.0% (19/50) of responders proceeding to HSCT
  - In a subgroup of adults with AML, CR+CRh rate was 37.3% (19/51) and ORR was 68.6% (35/51), with 40.0% (14/35) of responders proceeding to HSCT
- Of 132 patients in the overall population, 25.0% had a Grade ≥3 TRAE, with Grade 3 QTc prolongation in 8.3% of patients and Grade 3 differentiation syndrome in 2.3% of patients
  - 10.6% of patients discontinued revumenib due to TRAEs
- Based on AUGMENT-101 phase 1 pharmacokinetics, clinical activity, and safety data, an RP2D of 276 mg (or 160 mg/m^2 if body weight <40 kg) q12h without a strong CYP3A4i was established
  - For concomitant use with a strong CYP3A4i, an RP2D of 163 mg (or 95 mg/m^2 if body weight <40 kg) q12h was established

PHASE 2

BASELINE CHARACTERISTICS

- As of July 24, 2023, 94 patients had received ≥1 dose of study drug and were included in the *KMT2Ar* safety population (Table 1)
  - At the time of the IA, 57 patients had the opportunity for sufficient follow-up to evaluate for efficacy
    - 57.9% of patients were female and 22.8% of patients were pediatric
    - Patients received a median of 2 prior lines of therapy (range, 1–11) and 45.6% had prior HSCT

Table 1. Phase 2 Patient Demographics and Baseline Characteristics[a]

Parameter	Efficacy population (n=57)	Safety population (n=94)[b]
Median age, y (range)	34.0 (1.3–75.0)	37.0 (1.3–75.0)
Sex, n (%)		
Female	33 (57.9)	56 (59.6)
Race, n (%)		
White	43 (75.4)	68 (72.3)
Non-White	10 (17.5)	14 (14.9)
Unknown	4 (7.0)	12 (12.8)
Leukemia type, n (%)		
AML	49 (86.0)	78 (83.0)
ALL	7 (12.3)	14 (14.9)
MPAL/Other	1 (1.8)	2 (2.1)
Co-mutations, n (%)		
FLT3	5 (8.8)	7 (7.4)
RAS	9 (15.8)	12 (12.8)
p53	4 (7.0)	5 (5.3)
Primary refractory, n (%)	14 (24.6)	18 (19.1)
Number of prior lines of therapy, median (range)	2 (1–11)	2 (1–11)
≥3 prior lines of therapy, n (%)	26 (45.6)	41 (43.6)
Prior venetoclax, n (%)	41 (71.9)	61 (64.9)
Prior HSCT, n (%)	26 (45.6)	47 (50.0)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *FLT3*, fms-related tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; MPAL, mixed-phenotype acute leukemia; *RAS*, rat sarcoma virus. [a]Data cutoff: July 24, 2023. [b]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

EFFICACY

- With a median follow-up time of 6.1 months in the efficacy population, the ORR was 63.2% (36/57; 95% CI, 49.3–75.6); CRc was 43.9% (25/57; 95% CI, 30.7–57.6)
- The primary endpoint of the pivotal phase 2 study was met at the IA, with a CR+CRh rate of 22.8% (13/57; 95% CI, 12.7–35.8; 1-sided *P* value, 0.0036), with 70.0% (7/10) of those patients (with available data) achieving negative measurable residual disease (MRD) status (Table 2)
- Responses stratified by *KMT2A* rearrangements and major subgroups are shown in Table 3 and Figure 1, respectively
  - CR+CRh rate was similar in adult (22.7% [10/44; 95% CI, 11.5–37.8]) and pediatric (23.1% [3/13; 95% CI, 5.0–53.8]) patients (Figure 1)
  - However, the study was not powered to evaluate differences among subgroups as the number of patients per subgroup are small
- At the IA, median overall survival was 8.0 (95% CI, 4.1–10.9) months (Figure 2)
- CR+CRh responses were rapid (median, 1.9 [range, 0.9–4.6] months; Figure 3) and durable (6.4 [95% CI, 3.4–not reached] months)
- 38.9% (14/36) of patients proceeded to HSCT, with 7 patients resuming revumenib after HSCT
  - 3 additional patients remained eligible to initiate revumenib after HSCT at the time of data cutoff

Table 2. Phase 2 Response[a]

Parameter	Efficacy population (n=57)
ORR, n (%)	36 (63.2)
Best response, n (%)	
CR	10 (17.5)
CRh	3 (5.3)
CRi	1 (1.8)
CRp	11 (19.3)
MLFS	10 (17.5)
PR	1 (1.8)
Other[b]	21 (36.8)
CR+CRh rate, n (%)	13 (22.8)
	95% CI, 12.7–35.8; 1-sided *P* value, 0.0036
CRc, n (%)	25 (43.9)
Negative MRD status in CRc, n (%)[c]	15/22 (68.2)
Negative MRD status in CR+CRh, n (%)[c]	7/10 (70.0)
No. of responders who proceeded to HSCT, n (%)	14/36 (38.9)

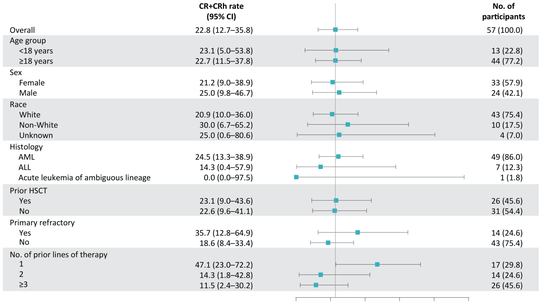
CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; MRD, measurable residual disease; ORR, overall response rate (CRc+MLFS+PR); PR, partial remission. [a]Data cutoff: July 24, 2023. [b]Includes no response, disease progression, and patients without postbaseline disease assessment. [c]MRD done locally; not all patients had MRD status reported.

Table 3. Phase 2 Responses Observed Across *KMT2A* Rearrangements[a]

	Summary of ORR		Summary of CR+CRh rate	
KMT2A rearrangement/translocation	n/N[b]	ORR (95% CI)	n/N[b]	CR+CRh rate (95% CI)
9;11	10/11	90.9 (58.7–99.8)	2/11	18.2 (2.3–51.8)
11;19	7/13	53.8 (25.1–80.8)	2/13	15.4 (1.9–45.4)
10;11	5/7	71.4 (29.0–96.3)	2/7	28.6 (3.7–71.0)
6;11	5/7	71.4 (29.0–96.3)	2/7	28.6 (3.7–71.0)
4;11	2/2	100 (15.8–100)	0/2	9 (0.0–84.2)
1;11	0/2	0 (0.0–84.2)	0/2	9 (0.0–84.2)
11;16	1/1	100	0/1	0
11;22	1/1	100	1/1	100
Unknown *KMT2A* fusion partner	5/13	38.5 (13.9–68.4)	4/13	31.0 (9.1–61.4)

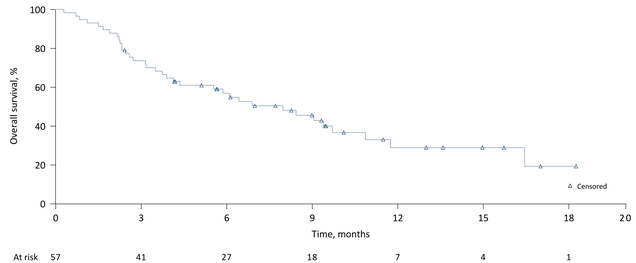
CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; *KMT2A*, histone-lysine N-methyltransferase 2A; MLFS, morphological leukemia-free state; ORR, overall response rate (CRc+MLFS+PR); PR, partial remission. [a]Data cutoff: July 24, 2023. [b]N = total number of *KMT2A* rearrangements/translocations.

Figure 1. Forest plot illustrating the estimated rate of CR+CRh for prespecified subgroups in the phase 2 efficacy population of AUGMENT-101.[a]



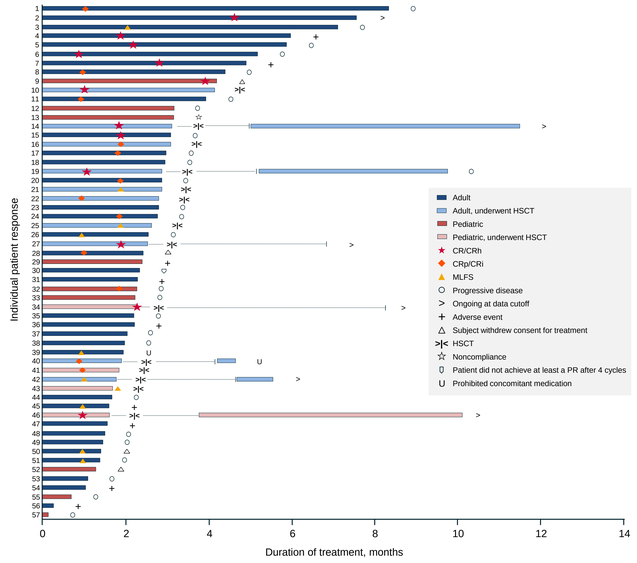
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; HSCT, hematopoietic stem cell transplant. [a]Data cutoff: July 24, 2023.

Figure 2. Kaplan-Meier estimate of overall survival in the phase 2 efficacy population of AUGMENT-101.[a]



[a]Data cutoff: July 24, 2023.

Figure 3. Swimmer plot illustrating the duration of treatment and key study events of patients in the phase 2 efficacy population of AUGMENT-101.[a]



CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; PR, partial remission. [a]Data cutoff: July 24, 2023.

SAFETY

- Overall, a manageable safety profile was observed among the 94 patients in the safety population (Table 4)
  - 6.4% and 12.8% of patients discontinued revumenib due to TRAEs and treatment-emergent adverse events, respectively
- Most common TRAEs (≥20%) were nausea (27.7%), differentiation syndrome (26.6%), and QTc prolongation (23.4%)
  - There were no treatment discontinuations due to differentiation syndrome, QTc prolongation, or cytopenias

Table 4. Phase 2 Safety Profile[a]

All terms	Safety population (n=94)[b]
Any grade TEAE, n (%)	93 (98.9)
Any grade TEAEs that occurred in ≥30% patients, n (%)	
Nausea	42 (44.7)
Febrile neutropenia	36 (38.3)
Diarrhea	33 (35.1)
Vomiting	29 (30.9)
Grade ≥3 TEAE, n (%)	86 (91.5)
Grade ≥3 TEAE that occurred in ≥10% patients, n (%)	
Febrile neutropenia	35 (37.2)
Anemia	17 (18.1)
Decreased neutrophil count	15 (16.0)
Decreased white blood cell count	15 (16.0)
Differentiation syndrome	15 (16.0)
Decreased platelet count	14 (14.9)
QTc prolongation	13 (13.8)
Sepsis	11 (11.7)
Hypokalemia	10 (10.6)
Serious AE, n (%)	72 (76.6)
TEAE leading to dose reduction, n (%)	9 (9.6)
TEAE leading to discontinuation, n (%)	12 (12.8)
TEAE leading to death, n (%)	14 (14.9)

AE, adverse event; TEAE, treatment-emergent AE. [a]Data cutoff: July 24, 2023. [b]Defined as patients with *KMT2Ar* acute leukemia having received at least 1 dose of revumenib.

CONCLUSIONS

- **The phase 1 study demonstrated promising efficacy and safety in heavily pretreated patients as previously reported[1]**
- **At the phase 2 IA, this pivotal study of revumenib in an independent cohort of patients with *KMT2Ar* acute leukemia met its primary endpoint with a CR+CRh rate of 22.8% (13/57; 95% CI, 12.7–35.8) and a 1-sided *P* value of 0.0036**
  - **Durable MRD-negative remissions and high rates of transplants were observed among responders**
- **Overall, a manageable safety profile was observed; discontinuations and dose reductions due to adverse events were low**
- **Enrollment in the *KMT2Ar* cohorts was stopped early for efficacy after meeting the primary efficacy endpoint at the phase 2 IA**
  - **A New Drug Application for *KMT2Ar* leukemia has been initiated under the FDA Real-Time Oncology Review program based on these data**
- **Enrollment in the independent *NPM1m* AML cohort is ongoing**

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