

Safety and activity of revumenib in combination with fludarabine/cytarabine (FLA) in patients with relapsed/refractory acute leukemias

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INTRODUCTION

- Menin–lysine methyltransferase 2A (*KMT2A*) interactions are a critical dependency in many acute leukemias, including those with *KMT2A* rearrangements (*KMT2Ar*), nucleophosmin 1 mutations (*NPM1m*), and nucleoporin 98 rearrangements (*NUP98*)¹
- Patients with these aberrations, particularly infant and pediatric patients with relapsed disease, have suboptimal response rates and poor overall survival¹
 - Fludarabine and cytarabine (FLA)-based regimens are commonly used in pediatric relapsed/refractory acute leukemia and are associated with high-grade adverse events (AE), including hematologic toxicity^{2,3}
- Single-agent revumenib, an oral selective menin inhibitor, has demonstrated encouraging activity with acceptable safety in patients with multiply relapsed acute leukemias¹
- AUGMENT-102 (NCT05326516) was designed to investigate the addition of revumenib to FLA in this patient population

AIM

- To describe the safety and preliminary activity and to determine the recommended phase 2 dose (RP2D) of revumenib in combination with FLA in the AUGMENT-102 trial (NCT05326516)

METHODS

- AUGMENT-102 is a phase 1, open-label, dose-escalation study of revumenib in combination with standard chemotherapy in patients with relapsed/refractory acute leukemia harboring *KMT2Ar*, *NPM1m*, or *NUP98* (**Figure 1**)
- Revumenib dose escalation used a Bayesian optimal interval design with 2 dose levels (DLs)

Figure 1. AUGMENT-102 study design.

Patient population

Patients aged ≥ 30 days with R/R acute leukemias harboring *KMT2Ar*, *NPM1m*, or *NUP98r* and adequate organ function; extramedullary and CNS involvement were eligible

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Revenumib (DL1: 113 mg q12h)^a or (DL2: 163 mg q12h)^b + FLA (fludarabine/cytarabine)^{c,d}

28-day cycle x 2 cycles

(all patients received a strong CYP3A4 inhibitor)

- Revumenib monotherapy is continued after completion of chemotherapy cycles
- Patients who proceeded to transplant could also resume revumenib monotherapy post transplant

Primary endpoints

- Occurrence of dose-limiting toxicities; frequency, duration, and severity of TEAEs, TRAEs, and SAEs
- Disease response was assessed before initiation of each cycle

Revumenib BSA dosing for patients <40 kg, DL1 equivalent 65 mg/m²Revumenib BSA dosing for patients <40 kg, DL2 equivalent 95 mg/m²Fludarabine 30 mg/m²/dose IV over 30 minutes × 5 days (days

Cytarabine 2000 mg/m²/dose IV over 1–3 hours × 5 days (days 1–5)

SA, body surface area; CNS, central nervous system; CYP3A4, cytochrome P450; DL, dose level; IV, intravenous; *KMT2A*, histone-lysine N-methyltransferase 2A rearrangements; *NPM1m*, nucleophosmin 1 mutation; *NUP98*, nucleoporin 98 rearrangements; q12h, every 12 hours; R/R, relapsed/refractory; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

RESULTS

Baseline Characteristics

- As of 15 January 2024, 27 patients (median age, 6 [range, 0.8–78] years) received revumenib plus FLA at DL1 (n=9) or DL2 (n=18) (**Table 1**)
- 20 patients (74.1%) were aged <18 years, and 6 (22.2%) were <2 years
- 19 patients (70.4%) had ≥3 prior lines of treatment, including 11 (40.7%) with prior hematopoietic stem cell transplant (HSCT)
- 18 patients (66.7%) received prior FLA-containing therapies

Table 1. Patient Demographics and Baseline Characteristics^a

	Dose level 1 (n=9)	Dose level 2 (n=18)	Total population (N=27)
Median age (range), y	4.0 (0.8–78.0)	6.5 (1.0–77.0)	6.0 (0.8–78.0)
Age <18 y, n (%)	5 (55.6)	15 (83.3)	20 (74.1)
Age <6 y, n (%)	5 (55.6)	8 (44.4)	13 (48.1)
Sex, n (%)			
Female	5 (55.6)	8 (44.4)	13 (48.1)
Leukemia type, n (%)			
AML	6 (66.7)	16 (88.9)	22 (81.5)
ALL	2 (22.2)	1 (5.6)	3 (11.1)
MPAL	1 (11.1)	1 (5.6)	2 (7.4)
Alteration type, n (%) ^b			
<i>KMT2Ar</i>	8 (88.9)	15 (83.3)	23 (85.2)
<i>NPM1m</i>	1 (11.1)	1 (5.6)	2 (7.4)
<i>NUP98r</i>	0	1 (5.6)	1 (3.7)
Number of prior lines of therapy, median (range)	3 (1–6)	3 (1–18)	3 (1–18)
Prior FLA-containing therapies, n (%)	5 (55.6)	13 (72.2)	18 (66.7)
Prior HSCT, n (%)	4 (44.4)	7 (38.9)	11 (40.7)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FLA, fludarabine and cytarabine; HSCT, hematopoietic stem cell transplant; *KMT2A*, histone-lysine N-methyltransferase 2A rearrangements; MPAL, mixed-phenotype acute leukemia; *NPM1*m, nucleophosmin 1 mutation; *NUP98*, nucleoporin 98 rearrangements. *Data cutoff: 15 January 2024; *Missing alteration identified in 1 patient with *KMT2A*.

Safety

- Grade ≥ 3 AEs were reported in 100% and 88.9% of patients at DL1 and DL2, respectively (**Table 2**)
 - Most common grade ≥ 3 AEs occurred more frequently at DL1 versus DL2
- QT interval prolongation (grade 3) was reported in 1 patient (3.7%) at DL1
- No differentiation syndrome was reported
- There was 1 AE leading to death (sepsis at DL1) not related to revumenib
- Treatment-related AEs leading to dose reduction and discontinuation were reported in 1 patient each at DL1

Table 2. Safety Profile^a

	Dose level 1 (n=9)	Dose level 2 (n=18)
TEAEs, n (%) ^b		
Grade ≥3 TEAEs	9 (100.0)	16 (88.9)
>20% (overall)		
Decreased platelet count	7 (77.8)	10 (55.6)
Anemia	6 (66.7)	9 (50.0)
Febrile neutropenia	5 (55.6)	8 (44.4)
Decreased white blood cell count	4 (44.4)	6 (33.3)
Decreased neutrophil count	5 (55.6)	4 (22.2)
Increased alanine aminotransferase	3 (33.3)	3 (16.7)
Decreased lymphocyte count	3 (33.3)	3 (16.7)
Sepsis	3 (33.3)	3 (16.7)
TEAEs leading to revumenib discontinuation ^c	2 (22.2)	1 (5.6)
TEAEs leading to revumenib reduction ^d	1 (11.1)	0

ALT, alanine aminotransferase; DL, dose level; TEAE, treatment-emergent adverse event. ^aData cutoff: 15 January 2024. ^bMaximum tolerated dose was established in the first 28 days of study and within that window there was 1 dose limiting toxicity in DL2 of grade 4 decreased neutrophil count. ^cReasons for discontinuation include: 1 patient in DL1 due to sepsis; 1 patient in DL1 due to increased ALT, bacteremia, and increased bilirubin; and 1 patient in DL2 due to sepsis. ^dReasons leading to dose reduction include: 1 patient in DL1 due to increased ALT.

Efficacy

- Composite complete remission (CRc) was achieved in 5 patients at DL1 and 9 patients at DL2 (**Table 3; Figure 2**)
- Most patients with CRc and available data achieved measurable residual disease negativity (10/14; 71.4%)
- 7 patients underwent HSCT
 - 5 patients (35.7%) underwent HSCT after achieving remission from revumenib
 - 2 patients (14.3%) underwent HSCT after additional chemotherapy while in remission

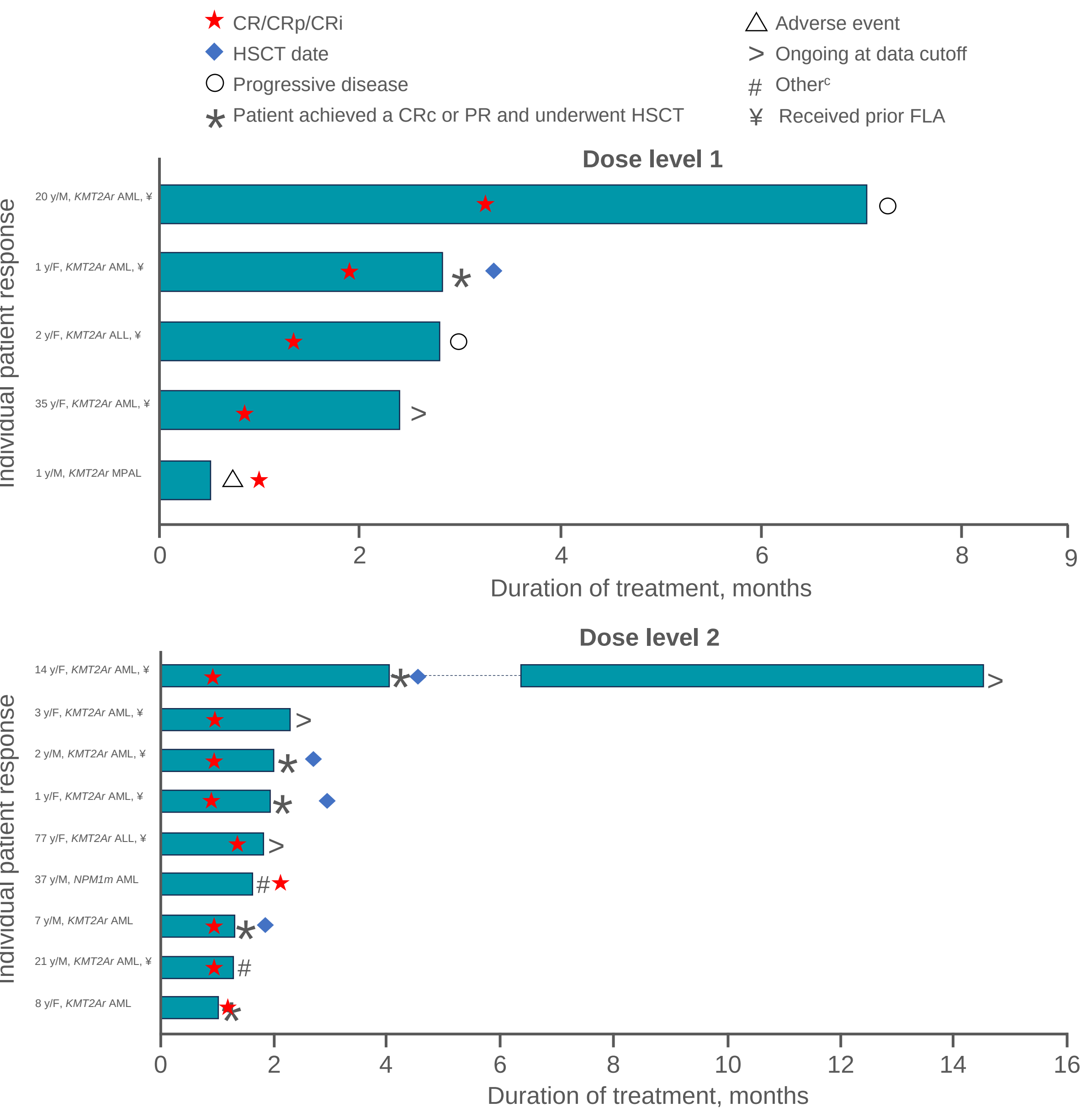
Table 3. Efficacy Profile^a

	Dose level 1 (n=9)	Dose level 2 (n=18)
ORR, n (%)	5 (55.6)	9 (50.0)
Best response, n (%)		
CR	2 (22.2)	4 (22.2)
CRi	2 (22.2)	3 (16.7)
CRp	1 (11.1)	2 (11.1)
Stable disease	1 (11.1)	6 (33.3)
PD	2 (22.2)	3 (16.7)
Missing	1 (11.1)	0
CRc, n (%)	5 (55.6)	9 (50.0)
	95% CI, 21.2–86.3	95% CI, 26.0–74.0
Median DOR (range), mo	2.6 (1.5–NR)	NR (9.2–NR)
Median TTR, mo	1.35	0.99
Negative MRD status in CRc, n (%)	3 (60.0)	7 (77.8)
Responders who proceeded to HSCT, n/N (%)	1/5 (20.0)	4/9 (44.4) ^b

CR, complete remission; CRc, composite CR (CR+CRp+CRi); CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; DOR, duration of response; HSCT, hematopoietic stem cell transplant; MRD, measurable residual disease; NR, not reached; ORR, overall response rate; PD, progressive disease; TTR, time to response. ^aData cutoff: 15 January 2024. ^bTwo additional patients underwent HSCT after additional therapy while in remission (dauorubicin and cytarabine, detectable).

CR, complete remission; CRc, composite CR (CR+CRp+CRi); CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; DOR, duration of response; HSCT, hematopoietic stem cell transplant; MRD, measurable residual disease; NR, not reached; ORR, overall response rate; PD, progressive disease; TTR, time to response. ^aData cutoff: 15 January 2024. ^bTwo additional patients underwent HSCT after additional therapy while in remission (daunorubicin and cytarabine, decitabine).

Figure 2. Swimmer plot illustrating the duration of treatment and key study events of responders in the AUGMENT-102 trial.^{a,b}



ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CR, complete remission; CRp, composite CR (CR+CRp+CRi); CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; F, female; FLA, fludarabine and cytarabine; HSCT, hematopoietic stem cell transplant; *KMT2A*, histone lysine methyltransferase 24 rearrangements; M, male; MPAL, mixed-phenotype acute leukaemia; MRD, measurable residual disease; *NPM1*, nucleophosmin 1 mutation. *Data cutoff: 15 January 2024. *Duration of treatment is calculated from first dose date to last dose date; duration of remission after HSCT is shown after the dashed line. *Other describes other reasons for end of treatment, which include death of patient, physician decision, or the need for a different chemotherapy before HSCT after achievement of CR with positive MRD.

CONCLUSIONS

- This study supports the selection of revumenib 163 mg q12h (95 mg/m² q12h if weight <40 kg) combined with FLA and a strong cytochrome P450 inhibitor as the RP2D
 - This dose corresponds with the monotherapy RP2D of revumenib
- The 50% overall response rate in DL2 of this heavily pretreated cohort of mostly pediatric patients is encouraging and warrants further efficacy studies of this combination
- Revumenib was tolerable in heavily pretreated patients with *KMT2Ar*, *NUP98r*, or *NPM1m* acute leukemias without increased frequency or severity of AEs compared with historic FLA data or revumenib monotherapy
 - Lower rates of cytopenias were reported with DL2 than DL1, which is consistent with faster remission at DL2
 - Lower rates of nonhematologic AEs in DL2 than DL1 also suggest that the AE profile was not driven by revumenib
 - There were no cases of differentiation syndrome
 - There were no increases in AEs with addition of revumenib compared with the safety profile of FLA previously reported
- Additional trials of revumenib combination therapy are ongoing

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