Revumenib Activity in Patients With *NUP98r* Acute Myeloid Leukemia: Results From the AUGMENT-101 Phase 1 Study

PS1501

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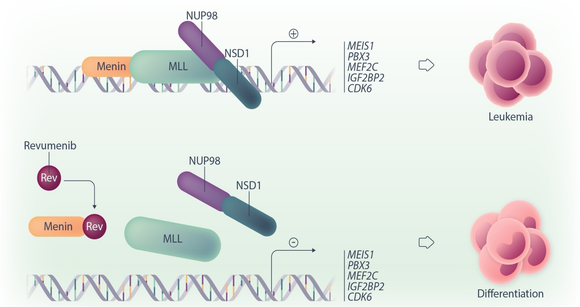
INTRODUCTION

- The menin–lysine methyltransferase 2A (KMT2A) interaction is a dependency in *KMT2A*-rearranged (*KMT2Ar*) and *NPM1*-mutated (*NPM1m*) acute leukemia (AL)[1,2] and is associated with upregulation of *HOX* genes
- Menin inhibition leads to abrogation of the oncogenic expression of these genes, resulting in an antileukemic effect (**Figure 1**)[2,3]
- *NUP98*-rearranged (*NUP98r*) AML is another genetic abnormality associated with upregulation of *HOX*, which is preclinically susceptible to menin inhibition[3,4]
- Revumenib, a first-in-class, potent, selective menin inhibitor that disrupts the menin–KMT2A interaction, was approved by the FDA for the treatment of relapsed/refractory (R/R) AL with a *KMT2A* translocation in patients aged ≥1 year,[5] based on results from the phase 1/2 AUGMENT-101 study (NCT04065399)[6,7]
  - Further, positive outcomes were reported in patients with *NPM1m* AML in the phase 1[6] and 2[8,9] portions of AUGMENT-101
  - In the phase 1 portion, patients with R/R AL were enrolled if they harbored genetic alterations leading to an upregulation of *HOX*, including patients with *NUP98r* R/R AML

AIM

- Here we describe the outcomes in patients with *NUP98r* R/R AML after treatment with revumenib in the phase 1 portion of AUGMENT-101

Figure 1. Upregulation of *HOX* Genes Leads to Leukemogenesis[3]



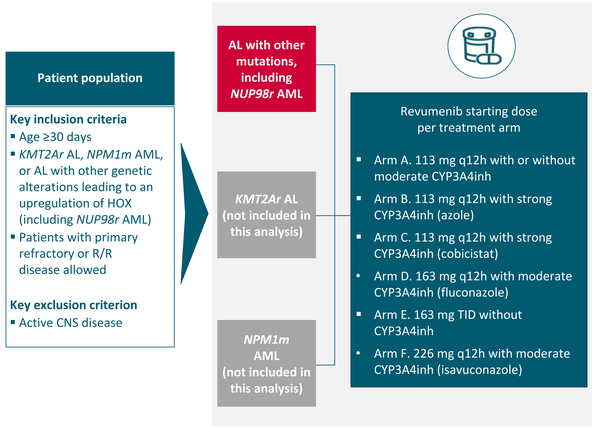
CDK6, cyclin-dependent kinase 6; HOX, homeobox; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; MEF2C, myocyte enhancer factor 2C; MEIS1, Meis homeobox 1; MLL, mixed-lineage leukemia; NSD1, nuclear receptor binding SET domain protein 1; NUP98, nucleoporin 98; PBX3, PBX homeobox 3; rev, revumenib.

METHODS

STUDY DESIGN

- The study design is shown in **Figure 2**; the methods have been previously published[6]

Figure 2. AUGMENT-101 (Phase 1 Study Design)



AL, acute leukemia; AML, acute myeloid leukemia; CNS, central nervous system; CYP3A4inh, cytochrome P450 3A4 inhibitor; HOX, homeobox; *KMT2Ar*, lysine methyltransferase 2A rearranged; *NPM1m*, nucleophosmin 1 mutated; *NUP98r*, nucleoporin 98 rearranged; q12h, every 12 hours; R/R, relapsed/refractory; TID, 3 times daily.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Five patients had *NUP98r* AML (**Table 1**)
- The majority of patients (60%) with *NUP98r* AML were adults (aged ≥18 years)

Table 1. Demographics and Baseline Characteristics of Patients With *NUP98r* AML

Patient	Age/sex	Extramedullary disease	No. of prior lines of therapy	Prior venetoclax	Prior HSCT
1	19 y/M	No	2	No	Yes
2	79 y/F	No	1	No	No
3	17 y/M	Yes	5	Yes	Yes
4	55 y/F	No	5	Yes	No
5	15 y/M	No	3	Yes	Yes

Data cutoff: 29 February 2024.
AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; *NUP98r*, nucleoporin 98 rearranged

EFFICACY

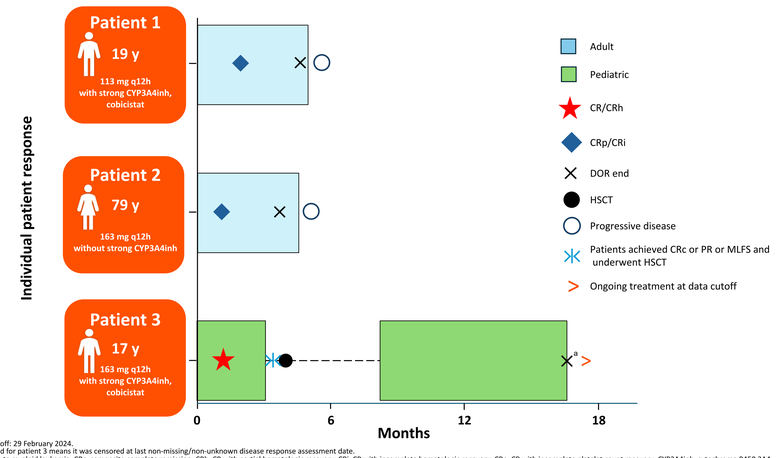
- Responses were seen at both 113 and 163 mg q12h doses
- Among patients with *NUP98r* AML, 3 attained morphological remission (60%; complete remission [CR] with partial hematologic recovery [CRh], n=1; CR with incomplete hematologic recovery [CRi], n=1; CR with incomplete platelet count recovery [CRp], n=1) (**Table 2**)
- One patient attained a measurable residual disease-negative response; this patient proceeded to hematopoietic stem cell transplant, resumed revumenib post transplant, and continued maintenance therapy as of the data cutoff (in cycle 10) (**Table 2, Figure 3**)

Table 2. Summary of Treatment Outcomes in Patients With *NUP98r* AML

Patient	Dose		Best response	MRD negativity[a]	Time to response (CRc), months	Duration of response (CRc), months	EFS, months	OS, months	Proceeded to HSCT while in remission	Maintenance duration and last response
1	113 mg q12h[b]	With strong CYP3A4inh, cobicistat	CRp	No	1.9	2.8	4.6	27.9[c]	No	—
2	163 mg q12h[b]	Without strong CYP3A4inh	CRi	No	1.0	2.8	3.7[c]	11.6[c]	No	—
3	163 mg q12h[d]	With strong CYP3A4inh, cobicistat	CRh	Yes	1.2	15.6	16.7[c]	16.7[c]	Yes	10 cycles at DCO with CR MRD–
4	163 mg TID[b]	Without strong CYP3A4inh	NR	No	NA	NA	1.8[c]	11.3[c]	No	—
5	113 mg q12h[b]	With strong CYP3A4inh, cobicistat	PD	No	NA	NA	0.9	13.2	No	—

Data cutoff: 29 February 2024.
[a]MRD assessed by flow cytometry. [b]Below the RP2D. [c]Censored. [d]RP2D.
AML, acute myeloid leukemia; CRc, composite complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet count recovery; CYP3A4inh, cytochrome P450 3A4 inhibitor; DCO, data cutoff; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; MRD, measurable residual disease; NA, not applicable; NR, no response; *NUP98r*, nucleoporin 98 rearranged; OS, overall survival; PD, progressive disease; q12h, every 12 hours; RP2D, recommended phase 2 dose; TID, 3 times daily.

Figure 3. Patients With *NUP98r* AML With Response



Data cutoff: 29 February 2024.
[a]DOR end for patient 3 means it was censored at last non-missing/non-unknown disease response assessment date.
AML, acute myeloid leukemia; CRc, composite complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet count recovery; CYP3A4inh, cytochrome P450 3A4 inhibitor; DOR, duration of response; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; *NUP98r*, nucleoporin 98 rearranged; PR, partial response; q12h, every 12 hours.

SAFETY

- Each patient with *NUP98r* AML experienced ≥1 treatment-emergent adverse event (TEAE)
  - Four of 5 patients had ≥1 grade 3 or higher TEAE
  - One patient had a TEAE leading to dose modification (a single dose was skipped)
- Four patients had ≥1 treatment-related adverse event (TRAE) (**Table 3**)
  - Two patients had 1 grade 3 TRAE each
  - There were no grade 4 or 5 TRAEs
- No cases of differentiation syndrome or QTc prolongation were reported
- No patients had an AE leading to treatment discontinuation or death
- The safety profile of revumenib remains consistent with previous reports, with no new safety signals reported in patients with *NUP98r* AML

Table 3. Summary of TRAEs in Patients With *NUP98r* AML

Patient	Dose		TRAE[a]			
			Grade 1	Grade 2	Grade 3	Dose modifications
1	113 mg q12h[b]	With strong CYP3A4inh, cobicistat	None	None	None	0
2	163 mg q12h[b]	Without strong CYP3A4inh	Dysgeusia, alopecia	None	Anemia	0
3	163 mg q12h[c]	With strong CYP3A4inh, cobicistat	None	None	Ejection fraction decreased	0
4	163 mg TID[b]	Without strong CYP3A4inh	Dysgeusia	None	None	0
5	113 mg q12h[b]	With strong CYP3A4inh, cobicistat	None	Paresthesia	None	0

Data cutoff: 29 February 2024.
[a]Grade 1, 2, 3 preferred term. [b]RP2D. [c]Below the RP2D.
AML, acute myeloid leukemia; CYP3A4inh, cytochrome P450 3A4 inhibitor; *NUP98r*, nucleoporin 98 rearranged; q12h, every 12 hours; RP2D, recommended phase 2 dose; TID, 3 times daily; TRAE, treatment-related adverse event.

LIMITATIONS

- The sample size was small, so no meaningful conclusions can be made pertaining to safety or efficacy
- In this phase 1 trial, efficacy was an exploratory endpoint

CONCLUSIONS

- **The safety profile of revumenib in patients with *NUP98r* AML was consistent with previous reports observed in *KMT2Ar* or *NPM1m* R/R AML, with no new safety signals observed[6-9]**
- **Despite the small sample size, meaningful clinical responses were seen in patients with *NUP98r* AML, with 60% (3 of 5 patients) achieving morphological response, warranting further study**
- **A phase 2 study evaluating revumenib monotherapy in R/R AL associated with *HOX* upregulation, including patients with *NUP98r* AML, has been initiated (NCT06229912)**
- **Additional studies evaluating revumenib in combination with chemotherapy in patients with *NUP98r* AML include SNDX-5613-0702 (NCT05326516), SAVE (NCT05360160), and SNDX-5613-0708 (NCT06226571)**

ACKNOWLEDGMENTS: The authors thank the study participants, their families, and all investigational site members involved in this study. Writing and editorial support was provided under the direction of the authors by Kathy Beirne, PhD, and Apurva Davé, PhD, of Nucleus Global, an Inizio company, and funded by Syndax Pharmaceuticals, Inc.

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