Revumenib Maintenance Therapy Following Revumenib-Induced Remission and Transplant

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INTRODUCTION

- The menin-KMT2A interaction is a key driver in acute leukemias that share a homeobox (*HOX*)/*MEIS* leukemogenic signature, such as histone-lysine N-methyltransferase 2A rearrangements (*KMT2Ar*), nucleoporin 98 rearrangements (*NUP98r*), or nucleophosmin 1 mutations (*NPM1m*)[1]
  - However, there are no approved therapies targeting the menin-KMT2A interaction[1]
- In the relapsed/refractory (R/R) state, patients with *KMT2Ar* and *NPM1m* acute leukemias have poor survival outcomes, thereby highlighting the need for targeted, efficacious, and well-tolerated therapies[2,3]
- The potent and selective oral menin-KMT2A inhibitor revumenib (SNDX-5613) induced complete remissions with clearance of residual disease in *KMT2Ar* and *NPM1m* acute leukemias refractory to multiple previous lines of therapy in the AUGMENT-101 phase 1 study[1]
- After response to revumenib, some patients received hematopoietic stem cell transplant (HSCT) as consolidation therapy and resumed treatment as posttransplant maintenance[1]

AIM

- To report outcomes following the resumption of revumenib after HSCT in patients with R/R acute leukemias treated in both phase 1 and 2 of the AUGMENT-101 multicenter, open-label, dose-escalation study (NCT04065399)

METHODS

- Patients aged ≥30 days with R/R acute leukemias with genetic alterations associated with *HOXA* overexpression, including *KMT2Ar*, *NPM1m*, or *NUP98r* leukemias, were enrolled in the phase 1 AUGMENT-101 study
  - Patients with R/R acute leukemias harboring either *KMT2Ar* or *NPM1m* alterations were enrolled in the phase 2 study
- Patients in the AUGMENT-101 trial who achieved composite complete remission (CRc), morphological leukemia-free state, or partial response could undergo HSCT without leaving the study
  - Revumenib was stopped before the HSCT conditioning regimen but, per a protocol amendment, it could be resumed after HSCT if the following conditions were met:
    - Patient was between 30- and 180-days post HSCT
    - Patient had successful engraftment as demonstrated by absolute neutrophil count ≥500/mm^3 and platelets ≥50,000/mm^3 without transfusions
    - Patient did not have acute or chronic graft-versus-host disease requiring systemic immunosuppression
    - Patient achieved CRc
- Prior to the protocol amendment, select patients received revumenib maintenance on single-patient protocols
- Patients received revumenib every 12 hours in 28-day cycles at the dose tolerated on AUGMENT-101 prior to HSCT
- Measurable residual disease (MRD) was assessed per local institution standard of care using multiparameter flow cytometry and/or polymerase chain reaction
- Data cutoff was July 24, 2023, for patients receiving revumenib on AUGMENT-101; last data update for patients who received revumenib maintenance on single-patient protocols is November 6, 2023

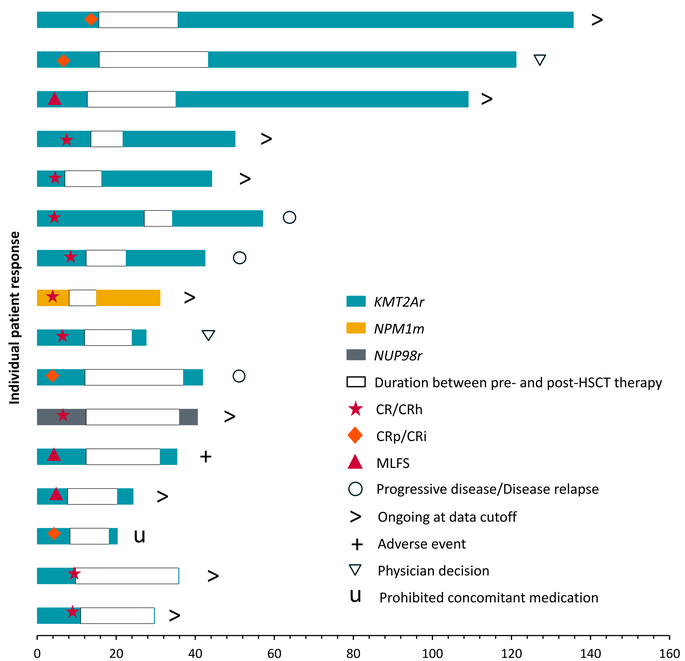
RESULTS

BASELINE CHARACTERISTICS

- As of the data cutoff, 16 patients with acute myeloid leukemia from the AUGMENT-101 study resumed revumenib post transplant (10 received revumenib on AUGMENT-101 via the amended protocol and 6 received revumenib via single-patient protocols) (Figure 1)
- Median age was 39 years (range, 1.3-71 years)
  - More than half the patients were female
  - 14 patients had leukemia with *KMT2Ar* and 1 patient each had *NUP98r* and *NPM1m* alterations
  - Patients received a median of 2 (range, 1-6) prior lines of therapy with 56% of patients having already received HSCT prior to enrollment in AUGMENT-101

Figure 1. Baseline characteristics and response of patients on revumenib post HSCT.[a]

Age, y/Sex	No. of prior regimens before AUGMENT-101	HSCT before AUGMENT-101, yes/no (#)[b]	HSCT details	Last response reported[c]	TRAE leading to dose modification post HSCT
22/F	4	Yes (2)	Nonmyeloablative; peripheral blood stem cells	Isolated CNS relapse, MRD− bone marrow	Dose decreased owing to leg pain
40/F	1	Yes (1)	HSCT	CR, MRD−[d]	Dose skipped/missed/held and decreased owing to thrombocytopenia
11/M	3	No	Myeloablative; bone marrow	CR, MRD−	Dose held owing to thrombocytopenia
41/M	1	No	Nonmyeloablative; peripheral blood stem cells	CR, MRD−	None
1.3/F	1	No	Myeloablative; bone marrow	CR, MRD not tested	None
71/F	1	Yes (1)	Stem cell boost[e]	CRh, MRD+	Dose decreased owing to thrombocytopenia
35/F	2	Yes (1)	Nonmyeloablative Peripheral blood stem cells	Relapse	Dose skipped owing to nausea and vomiting
39/F	2	Yes (1)	Myeloablative; bone marrow	CRh, MRD not tested	None
39/M	6	Yes (1)	Myeloablative; bone marrow, cord blood	CR, MRD−[f]	Dose skipped owing to hyperbilirubinemia and thrombocytopenia
41/F	3	No	Myeloablative	PD	None
17/M	5	Yes (1)	Myeloablative; peripheral blood stem cells	CRh, MRD not tested	None
26/F	3	No	Myeloablative; peripheral blood stem cells	NA	Dose discontinued owing to cytopenia and diarrhea
55/F	2	Yes (1)	Myeloablative; peripheral blood stem cells	CRp, MRD not tested	Dose skipped owing to thrombocytopenia
57/M	1	Yes (1)	Myeloablative; bone marrow	CRi, MRD−	None
5/M	2	No	Myeloablative; cord blood	CR, MRD not tested	None
56/M	1	No	Nonmyeloablative; peripheral blood stem cells	CR, MRD not tested	None



CNS, central nervous system; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; F, female; HSCT, hematopoietic stem cell transplant; M, male; MLFS, morphological leukemia-free state; MRD, measurable residual disease; NA, not available; PD, progressive disease; TRAE, treatment-related adverse event. [a]Data cutoff of July 24, 2023, for patients enrolled in AUGMENT-101; last data update for patients who received revumenib maintenance on single-patient protocols is November 6, 2023. Phase 1 patients may have received a dose lower than recommended phase 2 dose. Duration of therapy calculated from the start date to the end date +1 day. MRD status may be from earlier response assessment, or last response assessment with MRD status available, if this is the case. [b]All patients went on to HSCT/CD34 infusion after response to on-study revumenib. [c]Last response reported while on revumenib or prior to new antileukemic therapy. [d]Treatment discontinuation was based on physician/patient decision once patient achieved 2 years post transplant. [e]Discontinued study after an unconditioned stem cell boost for cytopenias; no HSCT after study discontinuation, but revumenib was resumed on a compassionate-use basis 1 month later. [f]Converted from MRD+.

EXPERIENCE ON REVUMENIB POST TRANSPLANT

- Revumenib was resumed between 49 and 180 days post transplant
- The duration of treatment in the maintenance setting ranged from 1 to 701 days, with treatment ongoing for 9 of the 16 patients
- CRc was maintained based on last status reported in 12 patients (75.0%) during treatment with revumenib post HSCT at time of data cutoff (Figure 1)
- MRD-negative remissions were maintained in 6 patients as of the data cutoff
  - MRD was not tested in 6 patients

SAFETY

- Dose of revumenib was reduced for 3 of 16 patients due to adverse events (AEs) of thrombocytopenia (n=2) and leg pain (n=1)
- Revumenib was discontinued in 1 of 16 patients because of cytopenia and diarrhea (n=1)

CONCLUSIONS

- **Maintenance treatment post HSCT with revumenib was feasible, with a tolerable safety profile, in a heavily pretreated R/R patient population, with few discontinuations due to AE (n=1)**
- **Durable responses were seen in the posttransplant setting, with 3 patients taking revumenib maintenance therapy for more than 1 year**

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