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Phase 1 Study of Revumenib in Combination With Intensive Chemotherapy in Patients With Newly Diagnosed Acute Myeloid Leukemia Harboring Genetic Alterations in *KMT2A*, *NPM1*, or *NUP98*: SNDX-5613-0708

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INTRODUCTION

- Acute leukemias (AL) harboring a *KMT2A* or *NUP98* rearrangement confer unfavorable prognoses,[1,2] and while *NPM1*-mutated AML without concurrent *FLT3*-internal tandem duplication (ITD) mutation is considered favorable risk, ~50% of adults with *NPM1*m will relapse[3]
- High relapse rates, persistent MRD, and short OS remain challenges in *KMT2A*r, *NPM1*m, and *NUP98*r AML[1,2,4-11]
  - At relapse, these subtypes have poor prognoses and frequent resistance to standard treatments but are susceptible to menin inhibition
- *KMT2A*r, *NPM1*m, and *NUP98*r enhance transcriptional activity of the menin-KMT2A interaction, leading to differentiation arrest and leukemogenesis[12,13]
- Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction that disrupts multiple key drivers of leukemogenesis (*KMT2A*r, *NPM1*m, and *NUP98*r)[14]
- Revumenib is the only menin inhibitor approved for R/R AL harboring a *KMT2A* translocation or an *NPM1* mutation in adult and pediatric patients (≥1 year) in the United States[15]
- The addition of revumenib to standard-of-care intensive chemotherapy (IC) may further decrease leukemic cell proliferation and enhance differentiation, thereby improving overall response to treatment

OBJECTIVE

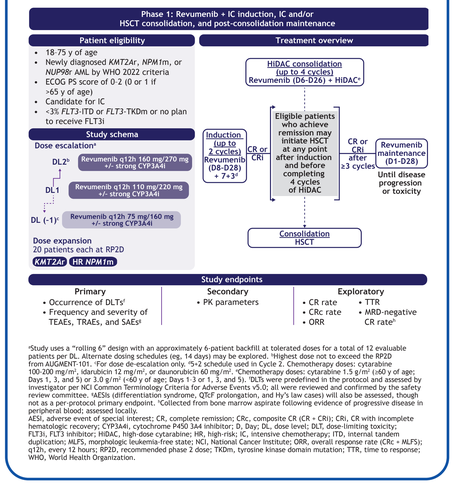
- To report preliminary data from the dose level (DL) 1 and DL2 cohorts of the dose-escalation portion of an ongoing phase 1 study of revumenib + IC for newly diagnosed AML harboring a *KMT2A* rearrangement, *NPM1* mutation, or *NUP98* rearrangement

METHODS

Study design

- SNDX-5613-0708 is a global, phase 1, multicenter, open-label, dose-escalation and -expansion study of revumenib + IC (NCT06226571; **Figure 1**)

Figure 1. Study design



[a]Study uses a "rolling 6" design with an approximately 6-patient backfill at tolerated doses for a total of 12 evaluable patients per DL. Alternate dosing schedules (eg, 14 days) may be explored. [b]Highest dose not to exceed the RP2D from AUGMENT-101. For dose de-escalation only. [c]5+2 schedule used in Cycle 2. Chemotherapy doses: cytarabine 100-200 mg/m², idarubicin 12 mg/m², or daunorubicin 60 mg/m². [d]Chemotherapy doses: cytarabine 1.5 g/m² (≤60 y of age; Days 1, 3, and 5) or 3.0 g/m² (>60 y of age; Days 1-3 or 1, 3, and 5). [e]DLTs were predefined in the protocol and assessed by investigator per NCI Common Terminology Criteria for Adverse Events v5.0; all were reviewed and confirmed by the safety review committee. [f]AESIs (differentiation syndrome, QTcF prolongation, and Hy's law cases) will also be assessed, though not as a per-protocol primary endpoint. [g]Collected from bone marrow aspirate following evidence of progressive disease in peripheral blood; assessed locally.
AESI, adverse event of special interest; CR, complete remission; CRc, composite CR (CR + CRi); CRi, CR with incomplete hematologic recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; D, Day; DL, dose level; DLT, dose-limiting toxicity; FLT3i, FLT3 inhibitor; HiDAC, high-dose cytarabine; HR, high-risk; IC, intensive chemotherapy; ITD, internal tandem duplication; MLFS, morphologic leukemia-free state; NCI, National Cancer Institute; ORR, overall response rate (CRc + MLFS); q12h, every 12 hours; RP2D, recommended phase 2 dose; TKDm, tyrosine kinase domain mutation; TTR, time to response; WHO, World Health Organization.

RESULTS

Patients

- As of September 30, 2025, 13 patients were dosed at DL1 and 17 dosed at DL2
- Patients in DL1 were younger than those in DL2 (median age, 43.0 and 57.0 years, respectively; **Table 1**)
- Most patients in both DL groups were White and had an ECOG PS score ≤1
- Nearly all patients received cytarabine 200 mg/m²

Table 1. Demographic and baseline characteristics

	DL1 (n = 13)	DL2 (n = 17)	Total (N = 30)
Age, median (range), years	43.0 (20-71)	57.0 (19-68)	48.5 (19-71)
Female, n (%)	8 (61.5)	14 (82.4)	22 (73.3)
Race, n (%)			
White	9 (69.2)	15 (88.2)	24 (80.0)
Black or African American	1 (7.7)	0	1 (3.3)
Asian	1 (7.7)	0	1 (3.3)
Not reported	2 (15.4)	0	2 (6.7)
Other	0	2 (11.8)	2 (6.7)
Ethnicity, not Hispanic, n (%)	10 (76.9)	17 (100)	27 (90.0)
ECOG PS score, n (%)			
0	7 (53.8)	6 (35.3)	13 (43.3)
1	3 (23.1)	11 (64.7)	14 (46.7)
2	3 (23.1)	0	3 (10.0)
Genetic aberration, n (%)			
*KMT2A*r	12 (92.3)	7 (41.2)	19 (63.3)
*NPM1*m	1 (7.7)	10 (58.8)	11 (36.7)
*NUP98*r	0	0	0
FLT3-ITD (allelic ratio of <3% *FLT3*-ITD/total *FLT3*)	0	2 (11.8)	2 (6.7)
FLT3-TKDm (no plan for FLT3 targeted therapy)	1 (7.7)	0	1 (3.3)

DL, dose level; ITD, internal tandem duplication; TKDm, tyrosine kinase domain mutation.

Safety

- At data cutoff, 11/13 patients dosed at DL1 and 10/17 dosed at DL2 were evaluable for dose-limiting toxicities
- One DLT of grade 3 QTcF prolongation was reported in DL1
  - This patient discontinued revumenib during Cycle 1; of note, at the end of Cycle 1, the patient had achieved MRD-negative CR and proceeded to HSCT
- Most common treatment-emergent AEs (TEAEs) of any grade (**Table 2**) were nausea and febrile neutropenia (n = 6, 46.2% each) in DL1, and febrile neutropenia (n = 9, 52.9%) and diarrhea (n = 7, 41.2%) in DL2
  - Most common grade ≥3 TEAEs were febrile neutropenia (n = 6, 46.2%) and platelet count decreased (n = 5, 38.5%) in DL1, and febrile neutropenia (n = 9, 52.9%), thrombocytopenia (n = 6, 35.3%), and anemia (n = 5, 29.4%) in DL2
- Most common treatment-related AEs (TRAEs; related to revumenib) of any grade (**Table 2**) were neutrophil count decreased (n = 4, 30.8%) and anemia, nausea, and vomiting (n = 3, 23.1% each) in DL1, and anemia (n = 3, 17.6%) in DL2
  - Most common grade ≥3 TRAEs were anemia and neutrophil count decreased (n = 3, 23.1% each) in DL1, and anemia (n = 3, 17.6%) in DL2
- Rate of patients who experienced QTcF prolongation was low (6.7%, 2 patients in DL1) and manageable per protocol guidance
  - Onset of this AE occurred within the first 2 cycles for both patients
  - First patient onset occurred on Day 38 (duration, 8 days; grade 3); second patient onset occurred on Day 1 (1 day; grade 3), Day 3 (2 days; grade 2), and Day 16 (1 day; grade 2)
- No cases of differentiation syndrome were reported
- One TEAE leading to death was reported and deemed not related to revumenib

Table 2. Summary of AEs

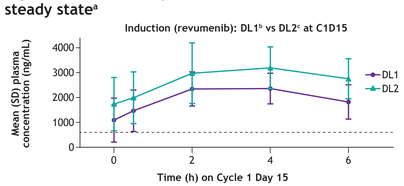
	DL1 (n = 13)		DL2 (n = 17)		Total (N = 30)	
Parameter, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	12 (92.3)	11 (84.6)	15 (88.2)	14 (82.4)	27 (90.0)	25 (83.3)
Any revumenib-related AE	7 (53.8)	4 (30.8)	7 (41.2)	6 (35.3)	14 (46.7)	10 (33.3)
AESI						
QTcF prolongation	2 (15.4)	2 (15.4)[a]	0	0	2 (6.7)	2 (6.7)[a]
SAE[b]	5 (38.5)	-	8 (47.1)	-	13 (43.3)	-
Febrile neutropenia	2 (15.4)	-	1 (5.9)	-	3 (10.0)	-
Sepsis	0	-	3 (17.6)	-	3 (10.0)	-
TEAEs leading to revumenib dose modifications						
Interruption	4 (30.8)	-	6 (35.3)	-	10 (33.3)	-
Reduction	2 (15.4)	-	0	-	2 (6.7)	-
Discontinuation[c]	3 (23.1)	-	1 (5.9)	-	4 (13.3)	-

[a]No grade 4 or 5 events reported. [b]Any SAE reported by ≥2 patients. [c]Due to decreased neutrophil count, pneumonitis, and QTcF prolongation (n = 1 each) in DL1 and intracranial hemorrhage (n = 1) in DL2.
AESI, adverse event of special interest; DL, dose level; QTcF, Fridericia's corrected QT interval; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Pharmacokinetics

- Dose-exposure proportionality between DL1 and DL2 was demonstrated (**Figure 2**; **Table 3**)
- PK profiles in this study are consistent with those in monotherapy studies,[14] indicating that the standard-of-care IC agents used in this study (daunorubicin and cytarabine) have no clinically relevant impact on exposure to revumenib and its primary metabolite, M1
- Drug concentrations exceeded the concentration resulting in the IC_{90} threshold at both DL1 and DL2, indicating potential for sustained pharmacologic activity

Figure 2. Revumenib plasma concentration at steady state[a]



Data cutoff, September 12, 2025. Horizontal dashed line indicates the IC_{90} of revumenib against menin-KMT2A interaction. [a]Cycle 1 Day 15. [b]For DL1, revumenib was given twice daily at 110 or 220 mg ± a strong CYP3A4i, respectively. [c]For DL2, revumenib was given twice daily at 160 or 270 mg ± a strong CYP3A4i, respectively.
CYP3A4i, cytochrome P450 3A4 inhibitor; DL, dose level; IC_{90}, concentration resulting in 90% of maximum inhibition.

Table 3. Summary of steady-state[a] PK parameters of plasma revumenib

Parameter, GM (% GCV)	DL1[b] (n = 7)	DL2[c] (n = 8)
C_{max}, ng/mL	2620 (26)	3430 (28)
C_{avg}, ng/mL	2030 (28)	2690 (35)
AUC, ng × h/mL	12,200 (28)	16,200 (35)

Data cutoff, September 12, 2025.
[a]Cycle 1 Day 15. [b]Revumenib was given twice daily at 110 or 220 mg ± a strong CYP3A4i, respectively. [c]Revumenib was given twice daily at 160 or 270 mg ± a strong CYP3A4i, respectively.
AUC, area under the curve; C_{avg}, average concentration; C_{max}, maximum concentration; CYP3A4i, cytochrome P450 3A4 inhibitor; DL, dose level; GCV, geometric coefficient of variation; GM, geometric mean.

Efficacy

- Among those in the response-evaluable population, ORR, composite CR (CRc), and CR rates were 100% (12/12), 100% (12/12), and 83.3% (10/12) in DL1, respectively, and 92.9% (13/14), 85.7% (12/14), and 57.1% (8/14) in DL2 (**Table 4**)
  - Data are preliminary and will continue to mature
- Median (range) time to CR was 0.7 (0.6-0.8) months in DL1 and 1.0 (0.7-1.3) in DL2
- In patients with CRc and MRD results available, all (8/8) patients in DL1 and 7/10 in DL2 achieved MRD-negative CRc by local assessment
- In patients with CR and MRD results available, all (7/7) patients in DL1 and 5/7 in DL2 achieved MRD-negative CR by local assessment
  - Median (range) time to MRD negativity in patients who achieved CR was 31.0 (28-33) days in DL1 and 30.0 (28-46) in DL2
- At data cutoff, 7 (53.8%) patients in DL1 had proceeded to HSCT
  - Of those, 4 (30.8%) patients resumed revumenib monotherapy following HSCT
- In Cycle 1, neutrophil recovery (≥1000 cells/μL) was achieved in 11/12 (91.7%) CRc responders in DL1 and 10/12 (83.3%) in DL2
  - Median (range) time to count recovery was 29 (19-35) days in DL1 and 29 (22-43) days in DL2
- In Cycle 1, platelet recovery (≥100,000 cells/μL) was achieved in 11/12 (91.7%) CRc responders in DL1 and 9/12 (75.0%) in DL2
  - Median (range) time to count recovery was 28 (22-31) days in DL1 and 29 (22-47) days in DL2

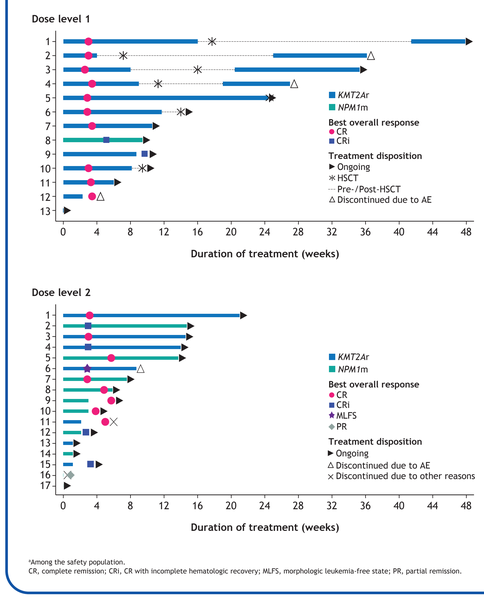
Table 4. Efficacy[a]

Parameter	DL1 (n = 12)	DL2 (n = 14)	Total (N = 26)
ORR,[b] n (%)	12 (100)	13 (92.9)	25 (96.2)
95% CI	73.5-100	66.1-99.8	80.4-99.9
CRc rate,[c] n (%)	12 (100)	12 (85.7)	24 (92.3)
95% CI	73.5-100	57.2-98.2	74.9-99.1
CR rate, n (%)	10 (83.3)	8 (57.1)	18 (69.2)
95% CI	51.6-97.9	28.9-82.3	48.2-85.7
MRD-negative status,[d,e] n (%)			
CRc	8 (100)	7 (70.0)	15 (83.3)
CR	7 (100)	5 (71.4)	12 (85.7)
Time to MRD-negative status, median (range), days			
CRc	31.0 (28-78)	30.0 (28-70)	31.0 (28-78)
CR	31.0 (28-33)	30.0 (28-46)	30.5 (28-46)

[a]Among the response-evaluable population. [b]ORR = CRc + MLFS. [c]CRc = CR + CRi + CRp. [d]For patients who had available MRD-negativity results in the response evaluable population. [e]MRD-negative status determined locally by flow cytometry or PCR: DL1 (flow cytometry: n = 7; PCR: n = 1); DL2 (flow cytometry: n = 5; PCR: n = 1; unknown: n = 1).
CR, complete remission; CRc, composite CR (CR + CRi); CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state.

- At data cutoff, follow-up time was longer for DL1 than DL2
- Treatment is ongoing in the majority of patients (10/13 [76.9%] in DL1 and 14/17 [82.4%] in DL2; **Figure 3**)

Figure 3. Duration of treatment in *KMT2A*r and *NPM1*m AML[a]



[a]Among the safety population.
CR, complete remission; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; PR, partial remission.

CONCLUSIONS

- The safety profile of revumenib + IC was similar across both DLs and comparable to IC alone[16]
- Revumenib's overall safety profile remains consistent with previously reported data, with no new safety signals when administered in combination with IC
- QTcF prolongation was infrequent and managed successfully using established mitigation approaches; no cases of differentiation syndrome were reported
- Preliminary data suggest deep responses, with nearly all tested patients achieving MRD-negative CR
- The robust clinical activity seen with revumenib + IC in newly diagnosed *KMT2A*r and *NPM1*m AML, regardless of DL, supports further exploration of this combination in the phase 3 REVEAL-ND study in fit patients with *NPM1*m AML (NCT07211958)

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