Revumenib + Intensive Chemotherapy for Newly Diagnosed Acute Myeloid Leukemia Harboring Genetic Alterations in *KMT2A*, *NPM1*, or *NUP98*: Updated Phase 1 Results From SNDX-5613-0708

AML-712

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INTRODUCTION

- Acute leukemias (AL) harboring *KMT2A* or *NUP98* rearrangements (*KMT2A*r or *NUP98*r) are associated with poor clinical outcomes,[1,2] and adults with newly diagnosed *NPM1*-mutated (*NPM1*m) acute myeloid leukemia (AML) that lacks a concurrent *FLT3* mutation relapse in ~50% of cases[3,4]
  - High relapse rates, persistent measurable residual disease (MRD), and short overall survival remain challenges in AL harboring these genetic alterations[1,2,5-7]
- These genetic alterations promote leukemogenesis by sustaining the menin-KMT2A interaction, which blocks hematopoietic differentiation[4,8]
- Revumenib, a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction, is used for the treatment of relapsed/refractory (R/R) AML harboring an ***NPM1* mutation** or R/R AL with a ***KMT2A* translocation** in adult and pediatric patients 1 year and older[9,10]
- Adding revumenib to intensive chemotherapy (IC) may further decrease leukemic cell proliferation and enhance differentiation, improving overall response to treatment

OBJECTIVE

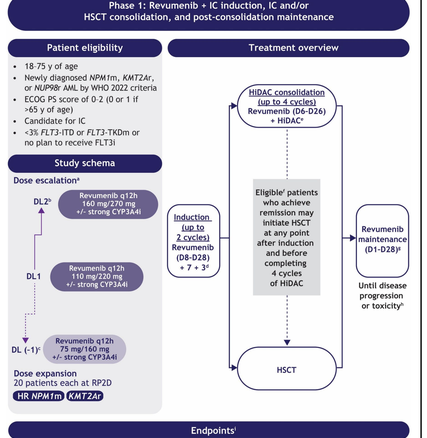
- To report updated findings from the dose level (DL) 1 and DL2 cohorts of the dose-escalation portion of an ongoing phase 1 study of revumenib + IC in newly diagnosed AML with an *NPM1* mutation, *KMT2A* rearrangement, or *NUP98* rearrangement

METHODS

Study design

- SNDX-5613-0708 (NCT06226571) is a multicenter, open-label, nonrandomized, dose-escalation and -expansion study of revumenib + IC (**Figure 1**)
  - The safety population included all patients who received ≥1 dose of revumenib, and patients in the response-evaluable population received ≥1 dose of revumenib and had ≥1 post-baseline response assessment

Figure 1. Study design



[a]Study uses a "rolling 6" design with a backfill of approximately 6 patients 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. [c]For dose de-escalation only. [d]5 + 2 schedule used in Cycle 2. Chemotherapy doses: cytarabine 100-200 mg/m^2, idarubicin 12 mg/m^2, or daunorubicin 60 mg/m^2. [e]Chemotherapy doses: cytarabine 1.5 g/m^2 (≤60 years of age; Days 1, 3, and 5) or 3.0 g/m^2 (>60 years of age; Days 1-3 or 1, 3, and 5). [f]Patient must have achieved CR or CRi. [g]Patient must have achieved CR or CRi after ≥3 cycles. [h]Treatment can continue for up to 2 years. [i]Relevant to the current analysis. [j]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. [k]AESIs (differentiation syndrome, grade ≥2 QTcF prolongation, and potential Hy's Law cases) will also be assessed, though not as a per-protocol primary endpoint. [l]For response and MRD assessments, bone marrow aspirate was collected following evidence of progressive disease in peripheral blood. [m]CRc = CR + CRi. [n]ORR = CRc + MLFS. [o]Assessed locally.

AESI, adverse event of special interest; CR, complete remission; CRc, composite CR; CRi, CR with incomplete hematologic recovery; CYP3A4i, cytochrome P450 3A4 inhibitor; D, Day; DL, dose level; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FLT3i, FLT3 inhibitor; HIDAC, high-dose cytarabine; HR, high-risk; IC, intensive chemotherapy; ITD, internal tandem duplication; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NCI, National Cancer Institute; ORR, overall response rate; PK, pharmacokinetic; q12h, every 12 hours; RP2D, recommended phase 2 dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TKDm, tyrosine kinase domain mutation; TRAE, treatment-related adverse event; TTR, time to response; WHO, World Health Organization.

RESULTS

Patients

- As of 30 November 2025, 15 patients were dosed at DL1 and 20 were dosed at DL2
- Patients in DL1 were younger than those in DL2 (median age, 43.0 and 57.5 years, respectively; **Table 1**), with a better baseline Eastern Cooperative Oncology Group performance status score (0: 53% vs 40%; 1-2: 47% vs 60%)
- More patients had a *KMT2A*r in DL1 than in DL2 (87% vs 40%); patients with *NUP98*r were eligible; however, none had enrolled at the time of analysis
- During induction, patients received either cytarabine 100 or 200 mg/m^2

Table 1. Demographic and baseline characteristics

	DL1 (n = 15)	DL2 (n = 20)	Total (N = 35)
Age, median (range), y	43.0 (20.0-73.0)	57.5 (19.0-68.0)	50.0 (19.0-73.0)
Female, n (%)	10 (67)	16 (80)	26 (74)
Race, n (%)			
White	10 (67)	17 (85)	27 (77)
Black or African American	1 (7)	0	1 (3)
Asian	2 (13)	1 (5)	3 (9)
Not reported	2 (13)	1 (5)	3 (9)
Other	0	1 (5)	1 (3)
Ethnicity, not Hispanic, n (%)	11 (73)	19 (95)	30 (86)
ECOG PS score, n (%)			
0	8 (53)	8 (40)	16 (46)
1	4 (27)	12 (60)	16 (46)
2	3 (20)	0	3 (9)
Genetic aberration, n (%)			
*NPM1*m	2 (13)	12 (60)	14 (40)
*KMT2A*r	13 (87)	8 (40)	21 (60)
*NUP98*r	0	0	0
Co-occurring mutations, n (%)			
FLT3-ITD (allelic ratio of <3% *FLT3*-ITD/total *FLT3*)	0	3 (15)	3 (9)
FLT3-TKDm (no plan for FLT3-targeted therapy)	1 (7)	0	1 (3)

DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; ITD, internal tandem duplication; TKDm, tyrosine kinase domain mutation.

Safety

- As of 30 November 2025, 14/15 patients dosed at DL1 and 14/20 dosed at DL2 were evaluable for dose-limiting toxicities (DLTs) per protocol criteria (received ≥75% of planned dosing or experienced a DLT, assessed from first revumenib dose [Cycle 1 Day 8] through Day 42 of last induction cycle or start of consolidation, whichever occurred first)
  - One DLT of grade 3 QTcF prolongation was reported in DL1
    - This patient discontinued revumenib during Cycle 1; at the end of Cycle 1, the patient had achieved MRD-negative complete remission (CR) and proceeded to hematopoietic stem cell transplant (HSCT)
- Rate of patients who experienced a treatment-emergent adverse event (TEAE) of QTcF prolongation was similar across both DLs (**Table 2**) and manageable per protocol guidance, with a median (range) time to initial onset of 3.0 days (1.0-38.0) for DL1 and 21.0 days (8.0-58.0) for DL2
  - Median (range) duration was similar between DLs (1.0 day [1.0-8.0] for DL1 and 1.5 days [1.0-3.0] for DL2)
- Rate of patients who experienced differentiation syndrome was low (5%, 1 patient in DL2; grade 3)
  - Initial onset occurred on Day 5 (duration, 2 days)
  - Case was manageable with steroid treatment per protocol guidance
- No cases of Hy's Law were reported
- One TEAE leading to death was reported (DL2; intracranial hemorrhage) and deemed not related to revumenib

Table 2. Summary of TEAEs (≥25% any grade, ≥15% grade ≥3) and TRAEs (≥15% any grade, ≥10% grade ≥3) in the total population

Parameter, n (%)	DL1 (n = 15)		DL2 (n = 20)		Total (N = 35)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	14 (93)	13 (87)	20 (100)	19 (95)	34 (97)	32 (91)
Thrombocytopenia/platelet count decreased[a]	8 (53)	7 (47)	13 (65)	13 (65)	21 (60)	20 (57)
Febrile neutropenia	8 (53)	8 (53)	13 (65)	11 (55)	21 (60)	19 (54)
Diarrhea	6 (40)	0	13 (65)	1 (5)	19 (54)	1 (3)
Neutropenia/neutrophil count decreased[a]	8 (53)	7 (47)	9 (45)	9 (45)	17 (49)	16 (46)
Nausea	6 (40)	0	7 (35)	0	13 (37)	0
Anemia	4 (27)	4 (27)	7 (35)	7 (35)	11 (31)	11 (31)
Hypokalemia	3 (20)	0	8 (40)	4 (20)	11 (31)	4 (11)
Vomiting	4 (27)	1 (7)	6 (30)	0	10 (29)	1 (3)
Hypophosphatemia	4 (27)	0	5 (25)	0	9 (26)	0
White blood cell count decreased	4 (27)	4 (27)	4 (20)	4 (20)	8 (23)	8 (23)
Revumenib-related TEAEs	10 (67)	5 (33)	13 (65)	12 (60)	23 (66)	17 (49)
Anemia	3 (20)	3 (20)	3 (15)	3 (15)	6 (17)	6 (17)
Thrombocytopenia	2 (13)	1 (7)	3 (15)	3 (15)	5 (14)	4 (11)
Platelet count decreased	2 (13)	2 (13)	2 (10)	1 (5)	4 (11)	3 (9)
Neutropenia	1 (7)	1 (7)	3 (15)	2 (10)	4 (11)	3 (9)
Neutrophil count decreased	4 (27)	3 (20)	2 (10)	2 (10)	6 (17)	5 (14)
QTcF prolongation[b]	3 (20)	1 (7)	5 (25)	2 (10)	8 (23)	3 (9)
Serious TEAEs[c]	7 (47)		10 (50)		17 (49)	
Febrile neutropenia	3 (20)		2 (10)		5 (14)	
Sepsis	1 (7)		2 (10)		3 (9)	
Gastroenteritis viral	1 (7)		1 (5)		2 (6)	
Pneumonia	2 (13)		0		2 (6)	
TEAEs of special interest	3 (20)		5 (25)		8 (23)	
QTcF prolongation[d]	2 (13)		4 (20)		6 (17)	
Differentiation syndrome	0		1 (5)		1 (3)	
Alanine aminotransferase increased	1 (7)		0		1 (3)	
TEAEs leading to dose modifications						
Interruption	7 (47)		12 (60)		19 (54)	
Reduction	2 (13)		0		2 (6)	
TEAEs leading to discontinuation[e]	3 (20)		1 (5)		4 (11)	
TEAEs leading to death[f]	0		1 (5)		1 (3)	

[a]Combined term. [b]In DL1, events were grade 1, grade 2, and grade 3 (n = 1 each); in DL2, events were grade 1 (n = 3) and grade 3 (n = 2). [c]Any serious TEAE reported by ≥2 patients from the total population. [d]Classified as grade ≥2 based on average of triplicate electrocardiograms. [e]Due to QTcF prolongation, neutropenia/neutrophil count decreased, and pneumonitis (n = 1 each) in DL1 and intracranial hemorrhage (n = 1) in DL2. [f]Due to intracranial hemorrhage (n = 1) in DL2; deemed not related to revumenib. DL, dose level; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

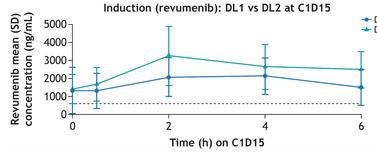
Dosing

- Median (range) duration of follow-up was 4.8 months (1.5-16.0) in DL1 and 2.9 months (0.7-6.2) in DL2 as of 30 November 2025
- Median (range) number of revumenib cycles received was 3 (1-8) in DL1 and 2 (1-5) in DL2 as of data cutoff
- Median (range) relative dose intensity was 89.3% (56.3-104.8) in DL1 and 92.5% (19.1-160.7) in DL2

Pharmacokinetics

- As of 30 October 2025, dose-exposure proportionality between DL1 and DL2 was demonstrated (**Figure 2**; **Table 3**)
- Pharmacokinetic profiles in this study are consistent with those in the monotherapy study,[11] indicating that the 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 effective antileukemic activity through sustained menin inhibition

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



DCO: 30 Oct 2025. Horizontal dashed line indicates the IC_{90} of revumenib against menin-KMT2A interaction.
[a]C1D15. [b]Revumenib was given twice daily at 110 or 220 mg with or without a strong CYP3A4i, respectively. [c]Revumenib was given twice daily at 160 or 270 mg with or without a strong CYP3A4i, respectively.
C, Cycle; CYP3A4i, cytochrome P450 3A4 inhibitor; D, Day; DCO, data cutoff; DL, dose level; IC_{90}, concentration resulting in 90% of maximum inhibition; SD, standard deviation.

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

Parameter, GM (% GCV)	DL1[b] (n = 8)	DL2[c] (n = 13)
C_{max}, ng/mL	2710 (31)	3250 (46)
C_{avg}, ng/mL	1690 (55)	2410 (45)
AUC, ng·h/mL	10,100 (55)	14,400 (45)

DCO: 30 Oct 2025.
[a]C1D15. [b]Revumenib was given twice daily at 110 or 220 mg with or without a strong CYP3A4i, respectively. [c]Revumenib was given twice daily at 160 or 270 mg with or without a strong CYP3A4i, respectively.
AUC, area under the curve; C_{avg}, average concentration; C_{max}, maximum concentration; CYP3A4i, cytochrome P450 3A4 inhibitor; D, Day; DCO, data cutoff; DL, dose level; GCV, geometric coefficient of variation; GM, geometric mean; PK, pharmacokinetic.

Efficacy

- Among those in the response-evaluable population, overall response rate, composite CR (CRc) rate, and CR rate were high and similar across both DLs (**Table 4**)
- In patients with CRc and MRD results available, 10/12 (83.3%) patients in DL1 and 15/17 (88.2%) in DL2 achieved MRD-negative CRc by local assessment
- In patients with CR and MRD results available, all (9/9) patients in DL1 and 11/14 (78.6%) in DL2 achieved MRD-negative CR by local assessment
- As of 30 November 2025, 9/15 (60%) patients in DL1 and 2/20 (10%) in DL2 had proceeded to HSCT; this difference may be due to a higher proportion of patients with *KMT2A*r in DL1 and shorter follow-up in DL2
  - All patients in DL1 and DL2 who proceeded to HSCT had *KMT2A*r AML; of these, 6/9 (66.7%) patients in DL1 resumed revumenib maintenance monotherapy following HSCT at the last tolerated dose and 3/6 (50.0%) were continuing treatment as of the data cutoff
- One patient in DL2 received post-consolidation maintenance therapy without undergoing HSCT
- Time to neutrophil and platelet count recovery was comparable across DLs and consistent with time to count recovery with IC alone,[12,13] suggesting that revumenib did not adversely affect recovery (**Table 5**)
- Treatment is ongoing in most patients (10/15 [66.7%] in DL1 and 17/20 [85.0%] in DL2) irrespective of their *NPM1*m or *KMT2A*r genetic aberration (**Figure 3**)

Table 4. Efficacy[a]

Parameter	DL1 (n = 15)	DL2 (n = 20)	Total (N = 35)
ORR,[b] n (%)	15 (100)	19 (95.0)	34 (97.1)
95% CI	78.2-100.0	75.1-99.9	85.1-99.9
CRc rate,[c] n (%)	15 (100)	19 (95.0)	34 (97.1)
95% CI	78.2-100.0	75.1-99.9	85.1-99.9
CR rate, n (%)	12 (80.0)	15 (75.0)	27 (77.1)
95% CI	51.9-95.7	50.9-91.3	59.9-89.6
Time to CR, median (range), d	21.0 (18.0-35.0)	26.0 (18.0-70.0)	23.0 (18.0-70.0)
MRD-negative status,[d,e] n/N (%)			
CRc	10/12 (83.3)	15/17 (88.2)	25/29 (86.2)
CR	9/9 (100)	11/14 (78.6)	20/23 (87.0)
Time to MRD-negative status, median (range), d			
CRc	31.0 (28.0-65.0)	46.0 (28.0-77.0)	33.0 (28.0-77.0)
CR	31.0 (28.0-65.0)	34.0 (28.0-77.0)	31.5 (28.0-77.0)

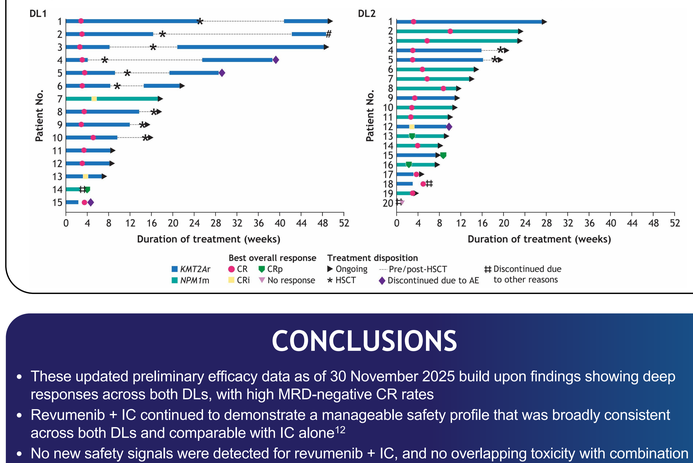
[a]Among the response-evaluable population. [b]ORR = CRc + MLFS. [c]CRc = CR + CRi. [d]For patients who had available MRD-negativity results in the response-evaluable population. [e]MRD-negative status determined locally: DL1 (flow cytometry: n = 10; PCR: n = 1; NGS: n = 1); DL2 (flow cytometry: n = 13; PCR: n = 3; other: n = 1).
CR, complete remission; CRc, composite CR; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; DL, dose level; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NGS, next-generation sequencing; ORR, overall response rate.

Table 5. Neutrophil and platelet recovery among CRc responders during induction Cycle 1

	DL1 (n = 15)	DL2 (n = 19)	Total (N = 34)
Neutrophil recovery (≥1000 cells/μL),[a] n (%)	13 (86.7)	15 (78.9)	28 (82.4)
Time to count recovery, median (range), d	29.0 (8.0-42.0)	29.0 (22.0-55.0)	29.0 (8.0-55.0)
Platelet recovery (≥100,000 cells/μL),[a] n (%)	13 (86.7)	17 (89.5)	30 (88.2)
Time to count recovery, median (range), d	28.0 (22.0-43.0)	29.0 (22.0-47.0)	29.0 (22.0-47.0)

[a]From induction Cycle 1 Day 1. CRc, composite complete remission; DL, dose level.

Figure 3. Duration of treatment in *NPM1*m and *KMT2A*r AML in the safety population



CONCLUSIONS

- These updated preliminary efficacy data as of 30 November 2025 build upon findings showing deep responses across both DLs, with high MRD-negative CR rates
- Revumenib + IC continued to demonstrate a manageable safety profile that was broadly consistent across both DLs and comparable with IC alone[12]
- No new safety signals were detected for revumenib + IC, and no overlapping toxicity with combination use was observed
- Time to neutrophil and platelet recovery was comparable to that of IC alone[13,14]
- Overall, these safety and efficacy findings are consistent in patients with *KMT2A*r and *NPM1*m AML and support continued evaluation of revumenib + IC at DL2 in the phase 3 REVEAL-ND trial (NCT07211958)

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