2025 DEBATES AND DIDACTICS in Hematology and Oncology

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Targeted Treatment with Menin Inhibitors

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Disclosures

Consultant/Advisor/Speaker: SYNDAX Pharmaceuticals

Targeted Treatment with Menin Inhibitors

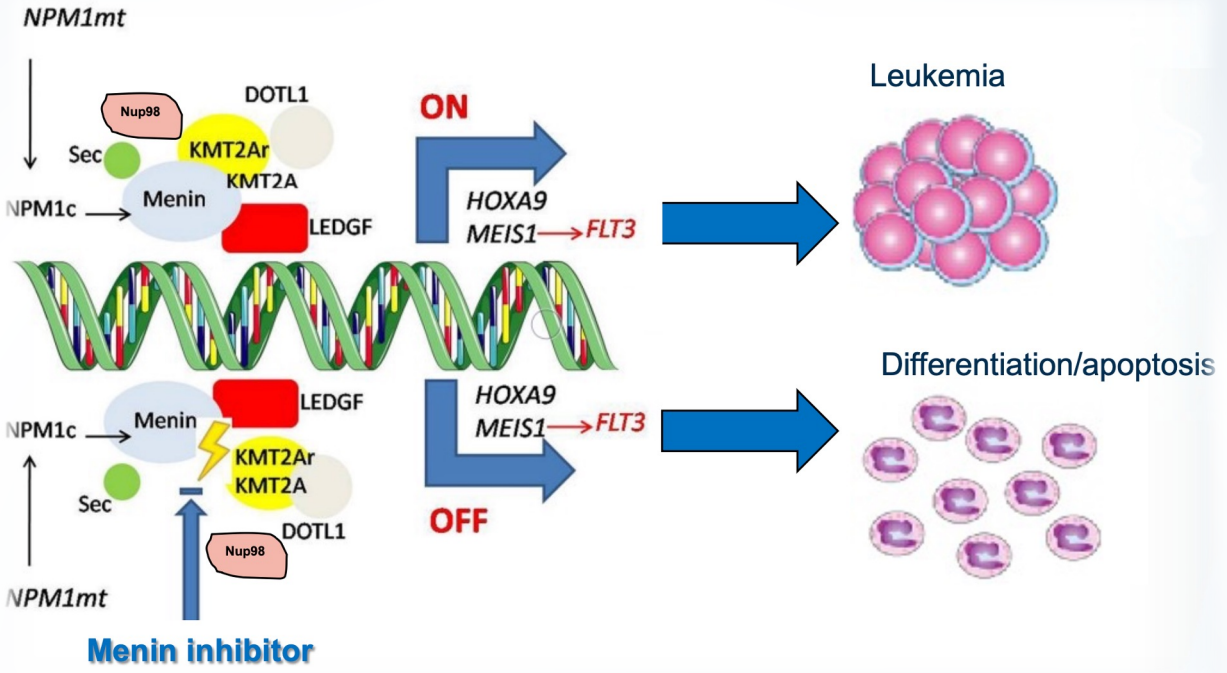
Objectives:

- Menin pathway as a target in leukemia
- Menin inhibitors with efficacy data
- Menin-targeted agents in the pipeline/ongoing trials

Menin as a Target in Leukemia

- *KMT2A* rearrangements occur in ~ 10-15% of acute leukemias.
- *NPM1* mutations occur in ~ 30% of AML.
- *Nup98* rearrangements occur in 4-5% of AML.

- Menin is a scaffold nuclear protein, interacts with cell signaling and gene regulators, and drives leukemogenesis via its interaction with KMT2A (menin-KMT2A complex).



Kuhn M, Armstrong S. Cancer Cell 2015; 27(4):431-3, Thomas X. Oncol Ther 2024; 12: 57-72, Heikamp EB, Henrich JA, Perner F, et al. Blood 2022 139(6): 894-906, Issa GC et al. *Leukemia* (2021), 35:2482-2495.

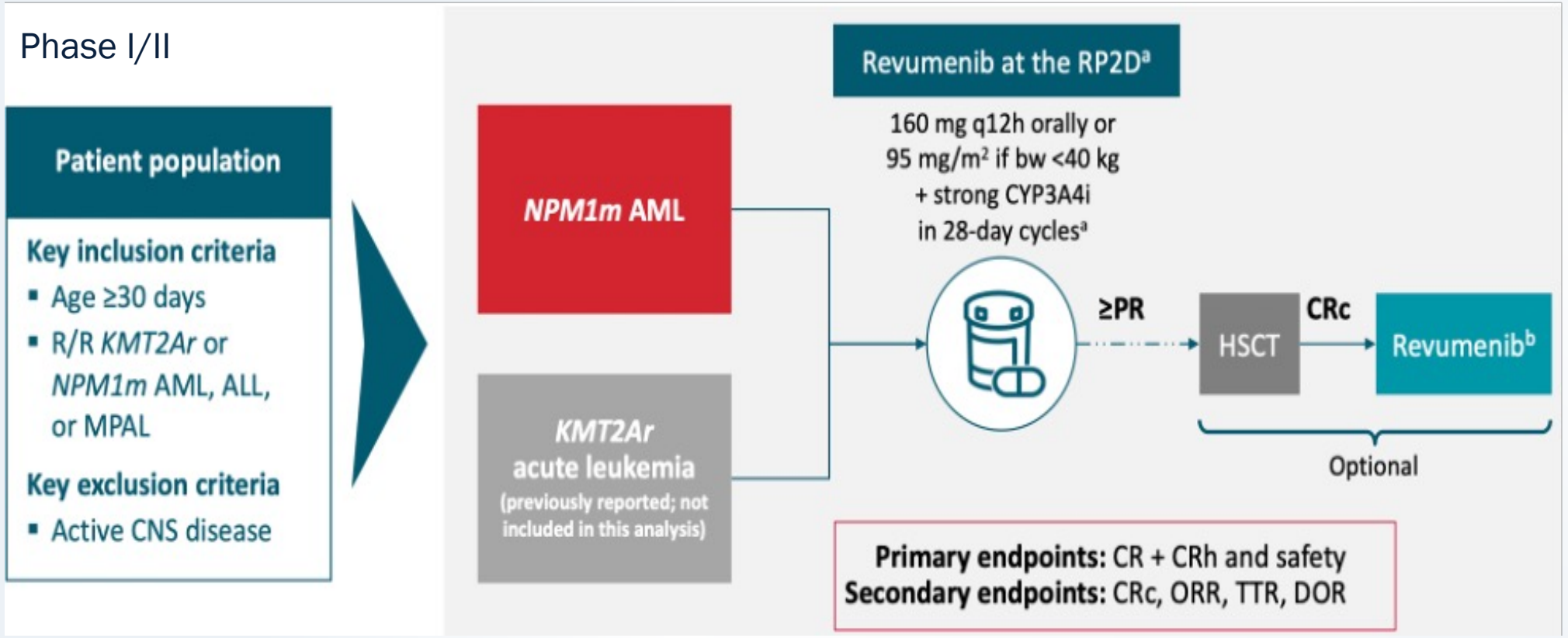
Menin Inhibitors in Clinical Development for Acute Leukemias with *KMT2Ar* or *NPM1* mut

Agent	For relapsed/refractory disease	For newly diagnosed disease
Revumenib * (SNDX-5613)	ALL/MPAL with *KMT2Ar,* AML with *KMT2Ar** or *NPM1m* Ph ½ monotherapy -Phase 1/2 with inqovi + venetoclax	-Phase 1/2 with azacitidine + venetoclax (BEAT AML) -Phase 1/2 with inqovi + venetoclax -Phase 1/2 with intensive chemo (7+3)
Ziftomenib (KO-539)	AML with *KMT2Ar,* AML with *NPM1m* Ph ½ monotherapy, combination with aza + ven, combination with FLT3 inhibitor	-Phase 1-2 combination with azacitidine + venetoclax -Phase 1 combination with 7+3 (fit) -Phase 3 combination with 7+3
Bleximenib (JNJ-75276617)	AML with *KMT2Ar* , AML with *NPM1m* Ph ½, monotherapy and combinations	-Phase 3 azacitidine + venetoclax with/without bleximenib -Phase 1 with 7+3 (fit), with Azacitidine + venetoclax (frail) -Phase 3 with 7+3 coming
Enzomenib (DSP-5336)	Ph1: R/R AML, ALL Ph2: AML or ALL with *KMT2Ar* or AML with *NPM1m*	
BN104	AML with *KMT2Ar,* AML with *NPM1m* AML with *NUP98r* Ph ½ monotherapy	-Phase 1/2 with 7+3 (fit), with azacitidine + venetoclax (frail)

* FDA approved for R/R acute leukemia with *KMT2A* translocation

Revumenib for R/R Acute Leukemia with *KMT2Ar* - AUGMENT-101

NCT04065399



- Revumenib 270 mg or 163 mg (95 mg/m^2 if < 40 kg) q12h with a strong CYP3A4 inhibitor po on 28-day cycles, until toxicity or no response after 4 cycles

Issa GC, Aldoss I, Thirman MJ, DiPersio J, Arellano M,... Stein EM. J Clin Oncol. 2025 Jan;43(1):75-84. doi: 10.1200/JCO.24.00826. Epub 2024 Aug 9. PMID: 39121437; PMCID: PMC11687943.

Revumenib for R/R Acute Leukemia with *KMT2Ar* - AUGMENT-101

Parameter	Efficacy population (n=57)	Safety population (N=94)
Median age, y (range)	34 (1.3-75)	37 (1.3-75)
Adult/Pediatric	44/13	71/23
Female/Male	33/24	56/38
ALL, n (%)	7 (12.3)	14 (14.9)
AML, n (%)	49 (86)	78 (83)
MPAL, n (%)	1 (1.8)	2 (2)
# prior lines of therapy, median (range)	2 (1-11)	2 (1-11)
Prior venetoclax, n (%)	41 (71.9)	61 (64.9)
Prior HSCT, n (%)	26 (45.6)	47 (50)

Issa GC, Aldoss I, Thirman MJ, DiPersio J, Arellano M,... Stein EM. J Clin Oncol. 2025 Jan;43(1):75-84. doi: 10.1200/JCO.24.00826. Epub 2024 Aug 9. PMID: 39121437; PMCID: PMC11687943.

Revumenib for R/R Acute Leukemia with *KMT2Ar* - AUGMENT-101

Safety	Safety population (n=94)
Any grade TRAE, n (%)	77 (81.9)
Any grade TRAE in ≥ 20% patients, n (%)	
Nausea	26 (27.7)
Differentiation syndrome	25 (26.6)
QTc prolongation	22 (23.4)
Grade ≥ 3 TRAE, n (%)	51 (54.3)
Febrile neutropenia	13 (13.8)
Differentiation syndrome	15 (16)
QTc prolongation	13 (13.8)
Cytopenias, n (%)	42 instances (44.7)
TRAE leading to discontinuation	6 (6.4)

Issa GC, Aldoss I, Thirman MJ, DiPersio J, Arellano M,... Stein EM. J Clin Oncol. 2025 Jan;43(1):75-84. doi: 10.1200/JCO.24.00826, Abdur Jamil, Zaheer Qureshi, Rimsha Siddique, et. Al. *Blood* 2024; 144 (Supp 1): 6065. doi: https://doi.org/10.1182/blood-2024-201875

Revumenib for R/R Acute Leukemia with *KMT2Ar* - AUGMENT-101

Response	Pooled efficacy (n=57)	AML efficacy (n=49)
ORR, n (%)	36 (63.2)	32 (65.3)
Best response, n (%)		
CR	10 (17.5)	9 (18.4)
CRh/CRi/CRp	3/1/11 (26.3)	3/1/9 (26.5)
CRc	25 (43.9)	22 (44.9)
MLFS	10 (17.5)	10 (20.4)
PR	1 (1.8)	12 (24.5)
MRD-negative CRc, n (%)	15/22 (68.2)	13/19 (68.4)

Summary:

- CR+CRh 22.8%, ORR 63.2% in a heavily pre-treated population.
- Fewer than 10% of treated patients discontinued due to a treatment-related adverse event.
- FDA approved on Nov 15, 2024 for pts. with R/R acute leukemia with *KMT2A* translocation.

Issa GC, Aldoss I, Thirman MJ, DiPersio J, Arellano M,... Stein EM. J Clin Oncol. 2025 Jan;43(1):75-84. doi: 10.1200/JCO.24.00826. Epub 2024 Aug 9. PMID: 39121437; PMCID: PMC11687943.

Phase 2 R/R *NPM1*m AML: Demographics and Baseline Characteristics

Parameter		Efficacy population (n=77)[a]	Safety population (N=84)[b]
Age	Median (range), y	63 (11-84)	63 (11-84)
	<18 y, n (%)	1 (1.3)	1 (1.2)
	≥18 to <65 y, n (%)	38 (49.4)	42 (50.0)
	≥65 y, n (%)	38 (49.4)	41 (48.8)
Sex, n (%)	Female	45 (58.4)	50 (59.5)
	Male	32 (41.6)	34 (40.5)
Race, n (%)	White	43 (55.8)	48 (57.1)
	Non-White	15 (19.5)	16 (19.0)
	Unknown[c]	19 (24.7)	20 (23.8)
Disease status at baseline, n (%)	Primary refractory	5 (6.5)	7 (8.3)
	Relapsed refractory	38 (49.4)	41 (48.8)
	Early untreated relapse[d]	22 (28.6)	23 (27.4)
	Late untreated relapse[e]	12 (15.6)	13 (15.5)

a. Patients who received ≥1 dose of revumenib, had centrally confirmed NPM1m AML, and ≥ 5% blasts in marrow at baseline within 28 days prior to start of study. b. All patients with NPM1m AML who received ≥1 dose of revumenib. c. Includes missing. D. Early untreated relapse defined as relapse <1 year from prior remission. E. Late untreated relapse defined as relapse ≥1 year from prior remission.

Phase 2 R/R NPM1m AML: Baseline Mutation Status and Treatment History

Parameter, n (%)		Efficacy population (n=77)[a]	Safety population (N=84)[b]
Co-occurring mutations[c]	*FLT3*-ITD	23 (29.9)	26 (31.0)
	FLT3-TKD	6 (7.8)	6 (7.1)
	RAS	3 (3.9)	3 (3.6)
	TP53	4 (5.2)	4 (4.8)
	IDH1	11 (14.3)	11 (13.1)
	IDH2	10 (13.0)	10 (11.9)
No. of lines of prior therapy	Median (range)	2 (1-7)	2 (1-7)
	≥3	27 (35.1)	29 (34.5)
	≥4	15 (19.5)	16 (19.0)
Previous therapies	Venetoclax	57 (74.0)	62 (73.8)
	HSCT	18 (23.4)	20 (23.8)
	>1 prior HSCT	6 (7.8)	8 (9.5)
	FLT3 inhibitor	31 (40.3)	32 (38.1)
	IDH1 inhibitor	5 (6.5)	5 (6.0)
	IDH2 inhibitor	5 (6.5)	5 (6.0)

a. All patients who received ≥1 dose of revumenib and had centrally confirmed NPM1m AML and ≥5% blasts in bone marrow at baseline within 28 days prior to start of study.
b. All patients with NPM1m AML who received ≥1 dose of revumenib. c. Co-mutation testing was conducted locally at the discretion of the investigator.
AML, acute myeloid leukemia; FLT3, fms related receptor tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; IDH, isocitrate dehydrogenase (NADP(+)); ITD, internal tandem duplication; NPM1m, nucleophosmin 1 mutated; TKD, tyrosine kinase domain; TP53, tumor protein p53.

Safety of Revumenib in R/R *NPM1*m AML

Overall incidence, n (%)	Safety population (N=84)[a] TEAEs	TRAEs
Any grade	83 (98.8)	66 (78.6)
Grade ≥3	77 (91.7)	50 (59.5)
Serious AE	64 (76.2)	31 (36.9)
AEs leading to:		
Dose reduction	10 (11.9)	10 (11.9)
Dose interruption	56 (66.7)	42 (50.0)
Treatment discontinuation	25 (29.8)	4 (4.8)[b]
Death	21 (25.0)	1 (1.2)[c]

Any-grade TEAEs in ≥20% of patients, n (%)	Safety population (N=84)[a]
QTc prolongation	36 (42.9)
Vomiting	31 (36.9)
Febrile neutropenia	29 (34.5)
Hypokalemia	27 (32.1)
Nausea	24 (28.6)
Anemia	23 (27.4)
Diarrhea	23 (27.4)
Fatigue	20 (23.8)
Pyrexia	20 (23.8)
Epistaxis	18 (21.4)
Peripheral edema	18 (21.4)

Grade ≥3 TEAEs in ≥10% of patients, n (%)	Safety population (N=84)[a]
Febrile neutropenia	28 (33.3)
Anemia	21 (25.0)
QTc prolongation	19 (22.6)
Decreased platelet count	14 (16.7)
Sepsis	13 (15.5)
Pneumonia	12 (14.3)
Thrombocytopenia	12 (14.3)
Differentiation syndrome	11 (13.1)
Decreased WBC count	10 (11.9)
Decreased neutrophil count	9 (10.7)

- In the safety population, discontinuation due to treatment-related AEs occurred in <5% of patients
- The safety profile was consistent with prior reports

b. Reasons for T) discontinuation: Cardiac arrest, differentiation syndrome, osteomyelitis, QTc prolonged + syncope (n=1 each).
c. Reason for TR death: Classified as cardiac arrest; investigator reported 2 possible causes of death: intracranial hemorrhage or arrhythmia (autopsy not performed).

TEAEs = treatment-emergent adverse events
TRAEs = treatment-related adverse events
AEs = adverse events
TR= treatment-related

Efficacy of Revumenib in R/R *NPM1*m AML

Parameter	Efficacy population (n=77)[a]
ORR, n (%) (at median 1.8 mos.)	37 (48.1)
CR + CRh rate, n (%) (at median 2.8 mos.)	20 (26.0)
95% CI	16.6-37.2
CRc rate, n (%)	25 (32.5)
95% CI	22.2-44.1
MRD-negative status, n/n (%)[b] (at median 2.8 mos.)	
CR + CRh[c]	12/19 (63.2)
CRc[d]	13/23 (56.5)

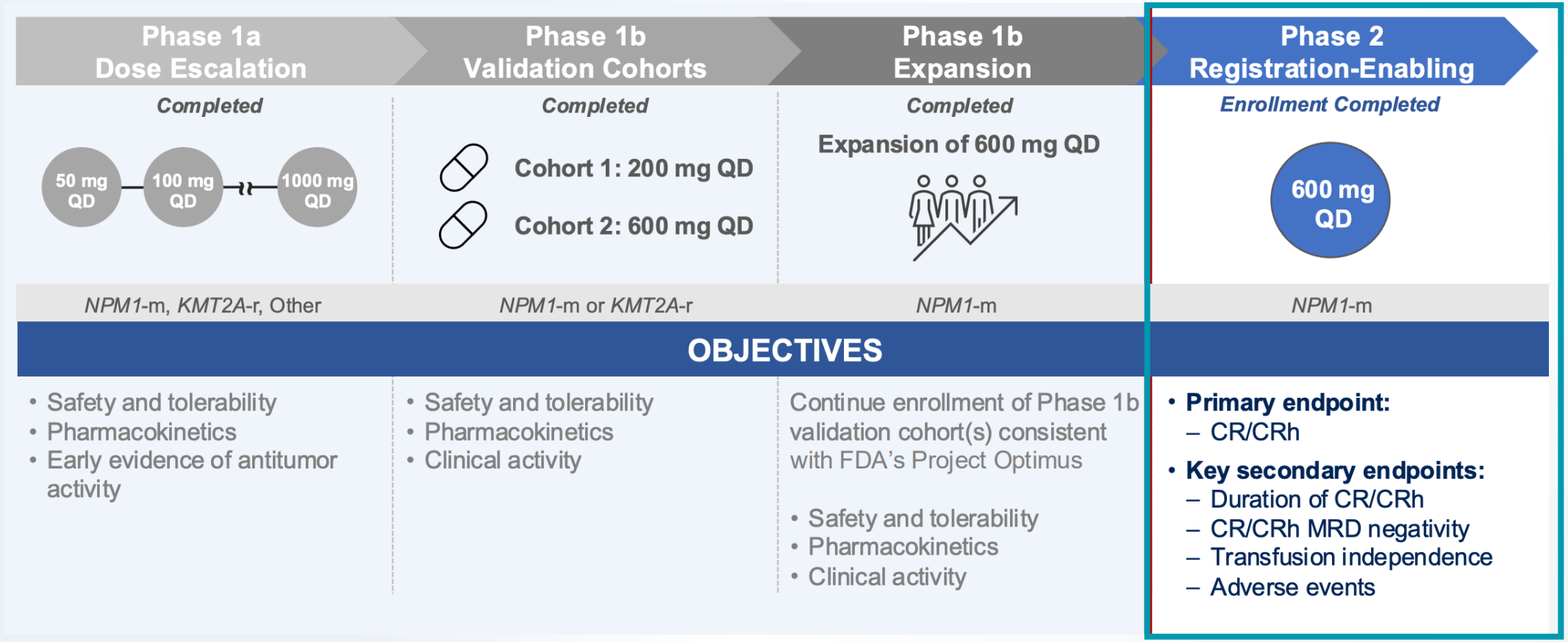
Best overall response, n (%)	Efficacy population (n=77)[a]
CR	16 (20.8)
CRh	4 (5.2)
CRi	2 (2.6)
CRp	3 (3.9)
MLFS	10 (13.0)
PR	2 (2.6)
PD	5 (6.5)
No response	22 (28.6)
Other[e]	13 (16.9)

- Median duration of CR/CRh, 4.7 mos. (95% CI, 2.1-8.2)
- Median overall survival (OS), 4.8 (95%CI,3.4-8.4) mos.; for CR + CRh responders, 23.3 (95%CI,7.2-not reached) mos.

Summary:

- CR+CRh 26% and ORR 48% in a heavily pre-treated population.
- Fewer than 5% of treated patients discontinued due to a treatment-related adverse event.
- PDUFA date: October 25, 2025

Ziftomenib in Patients with Relapsed/Refractory NPM1m, KMT2Ar AML



Wang et al. ASCO Abs #6506

Ziftomenib in Patients with Relapsed/Refractory NPM1m AML

n (%)	Ziftomenib RP2D 600 mg QD Phase 2 (N = 92)	Ziftomenib RP2D 600 mg QD Pooled Phase 1b/2 (N = 112)
Median age, yrs (range)	**69 (33–84)**	**69 (22–86)**
18–64 yrs	33 (36)	42 (38)
≥ 65 yrs	59 (64)	70 (63)
Female	49 (53)	63 (56)
Race		
White	75 (82)	88 (79)
Non-White	17 (18)	24 (21)
Region		
United States/Canada	45 (49)	57 (51)
Europe	47 (51)	55 (49)
ECOG PS		
0	27 (29)	30 (27)
1	49 (53)	63 (56)
2	16 (17)	19 (17)
Bone marrow aspirate blasts %, median (range)	39.5 (0.5–98)	44.0 (0.5–98)

n (%)	Ziftomenib RP2D 600 mg QD Phase 2 (N = 92)	Ziftomenib RP2D 600 mg QD Pooled Phase 1b/2 (N = 112)
Co-mutations, n/N[a]		
***FLT3*-ITD**	**38/84 (45)**	**43/102 (42)**
***FLT3*-TKD**	**9/84 (11)**	**11/102 (11)**
IDH1-m	10/80 (13)	13/97 (13)
IDH2-m	16/81 (20)	22/96 (23)
Median prior therapies (range)	**2 (1–7)**	**2 (1–7)**
1	32 (35)	37 (33)
2	30 (33)	37 (33)
≥ 3	30 (33)	38 (34)
Prior HSCT	22 (24)	26 (23)
Prior venetoclax	**54 (59)**	**67 (60)**
Prior menin inhibitor	1 (1)	1 (1)

[a]Among patients with available co-mutation data at baseline.

Wang ES, et al. Presented at ASCO 2025 [abstract #6506].

Ziftomenib in Patients with Relapsed/Refractory *NPM1*m AML

TRAEs in ≥ 5% of patients

	Ziftomenib RP2D 600 mg QD			
	Phase 2 (N = 92)		Pooled Phase 1b/2 (N = 112)	
Event, n (%)	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Any ziftomenib-related AE	64 (70)	37 (40)	77 (69)	45 (40)
Hematologic AEs				
Anemia	5 (5)	5 (5)	6 (5)	6 (5)
Neutropenia	6 (7)	6 (7)	6 (5)	6 (5)
Nonhematologic AEs				
Differentiation syndrome	**22 (24)**	**14 (15)[a]**	**26 (23)**	**15 (13)[a]**
Pruritus	15 (16)	0	16 (14)	0
Nausea	8 (9)	0	13 (12)	0
Diarrhea	8 (9)	0	10 (9)	2 (2)
Alanine aminotransferase increased	6 (7)	2 (2)	7 (6)	2 (2)
Decreased appetite	5 (5)	0	6 (5)	0

- [a] No Grade 4–5 differentiation syndrome
- Overall, QT prolongation seen in 3 patients, 2 on concomitant QT-prolonging medications and 1 had underlying arrhythmia.

Wang et al. ASCO Abs #6506

Ziftomenib in Patients with Relapsed/Refractory *NPM1*m AML

n (%)	Ziftomenib RP2D 600 mg QD Phase 2 (N = 92)	Ziftomenib RP2D 600 mg QD Pooled Phase 1b/2 (N = 112)
CR/CRh	**21 (23)**	**28 (25)**
Overall response	**30 (33)**	**39 (35)**
CR	13 (14)	20 (18)
CRh	8 (9)	8 (7)
CRi/CRp	3 (3)	4 (4)
MLFS	5 (5)	6 (5)
PR	1 (1)	1 (1)
Other[a]	62 (67)	73 (65)
Median duration of response, months (95% CI)		
CR/CRh	3.7 (1.9–NE)	3.7 (1.9–7.7)
CRc	4.6 (2.8–11.4)	5.1 (2.8–8.1)
ORR	4.6 (2.8–11.4)	4.6 (3.6–7.7)
Restricted mean duration of response[b], months (95% CI)		
CR/CRh	4.3 (3.1–5.6)	5.2 (3.6–6.7)
CRc	5.9 (4.0–7.7)	6.4 (4.6–8.1)
ORR	5.9 (4.4–7.5)	6.5 (4.9–8.1)
MRD negativity, n/N[c] (%)	**12/19 (63)**	**17/26 (65)**

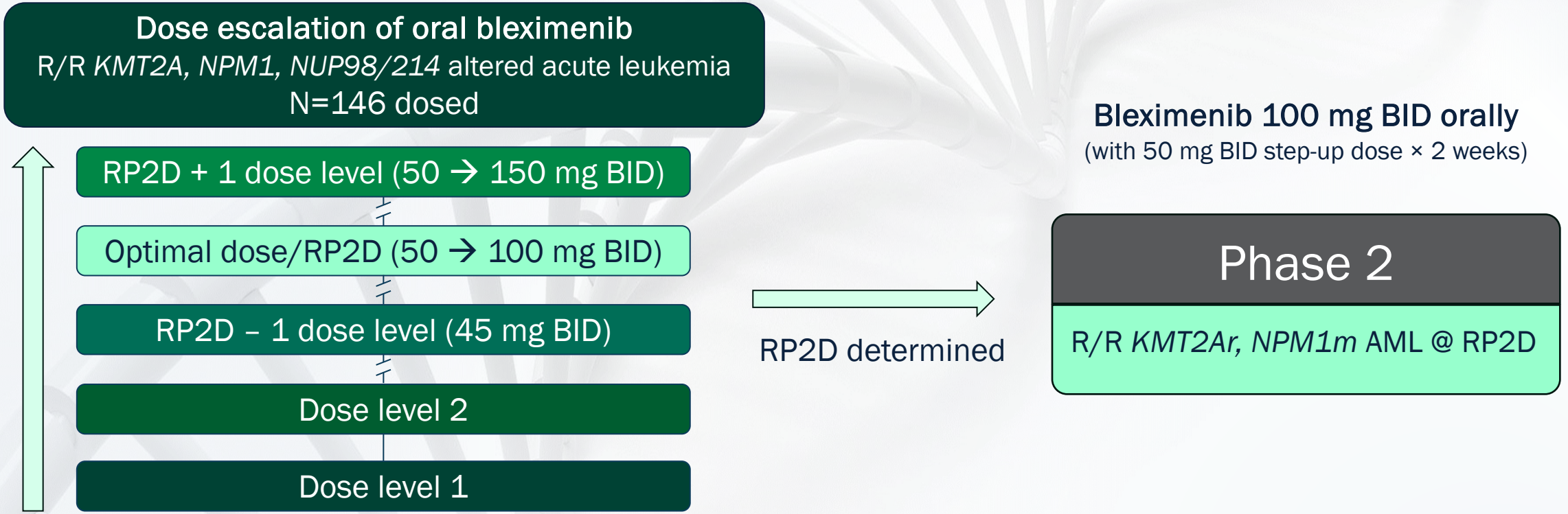
Summary:

- CR+CRh 23%, ORR 33% in a heavily pre-treated population.
- < 5% incidence of QT prolongation
- < 5% of treated patients discontinued due to a treatment-related adverse event.
- PDUFA date: November 30, 2025

- Median time to CR/CRh: 2.8 mos.(range 1-15)
- Median time to ORR: 1.9 mos. (range, 0.8-3.7)
- Median OS: 6.1 mos., 16.4 mos. for responders

Wang ES, et al. ASCO 2025 [abstract #6506].

Bleximenib in R/R Acute Leukemia with *KMT2Ar, NPM1m, NUP98r*



Emma Searle, *Blood* 2024; 144 (Supplement 1): 212.doi:https://doi.org/10.1182/blood-2024-207106

Bleximenib in R/R Acute Leukemia with *KMT2Ar, NPM1m, NUP98r:* Baseline demographics

Characteristic	Overall population (N=146)
R/R acute leukemia type, n (%)	
AML	132 (90.4)
ALL	7 (4.8)
Other acute leukemias	7 (4.8)
Age, median (range), years	60 (17–85)
Female, n (%)	80 (54.8)
Genetic alterations, n (%)	
KMT2A	83 (56.8)
NPM1	58 (39.7)
NUP98 or *NUP214*	5 (3.5)
Number of prior LOT, median (range)	2 (1–7)
≥1 prior HSCT, n (%)	36 (24.7)
ECOG PS, n (%)	
0	55 (37.7)
1	76 (52.1)
2	14 (9.6)

Bleximenib in R/R Acute Leukemia with *KMT2Ar, NPM1m, NUP98r:* Safety

Most Common TEAEs, in >15% Pts (All-dose; N=146)

TEAE, n (%)	All grade	Grade ≥3
Thrombocytopenia	53 (36.3)	46 (31.5)
Anemia	47 (32.2)	39 (26.7)
Nausea	44 (30.1)	1 (0.7)
Neutropenia	41 (28.1)	37 (25.3)
Constipation	32 (21.9)	1 (0.7)
Febrile neutropenia	28 (19.2)	27 (18.5)
Vomiting	28 (19.2)	2 (1.4)
Peripheral edema	26 (17.8)	0 (0)
ALT increased	25 (17.1)	4 (2.7)
Diarrhea	25 (17.1)	0 (0)

Related TEAEs at 90/100 mg BID, in ≥10% pts relative to 150 mg BID

	150 mg BID (n=33)		90/100 mg BID (n=31)	
TEAE, n (%)	All grade	Grade ≥3	All grade	Grade ≥3
Total	**28** (84.8)	**12** (36.4)	**17** (54.8)	**7** (22.6)
DS	**6** (18.2)	**3** (9.1)	**6** (19.4)	**2** (6.5)
Neutropenia	**6** (18.2)	**5** (15.2)	**1** (3.2)	**1** (3.2)
Thrombocytopenia	**4** (12.1)	**3** (9.1)	**3** (9.7)	**3** (9.7)
Nausea	**6** (18.2)	**0**	**4** (12.9)	**0**
Vomiting	**5** (15.2)	**1** (3.0)	**0** (0)	**0**
AST or ALT increased	**4**(12.1)	**0**	**1** (3.2)	**0**

- No QTc prolongation observed
- Median time to DS onset: 8 days

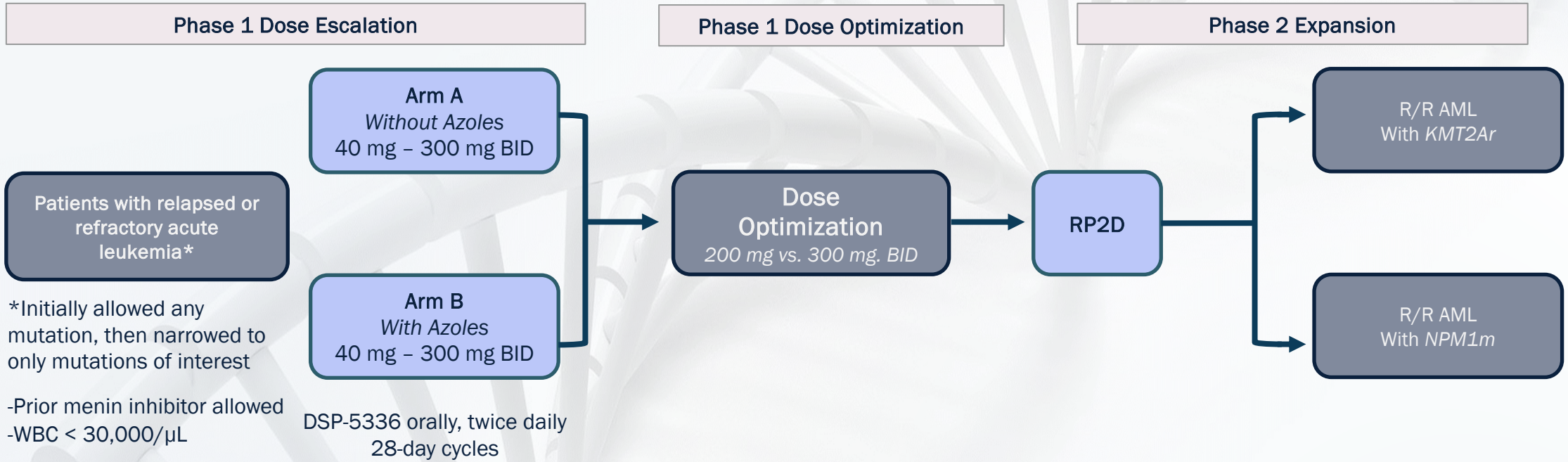
Bleximenib in R/R Acute Leukemia with *KMT2Ar, NPM1m, NUP98r:* Efficacy

Efficacy Parameter	Bleximenib 45 mg BID (n=11)	Bleximenib 90/100 mg BID (n=21)	Bleximenib 150 mg BID (n=20)
ORR (≥PR), n (%)	**4** (36.4)	**10** (47.6)	**11** (55.0)
Best response			
Composite CR (CR/CRh/Cri), n (%)	**2** (18.2)	**8** (38.1) (4/9 *KMT2Ar*, 4/12 *NPM1*m)	**8** (40.0)
CR/CRh, n (%)	**2** (18.2)	**7** (33.3) (3/9 *KMT2Ar*, 4/12 *NPM1*m)	**8** (40.0)
Median time to first response, months (range)	**1.5** (1.0-1.9)	**1.4** (0.9-4.7)	**1.0** (0.9-2.1)
Pts proceeded to allogeneic HCT (%)	**1** (9%)	**3** (14.3%)	**2** (10%)

Summary:

- Efficacy optimized at 100 mg BID, with 33% CR/CRh rate for bleximenib monotherapy in R/R AML
- Bleximenib monotherapy was well tolerated
- No QT prolongation

Enzomenib (DSP-5336) - 101 Study Design (global) NCT04988555



Primary objectives

- Phase 1: Assess safety, tolerability and determine RP2D
- Phase 2: Evaluate clinical activity, CR+CRh

J Zeidner et al. 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA.

Enzomenib 101: Baseline characteristics

	Overall (n=84)
Age (years)	
Median [range]	61.5 [20-89]
>= 65 years, n (%)	37 (44.0)
Sex, n (%)	
Female	48 (57.1)
Diagnosis, n (%)	
AML	79 (94.0)
ALL	3 (3.6)
MPAL	2 (2.4)
Race, n (%)	
Asian	27 (32.1)
White	44 (52.4)
Black or African American	8 (9.5)
Other or not reported	5 (6.0)
De novo/secondary, n (%)	
De novo	57 (67.9)
Therapy-related	14 (16.7)
MDS to AML	10 (11.9)
ELN2017 risk stratification by genetics, n (%)	
Favorable	14 (16.7)
Intermediate	22 (26.2)
Adverse	40 (47.6)

	Overall (n=84)
Patient genetics, n (%)	
KMT2Ar	**41 (48.8)**
w/FLT3-ITD	*1 (1.2)*
w/FLT3-TKD	*1 (1.2)*
NPM1m	**23 (27.4)**
w/FLT3-ITD	*8 (9.5)*
w/FLT3-TKD	*3 (3.6)*
Others	20 (23.8)
KMT2A rearrangement type, n (%)	
AF9 [t (9,11)]	10 (11.9)
AF6 [t (6,11)]	9 (10.7)
ELL [t (11,19) (q23, p13.1)]	6 (7.1)
AF4 [t (4,11)]	2 (2.4)
ENL [t (11,19) (q23, p13.3)]	2 (2.4)
AF10 [t (10,11)]	1 (1.2)
Other/not reported	11 (13.1)
Prior treatments	
Median prior regimens, # [range]	3.0 [1-9]
Prior transplant, n (%)	24 (28.6)
Prior venetoclax, n (%)	67 (79.8)
Bone marrow blast (%) at baseline	
Median [range]	59.5 (0.8 – 98.0)

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Enzomenib safety profile in R/R AML

Preferred Term	Total (N=84)	Gr >=3
Nausea	35 (41.7)	5 (6.0)
Vomiting	26 (31.0)	3 (3.6)
Sepsis	22 (26.2)	21 (25.0)
Diarrhea	21 (25.0)	1 (1.2)
Hypokalemia	21 (25.0)	5 (6.0)
Decreased appetite	20 (23.8)	4 (4.8)
Febrile neutropenia	20 (23.8)	20 (23.8)
Platelet count decreased	20 (23.8)	18 (21.4)
Headache	19 (22.6)	1 (1.2)
Hemorrhage	19 (22.6)	10 (11.9)
Dyspnea	17 (20.2)	4 (4.8)
Epistaxis	17 (20.2)	1 (1.2)
Pyrexia	17 (20.2)	2 (2.4)

Preferred Term	Total (N=84)	Gr >=3
Stomatitis	17 (20.2)	0 (0.0)
Pneumonia	15 (17.9)	14 (16.7)
Neutrophil count decreased	15 (17.9)	14 (16.7)
Alanine aminotransferase increased	14 (16.7)	1 (1.2)
Anemia	14 (16.7)	14 (16.7)
Arthralgia	14 (16.7)	2 (2.4)
Fatigue	14 (16.7)	1 (1.2)
Hypophosphatemia	14 (16.7)	1 (1.2)
Peripheral edema	14 (16.7)	0 (0.0)
Constipation	13 (15.5)	1 (1.2)
Cough	13 (15.5)	0 (0.0)

- No DLTs, treatment-related deaths, or discontinuations due to drug-related AEs
- Interruptions due to treatment-related AE in 16.7% (14/84) and dose reductions in 2.4% (2/84) subjects
- QTc prolongation: G3: 1% (1/84)
- Differentiation syndrome (DS): 10.7% (9/84), no mortality or permanent discontinuations due to DS

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Clinical activity of enzomenib in R/R AML

Clinical responses by ELN 2017	*KMT2Ar*			*NPM1m*		
	200 mg BID n = 8	300 mg BID n = 15	Total n = 23	200 mg BID n = 10	300 mg BID n = 7	Total n = 17
Objective Response Rate (CR + CRh + CRi + MLFS)	50% (4/8)	73.3% (11/15)	65.2% (15/23)	60% (6/10)	57.1% (4/7)	58.8% (10/17)
Composite CR (CR + CRh + CRi)	37.5% (3/8)	53.3% (8/15)	47.8% (11/23)	50% (5/10)	42.9% (3/7)	47.1% (8/17)
CR + CRh	12.5% (1/8)	40.0% (6/15)	30.4% (7/23)	50% (5/10)	42.9% (3/7)	47.1% (8/17)

(patients meeting CRh and CRi were counted as CRh)

Summary:

- Promising efficacy in *NPM1mut* and *KMT2Ar* cohorts
- Low incidence of QT prolongation (1%) and DS (10.7%)

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Menin Combinations with Efficacy Data

Drug/Study	Phase status	Pt. Population	Efficacy CRc (CR+CRh+CRi), MLFS	Key Toxicity	Ref.
Revumenib+Aza+Ven **(BEAT AML)**	1b	ND AML, N= 43 34 *NPM1*m 9 *KMT2Ar*	*NPM1*m: CRc 27 (79.4%), MLFS 2(5.9%) *KMT2Ar*: CRc 8 (88.9%), MLFS 1(11%)	G3 DS 2 (4.6%), G3 QT 5 (11.6%)	Zeidner, EHA 2025, HemaSphere 2025; 9(S1)
Ziftomenib+Aza+ven	1a	RR AML, N=34 14 *NPM1*m 20 *KMT2Ar*	*NPM1*m: CRc 7/11 (63.6%) *KMT2Ar*: CRc 3/13 (23%)	DS 12%	Fathi, ASH 2024 *Blood* (2024) 144 (Supplement 1): 2880.
Ziftomenib+7+3 (KOMET-007)	1a/1b	ND AML, N= 51 34 *NPM1*m 12 *KMT2Ar*	*NPM1*m: CRc 32 (94%), MLFS 1(3%) *KMT2Ar*: CRc 10 (83%)	33% ≥ G3 TRAE cytopenias, fever	Erba, EHA 2025, S136, HemaSphere 2025; 9(S1)
Bleximenib+Aza+Ven (ALE1002)	1b/2	RR (85), ND (40) AML	RR: CRc 42.5% (59.1% @RP2D) ND: CRc 72.1% (75% @RP2D)	cytopenias, fever, G3 DS 4%, G3 QT 0	Wei , EHA 2025; HemaSphere 2025; 9(S1)
• Pipeline	• Co-targeting with FLT3 inhibitors • All oral regimens • Maintenance • MRD eradication				

Summary

- Menin inhibitors are demonstrating efficacy as single-agents for patients with relapsed/refractory AML with KMT2A rearrangement or NPM1 mutations and in combinations for newly diagnosed patients.
- Revumenib, first menin inbitor FDA approved for patients with acute leukemia with *KMT2A* translocation
- On-target DS is seen across all menin inhibitors and QT prolongation with some, requiring high index of suspicion and prompt management
- Trials ongoing in combination with intensive chemotherapy, HMA, venetoclax, and co-targeting (FLT3) in the newly diagnosed and R/R AML

Q&A

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