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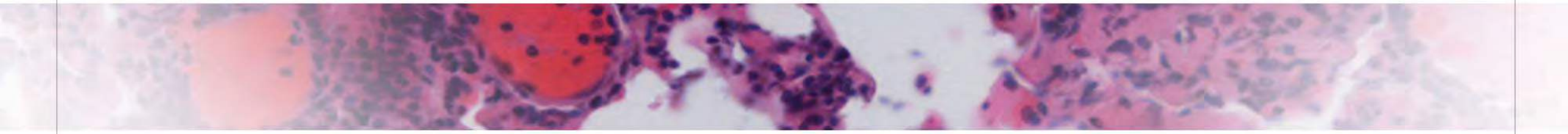

Ziftomenib in Combination with Venetoclax and Azacitidine in Relapsed/Refractory *NPM1*-m or *KMT2A*-r Acute Myeloid Leukemia: Updated Phase 1a/b Safety and Clinical Activity Results from KOMET-007

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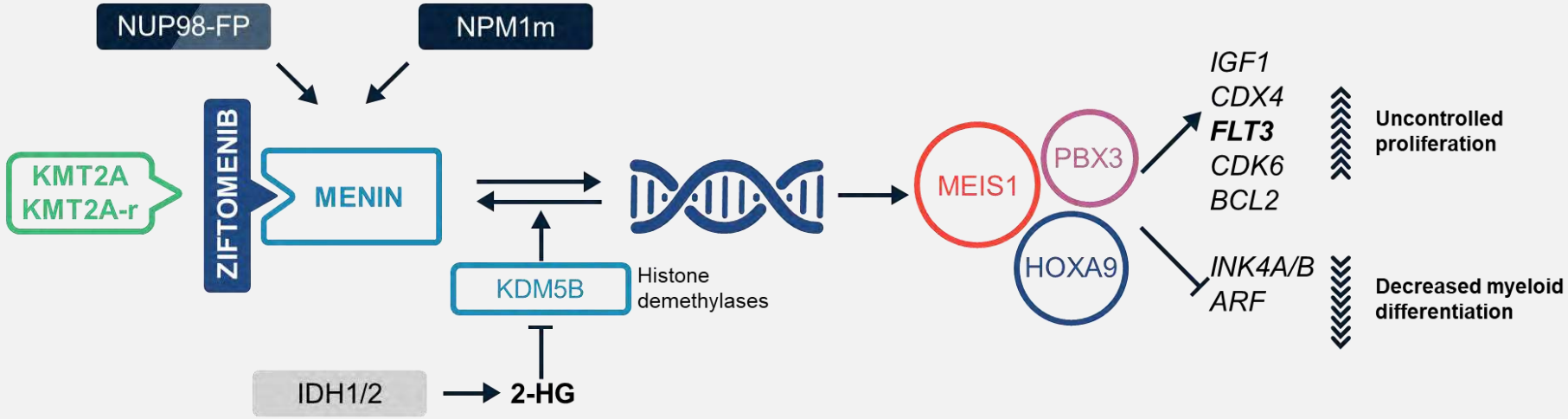
Ziftomenib Targets the Menin Pathway, a Foundational Target in AML

- Leukemogenesis is driven by *NPM1* mutations or *KMT2A* rearrangements in ~35–40% of AML cases[1,2]
- Nearly half of AML patients will develop relapsed/refractory (R/R) disease within a year, with a <20% expected response rate following venetoclax/azacitidine (Ven/Aza) and progressively poorer outcomes with each subsequent line of therapy[3–6]
- **Ziftomenib** is a potent, highly selective, oral menin inhibitor with clinical activity as both monotherapy and in combination for adults with R/R *NPM1*-m or *KMT2A*-r AML[7,8]
- Ziftomenib monotherapy was approved for R/R *NPM1*-m AML by the US FDA on November 13, 2025

Ziftomenib Mechanism of Action[9–18]

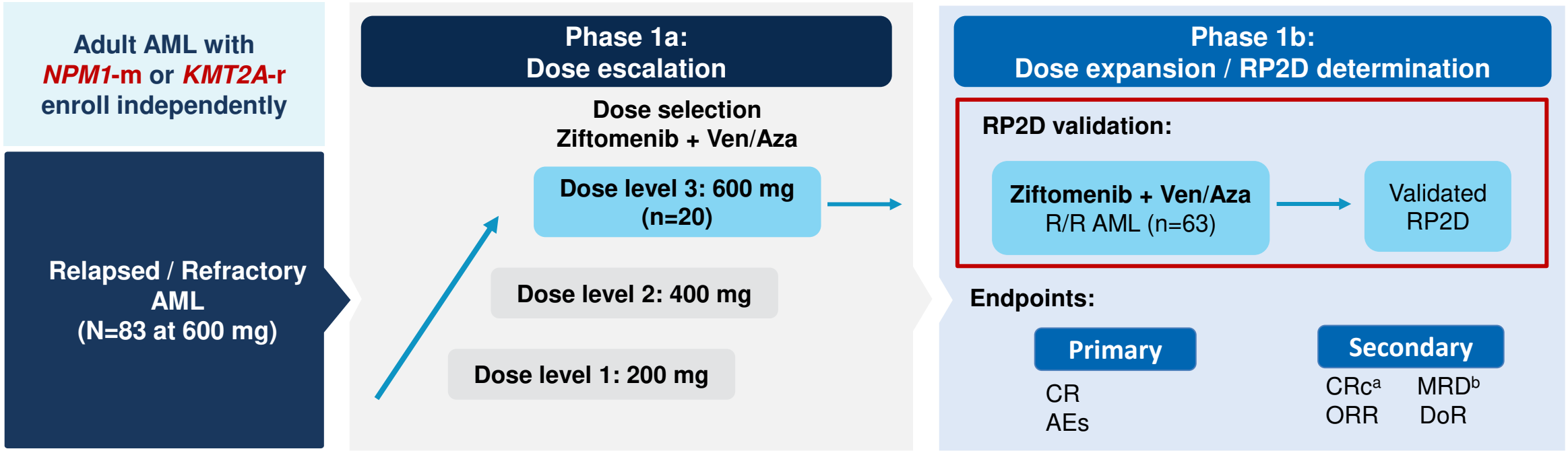


1. Papaemmanuil E et al. *N Engl J Med.* 2016;374(23):2209–21. **2.** Issa GC et al. *Leukemia.* 2021;35:2482–95. **3.** Koschade SE et al. *Ann Hematol.* 2022;101(8):1703–10. **4.** Zainaldin C et al. *Leuk Lymphoma.* 2022;63(13):3245–8. **5.** Bewersdorf JP et al. *Leuk Res.* 2022;122:106942. **6.** Issa GC et al. *Blood Adv.* 2023;28:7(6):933–42. **7.** Wang ES et al. *Lancet Oncol.* 2024;25(10):1310–24. **8.** Fathi AT et al. *Blood.* 2024;144(Suppl_1):2880. **9.** Collins CT, Hess JL. *Curr Opin Hematol.* 2016;23(4)354–61. **10.** Lu R et al. *Cancer Cell.* 2016;30(1):92–107. **11.** Ferreira HJ et al. *Oncogene.* 2016;35(23):3079-82. **12.** Jeong M et al. *Nat Genet.* 2014;46(1):17-23. **13.** Wang GG et al. *Blood.* 2005;106(1):254–64. **14.** Chowdhury R et al. *EMBO Rep.* 2011;12(5):463–9. **15.** Schmidt L et al. *Leukemia.* 2019;33(7):1608–19. **16.** Xu H et al. *Cancer Cell.* 2016;30(6):863-78. **17.** Brunetti L et al. *Cancer Cell.* 2018;34(3):499–512. **18.** Wang XQD et al. *Cancer Discov.* 2023;13(3):724–45

AML, acute myeloid leukemia, US FDA, U.S. Food and Drug Administration

KOMET-007: Ongoing Phase 1 Combination Trial of Ziftomenib in R/R AML

Ziftomenib + Ven/Aza Combination (NCT05735184)

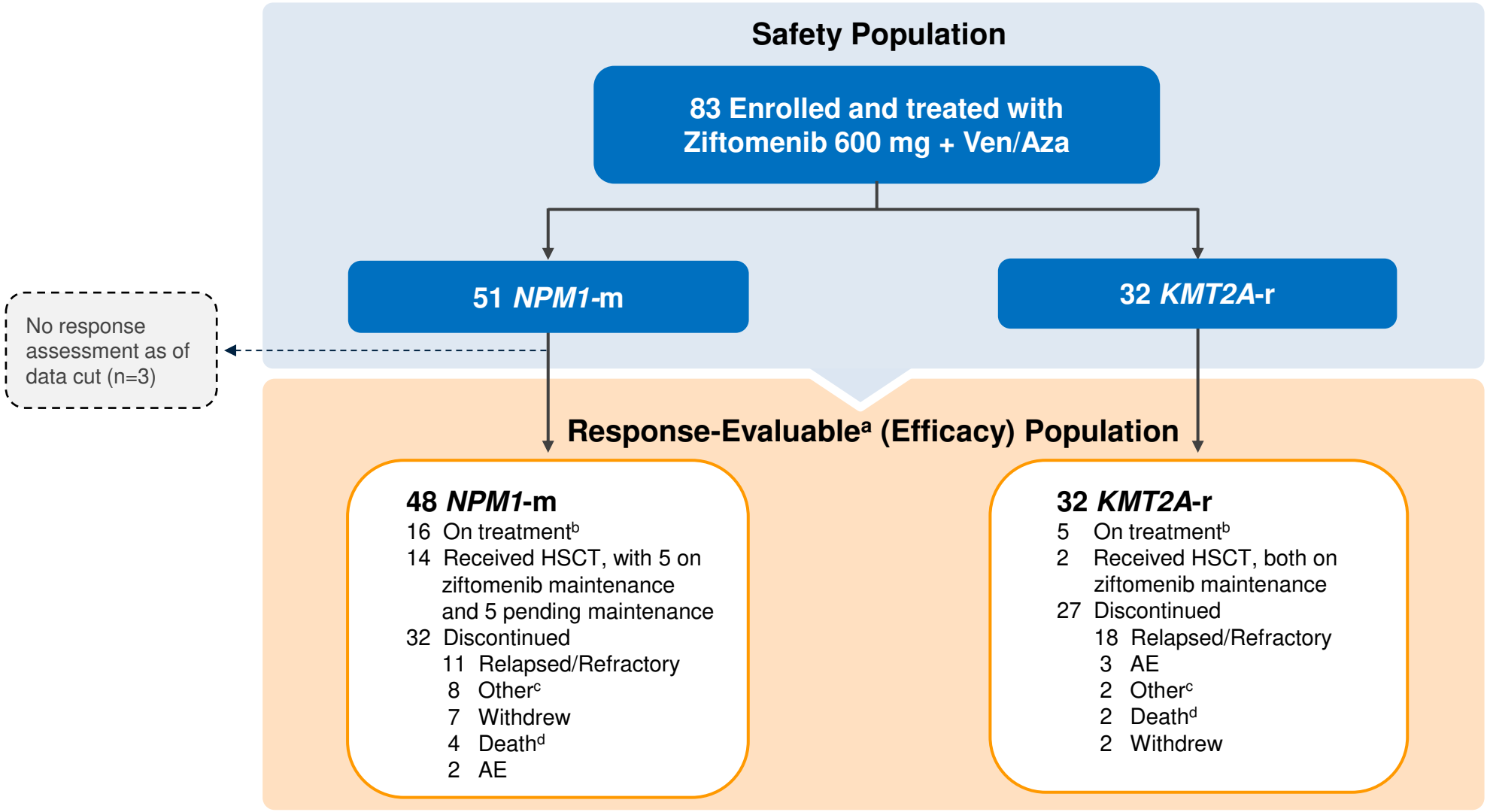


- Ziftomenib dosing started on Cycle 1 Day 8 and was administered continuously thereafter; Ven was administered per label in 28-day cycles; adjustments to cycle length based on Cycle 1 bone marrow biopsy results. Aza was administered on Cycle 1 Days 1–7; additional cycles based on bone marrow biopsy results
- **Here, we present updated safety and clinical activity in 83 patients with R/R AML treated with ziftomenib 600 mg once daily in combination with Ven/Aza**

[a]CR with full, partial, or incomplete hematologic recovery. [b]Locally assessed by next-generation sequencing, RT-qPCR, and multiparameter flow cytometry

AE, adverse event; CR, complete remission; CRc, composite complete remission; DoR, duration of response; MRD, measurable residual disease; ORR, overall response rate; RP2D, recommended phase 2 dose

KOMET-007: Safety and Efficacy Populations: R/R AML



[a]Patients who had ≥1 response assessment or who had died. [b]Patients who had not discontinued ziftomenib as of the data cutoff date. [c]Other reasons included: *NPM1*-m: physician decision (n=2), completed planned therapy (n=1), CNS disease (n=1), patient started another clinical trial (n=1), patient decision (n=3); *KMT2A*-r: patient deemed too ill to continue (n=1), physician decision (n=1). [d]Deaths included: *NPM1*-m: graft-vs-host disease (n=1), multiorgan failure (n=1), sepsis (n=1), respiratory failure (n=1); *KMT2A*-r: cardiac arrest (n=1), septic shock (n=1)

Data cutoff: Sep 24, 2025. CNS, central nervous system; HSCT, hematopoietic stem cell transplant

Baseline Characteristics and Disposition: R/R AML

n (%)	*NPM1*-m, 600 mg (N=51)	*KMT2A*-r, 600 mg (N=32)	All Patients, 600 mg (N=83)
Median age, years (range)	65 (25–85)	56 (19–76)	62 (19–85)
Female	23 (45)	17 (53)	40 (48)
Race			
White	37 (73)	22 (69)	59 (71)
Black / African American	5 (10)	2 (6)	7 (8)
Other / Non-White / Unknown	9 (18)	8 (25)	17 (20)
ECOG PS			
0	13 (26)	7 (22)	20 (24)
1	24 (47)	18 (56)	42 (51)
2	14 (28)	7 (22)	21 (25)
Selected co-mutations			
FLT3	21 (41)	3 (9)	24 (29)
IDH1/2	7 (14)	0	7 (8)
Both *FLT3* and *IDH1/2*	2 (2)	0	2 (2)
Median prior therapies (range)	1 (1–4)	1 (1–4)	1 (1–4)
Prior HSCT	10 (20)	6 (19)	16 (19)
Prior venetoclax	26 (51)	22 (69)	48 (58)
Prior menin inhibitors	1 (2)	7 (22)	8 (10)
Patients on treatment	16 (31)	5 (16)	21 (25)
Median follow-up, weeks (range)	26.3 (3.3–69.1)	16.9 (2.4–65.4)	24.6 (2.4–69.1)

Data cutoff: Sep 24, 2025. ECOG PS, Eastern Cooperative Oncology Group performance status

Safety and Tolerability of Ziftomenib with Ven/Aza: R/R AML

TEAEs in ≥25% of All Patients

n (%)	All TEAEs			Ziftomenib-Related TEAEs
	NPM1-m, 600 mg (N=51)	*KMT2A*-r, 600 mg (N=32)	All Patients, 600 mg (N=83)	All Patients, 600 mg (N=83)
Any grade	**49 (96)**	**32 (100)**	**81 (98)**	**48 (58)**
Nausea	19 (37)	15 (47)	34 (41)	13 (16)
Fatigue	25 (49)	6 (19)	31 (37)	12 (15)
Thrombocytopenia[a]	16 (31)	14 (44)	30 (36)	8 (10)
Febrile neutropenia	14 (28)	13 (41)	27 (33)	8 (10)
Diarrhea	17(33)	9 (28)	26 (31)	3 (4)
Leukopenia[b]	18 (35)	8 (25)	26 (31)	7 (8)
Neutropenia[c]	14 (28)	12 (38)	26 (31)	8 (10)
Vomiting	14 (28)	11 (34)	25 (30)	9 (11)
Anemia	11 (22)	13 (41)	24 (29)	8 (10)
Constipation	16 (31)	7 (22)	23 (28)	4 (5)
Pruritus	17 (33)	6 (19)	23 (28)	12 (15)
Decreased appetite	14 (28)	7 (22)	21 (25)	6 (7)
Hypokalemia	10 (20)	11 (34)	21 (25)	0

[a]Includes platelet count decreased and thrombocytopenia. [b]Includes white blood cell count decreased and leukopenia. [c]Includes neutrophil count decreased and neutropenia

Data cutoff: Sep 24, 2025. TEAE, treatment-emergent adverse event

Safety and Tolerability of Ziftomenib with Ven/Aza: R/R AML

Grade ≥3 TEAEs in ≥10% of All Patients

n (%)	All Grade ≥3 TEAEs			Grade ≥3 Ziftomenib-Related TEAEs
	NPM1-m, 600 mg (N=51)	*KMT2A*-r, 600 mg (N=32)	All Patients, 600 mg (N=83)	All Patients, 600 mg (N=83)
Grade ≥3	**46 (90)**	**30 (94)**	**76 (92)**	**33 (40)**
Thrombocytopenia[a]	15 (29)	13 (41)	28 (34)	7 (8)
Febrile neutropenia	14 (28)	12 (38)	26 (31)	8 (10)
Leukopenia[b]	18 (35)	8 (25)	26 (31)	7 (8)
Neutropenia[c]	14 (27)	12 (38)	26 (31)	8 (10)
Anemia	8 (16)	9 (28)	17 (21)	6 (7)
Sepsis	6 (12)	6 (19)	12 (15)	4 (5)

Ziftomenib-Related AEs of Interest

- No ziftomenib-related QTc prolongation was reported with the combination
- 2 (2%) patients discontinued due to ziftomenib-related AEs (both *KMT2A*-r*;* grade 4 sepsis and grade 3 stomatitis)
- 1 (1%) differentiation syndrome (*NPM1*-m, grade 3) successfully resolved with protocol-specified mitigation and patient resumed ziftomenib

[a]Includes platelet count decreased and thrombocytopenia. [b]Includes white blood cell count decreased and leukopenia. [c]Includes neutrophil count decreased and neutropenia
Data cutoff: Sep 24, 2025. QTc, corrected QT interval

Clinical Activity[a] of Ziftomenib with Ven/Aza: R/R AML

n (%)	*NPM1*-m, 600 mg (N=48)	*KMT2A*-r, 600 mg (N=32)
CRc	23 (48)	9 (28)
Median time to first CRc, weeks (range)	3.9 (2.7–15.6)	4.0 (2.6–18.9)
ORR	31 (65)	13 (41)
CR	13 (27)	2 (6)
CRh	6 (13)	5 (16)
CRi	4 (8)	2 (6)
MLFS	7 (15)	4 (13)
PR	1 (2)	0
NR	13 (27)	17 (53)
NE[b]	4 (8)	2 (6)
MRD negativity rate[c], n/N (%)	12/20 (60)	3/7 (43)
Median time to first MRD negativity, weeks (range)	8.8 (2.9–21.4)	8.1 (7.7–18.9)

- For *NPM1*-m, CR/CRh rates were 46% (13/28), 42% (5/12), and 14% (1/7) for patients with 1, 2, and ≥3 prior lines of therapy, respectively

[a]In patients with ≥1 response assessment or had died. [b]Not evaluable (1 *NPM1*-m) or not done (3 *NPM1*-m, 2 *KMT2A*-r). [c]Locally assessed among CRc responders (NGS, RT-qPCR, FISH, flow cytometry)
Data cutoff: Sep 24, 2025. CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NR, no response; ORR, objective response rate; PR, partial response

Clinical Activity[a] by Prior Venetoclax

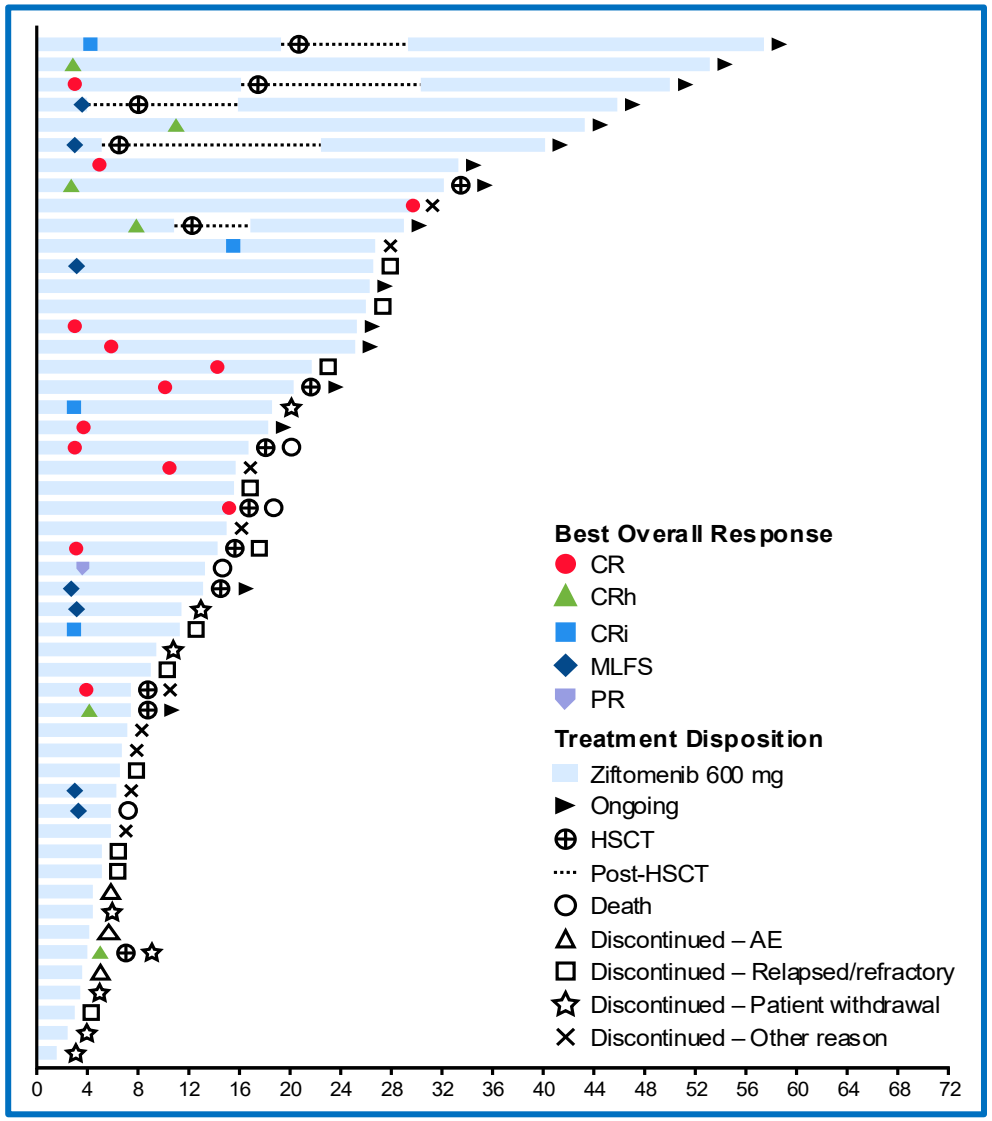
n (%)	No Prior Ven		Prior Ven	
	NPM1-m, 600 mg (N=23)	*KMT2A*-r, 600 mg (N=10)	*NPM1*-m, 600 mg (N=25)	*KMT2A*-r, 600 mg (N=22)
CRc	16 (70)	6 (60)	7 (28)	3 (14)
Median time to first CRc, weeks (range)	3.8 (2.7–15.6)	3.4 (2.6–15.1)	4.3 (2.9–14.3)	9.3 (7.7–18.9)
ORR	19 (83)	7 (70)	12 (48)	6 (27)
CR	10 (44)	2 (20)	3 (12)	0
CRh	4 (17)	3 (30)	2 (8)	2 (9)
CRi	2 (9)	1 (10)	2 (8)	1 (5)
MLFS	3 (13)	1 (10)	4 (16)	3 (14)
PR	0	0	1 (4)	0
NR	4 (17)	3 (30)	9 (36)	14 (64)
NE	0	0	4 (16)	2 (9)
MRD negativity rate[b], n/N (%)	7/13 (54)	1/4 (25)	5/7 (71)	2/3 (67)
Time to first MRD negativity, median (range), weeks	11.7 (3.1–16.6)	8.1 (8.1–8.1)	3.0 (2.9–21.4)	13.3 (7.7–18.9)

[a]In patients with ≥1 response assessment or had died. [b]Locally assessed among CRc responders

Data cutoff: Sep 24, 2025. CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NR, no response; ORR, objective response rate; PR, partial response

Duration of Treatment and Clinical Outcomes: R/R AML

NPM1-m



For *NPM1*-m, after a median follow-up of 27.4 weeks (range 3.3–69.1):

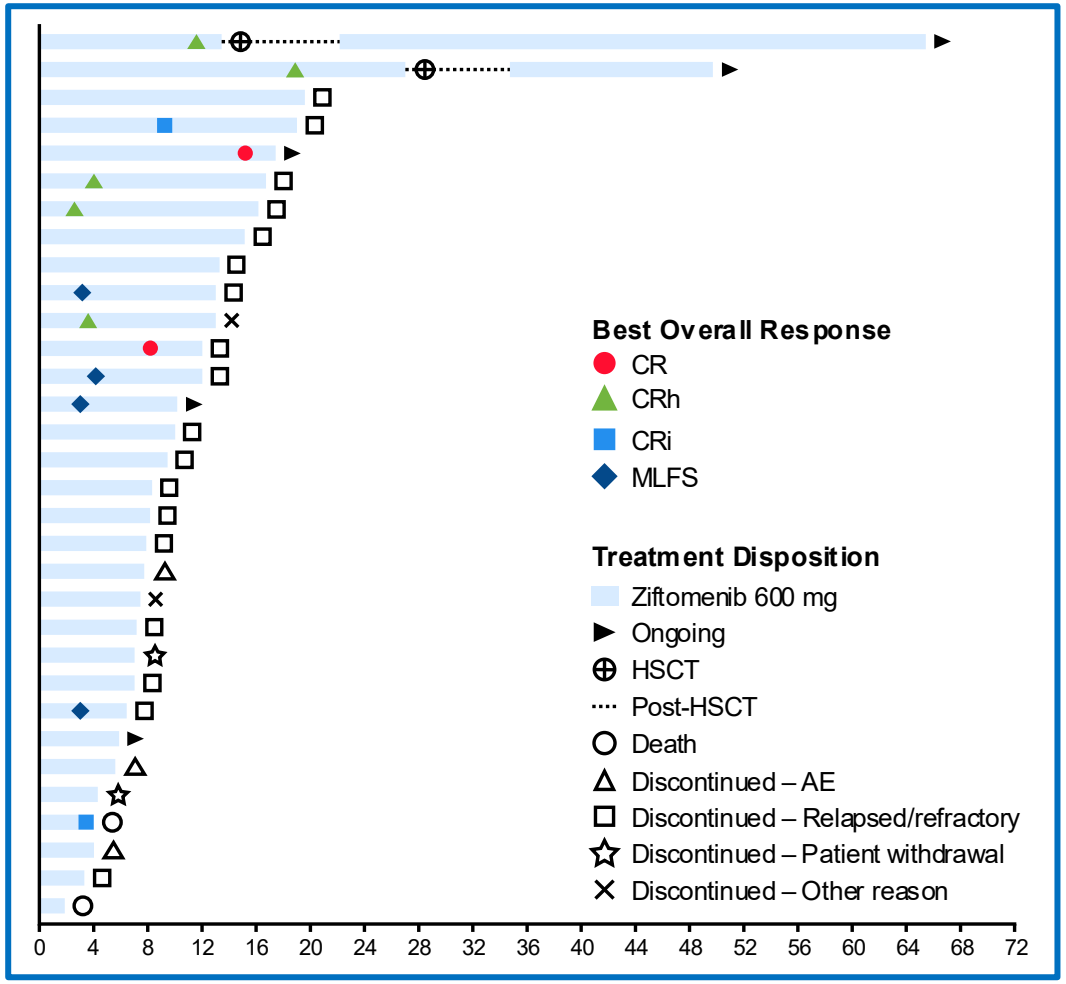
- Median duration of CRc was **39.9 weeks** (95% CI 16.1–NE)
  - Ven-naïve: 39.9 weeks (95% CI 12.9–NE)
- 14 *NPM1*-m patients received HSCT, and 5 went onto ziftomenib maintenance
- Median OS was **54.9 weeks** (95% CI 32.0–NE)

Data cutoff: Sep 24, 2025.

CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission
MLFS, morphologic leukemia-free state; HSCT, hematopoietic stem cell transplant; OS, overall survival; PR, partial response

Duration of Treatment and Clinical Outcomes: R/R AML

KMT2A-r



For *KMT2A*-r, after a median follow-up of 16.9 weeks (range 2.4–65.4):

- Median duration of CRc was **12.4 weeks** (95% CI 0.9–NE)
  - Ven-naïve: 10.0 weeks (95% CI 0.9–NE)
- 2 *KMT2A*-r patients received HSCT, and both went onto ziftomenib maintenance
- Median OS was **21.1 weeks** (95% CI 12.4–64.9)

Data cutoff: Sep 24, 2025.

CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission
MLFS, morphologic leukemia-free state; HSCT, hematopoietic stem cell transplant; OS, overall survival; PR, partial response

ANC and Platelet Recovery in CRc Responders: R/R AML

Median (range)	All Patients, 600 mg (N=32)[a]
Days to ANC recovery ≥0.5 × 10^9/L	36 (0–136)
Days to ANC recovery ≥1.0 × 10^9/L	45 (34–145)
Days to platelet count recovery ≥50 × 10^9/L	27 (0–139)
Days to platelet count recovery ≥100 × 10^9/L	28 (0–243)

- Times to neutrophil and platelet count recovery were comparable to those for Ven/Aza alone[1]

[a]Subset of patients who reached cutoff

1. Aldoss et al. *Haematologica*. 2018;103(9):e404–7.

Data cutoff: Sep 24, 2025. ANC, absolute neutrophil count

Conclusions

- **In the ongoing KOMET-007 study, ziftomenib 600 mg once daily in combination with Ven/Aza was well tolerated in R/R *NPM1*-m or *KMT2A*-r AML**
  - Low rates of ziftomenib-related myelosuppression
  - No ziftomenib-related QTc prolongation was reported
  - One case of differentiation syndrome (*NPM1*-m, grade 3) successfully resolved with protocol-specified mitigation, and patient resumed ziftomenib
- **Encouraging clinical activity was demonstrated in patients with R/R *NPM1*-m or *KMT2A*-r AML, including in patients with prior venetoclax exposure**
  - *NPM1*-m: 65% ORR and 48% CRc, with a median DoR of 39.9 weeks
    - Ven-naïve: 83% ORR and 70% CRc; Ven-exposed: 48% ORR and 28% CRc
  - *KMT2A*-r: 41% ORR and 28% CRc, with a median DoR of 12.4 weeks
    - Ven-naïve: 70% ORR and 60% CRc
- **Taken together, these data support further investigation of ziftomenib-based combinations in R/R *NPM1*-m and *KMT2A*-r AML**

Acknowledgments

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