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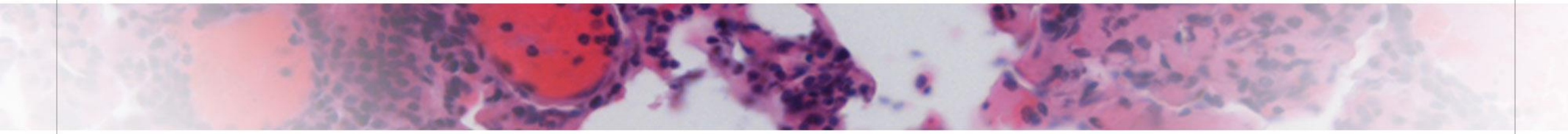

Ziftomenib Combined with Intensive Induction (7+3) in Newly Diagnosed *NPM1*-m or *KMT2A*-r Acute Myeloid Leukemia: Interim Phase 1a Results from KOMET-007

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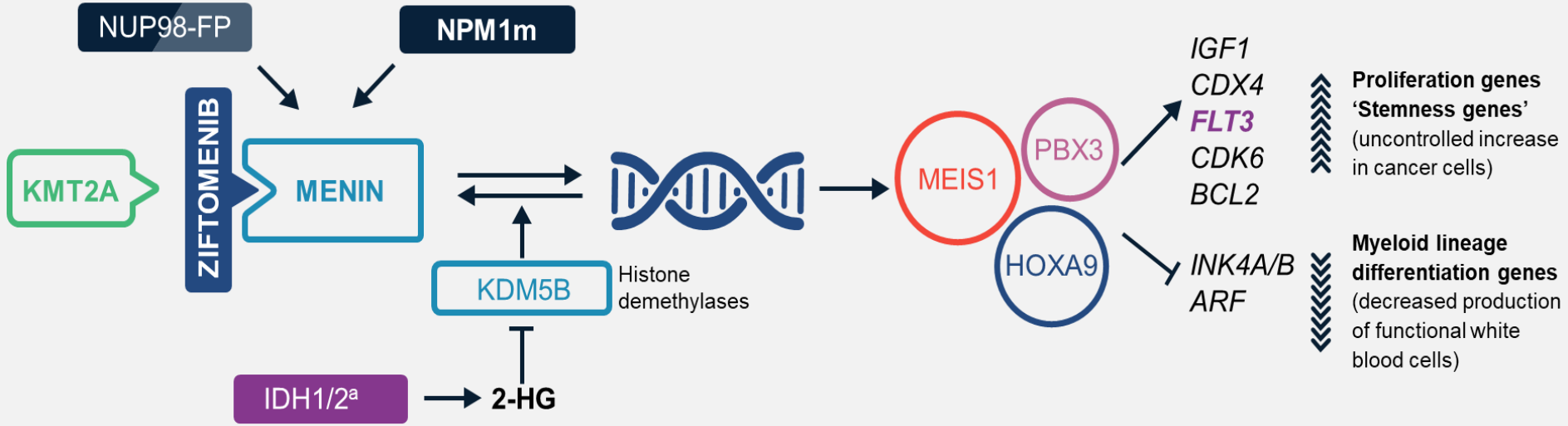
#214

Ziftomenib Targets the Menin Pathway, a Foundational Target in AML

- In ~35–40% of AML, leukemogenesis is driven by either *NPM1* mutations or *KMT2A* rearrangements,[1,2] which are upstream regulators of key genes critical for AML (eg, *HOXA9*/*MEIS1*)[3]
- KMT2A (MLL) and NPM1 sit upstream from major AML targets (ie, FLT3, BCL2 and IDH1/2)[4]
- Inhibiting the menin-KMT2A complex downregulates *HOXA9*/*MEIS1*, leading to differentiation of leukemic blasts[5]
- Ziftomenib – a potent, highly selective, oral, investigative menin inhibitor – has shown clinical activity (35% complete response [CR]/CR with partial hematologic recovery [CRh]) as monotherapy in adults with relapsed/refractory *NPM1*-m AML[6]

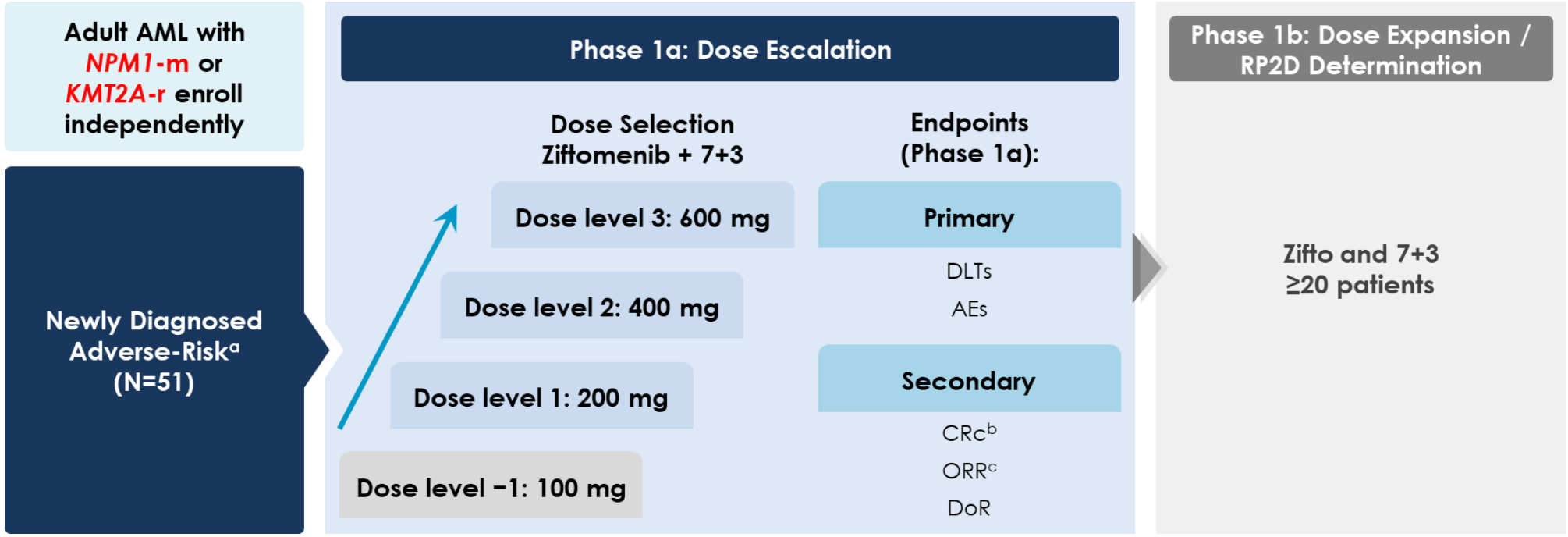
Ziftomenib Mechanism of Action[3, 7-14]



[a]Mutations in AML are loss of function. 1. Papaemmanuil et al. *N Engl J Med* 2016;375: 900-1; 2. Issa GC et al. *Leukemia* 2021;3:2482-95; 3. Collins and Hess. *Curr Opin Hematol* 2016;23(4)354-61; 4. Matthews AH et al. *Cancers* (Basel) 2022 Nov 29;14(23):5906. 5. Thomas. *Oncol Ther* 2024;12(1):57-72; 6. Wang ES et al. *Lancet Oncol* 2024;25(10):1310-24; 7. Lu et al. *Cancer Cell* 2016;30(1):92–107; 8. Ferreira et al. *Oncogene* 2016;35(23):3079-82; 9. Jeong et al. *Nat Genet* 2014;46(1):17-23; 10. Wang et al. *Blood* 2005;106(1):254–64; 11. Chowdhury et al. *EMBO Rep* 2011;12(5):463-9; 12. Schmidt et al. *Leukemia* 2019;33(7):1608-19; 13. Xu et al. *Cancer Cell* 2016;30(6):863-78; 14. Brunetti et al. *Cancer Cell* 2018;34(3):499–512.

KOMET-007: Ongoing Phase 1 Combination Trial of Ziftomenib in Patients with Newly Diagnosed Adverse-Risk[a] AML

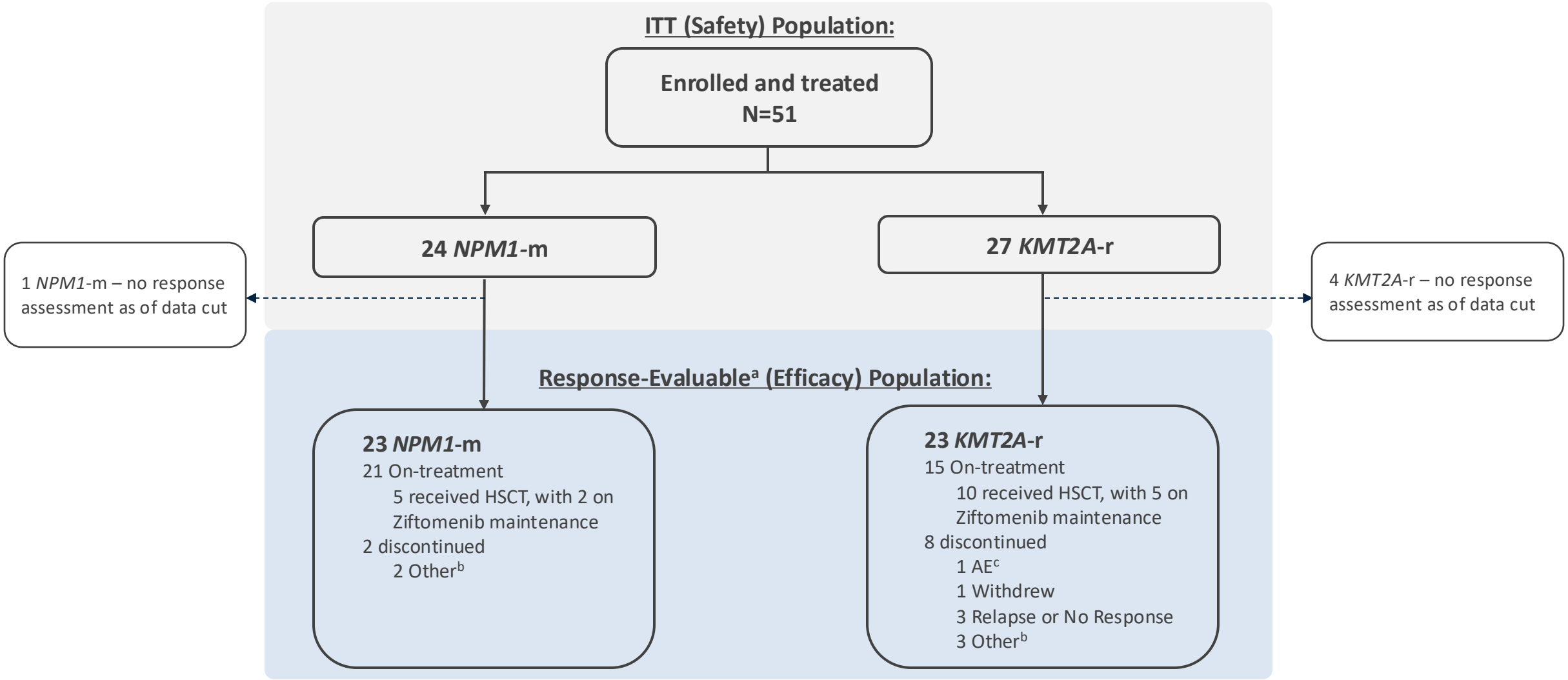
Ziftomenib / 7+3 combination (NCT05735184)



- Ziftomenib started on Cycle 1 Day 8 and administered continuously thereafter. Cytarabine administered on Cycle 1 Days 1–7; daunorubicin on Cycle 1 Days 1–3; re-induction cycles allowed based on bone marrow biopsy results
- Here, we present data from the dose escalation (Phase 1a) in patients with Adverse-Risk[a] AML (data cutoff: Oct 1, 2024)
- Dose expansion (Phase 1b) is ongoing and includes all newly diagnosed *NPM1*-m and *KMT2A*-r AML patients, with or without adverse-risk

[a]Adverse-risk *NPM1*-m AML defined as having high-risk cytogenetics per ELN criteria, age ≥60 yrs and/or treatment-related *NPM1*-m/*KMT2A*-r AML regardless of age. [b]CR, CRh, or CRi. [c]CRc or MLFS.
AE, adverse event; CRc, composite complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; DLT, dose limiting toxicity; DoR, duration of response; MLFS, morphologic leukemia-free state; RP2D, recommended phase 2 dose.

KOMET-007 Phase 1a in 1L AML: Safety and Efficacy Populations



[a]Patients who have ≥1 response assessment or who had died. [b]Other reasons included: *NPM1*-m: Pursuit of alternative treatment, due to ongoing history of arthralgia/bone pain; *KMT2A*-r: Enrolled into a different study, insurance logistical reason, pursuit of alternative treatment. [c]Unrelated to ziftomenib (death; septic shock).
AE, adverse event; ITT, intention-to-treat; HSCT, hematopoietic stem cell transplant.

Data cutoff: Oct 1, 2024

Baseline Characteristics and Disposition: 1L AML (N=51)

		NPM1-m				*KMT2A*-r			
	All Patients (N=51)	**200 mg (n=8)**	**400 mg (n=7)**	**600 mg (n=9)**	**Total (n=24)**	**200 mg (n=10)**	**400 mg (n=9)**	**600 mg (n=8)**	**Total (n=27)**
Median age, years (range)	**60 (18–74)**	65 (43–74)	66 (55–68)	66 (60–68)	**66 (43–74)**	53 (31–73)	51 (28–60)	40 (18–67)	**50 (18–73)**
Female, n (%)	31 (61)	4 (50)	4 (57)	4 (44)	12 (50)	7 (70)	6 (67)	6 (75)	19 (70)
Race, n (%)									
White	33 (65)	7 (88)	6 (86)	4 (44)	17 (71)	8 (80)	4 (44)	4 (50)	16 (59)
Non-White	18 (35)	1 (13)	1 (14)	5 (56)	7 (29)	2 (20)	5 (56)	4 (50)	11 (41)
ECOG PS 0, n (%)	16 (31)	4 (50)	4 (57)	4 (44)	12 (50)	0	2 (22)	2 (25)	4 (15)
1	18 (35)	3 (38)	1 (14)	4 (44)	8 (33)	3 (30)	2 (22)	5 (63)	10 (37)
2	7 (14)	1 (13)	1 (14)	1 (11)	3 (13)	3 (30)	1 (11)	0	4 (15)
Co-mutations, n (%)	17 (33)	2 (25)	1 (14)	5 (56)	8 (33)	4 (40)	2 (22)	3 (38)	9 (33)
FLT3	3 (6)	0	0	0	0	1 (10)	0	2 (25)	3 (11)
IDH1/2	7 (13)	2 (25)	0	5 (56)	7 (29)	0	0	0	0
Therapy-related AML, n (%)	11 (22)	1 (13)	1 (14)	1 (11)	3 (13)	3 (30)	2 (22)	3 (38)	8 (30)
Patients on study[a], n (%)	**45 (88)**	8 (100)	7 (100)	9 (100)	**24 (100)**	6 (60)	8 (89)	7 (88)	**21 (78)**
Median follow-up, weeks (range)	25 (2–66)	46 (35–66)	31 (29–34)	21 (17–24)	31 (17–63)	33 (2–43)	25 (15–31)	10 (4–17)	19 (2–43)

[a]Patients on-treatment or in long-term follow-up.

Data cutoff: Oct 1, 2024. ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety and Tolerability of Ziftomenib in Combination with 7+3 in 1L AML (N=51)

TEAEs in ≥30% of All Patients

TEAEs, n (%)	All Patients (N=51)	*NPM1*-m 200 mg (n=8)	*NPM1*-m 400 mg (n=7)	*NPM1*-m 600 mg (n=9)	*NPM1*-m Total (n=24)	*KMT2A*-r 200 mg (n=10)	*KMT2A*-r 400 mg (n=9)	*KMT2A*-r 600 mg (n=8)	*KMT2A*-r Total (n=27)
Any Grade	**48 (94)**	8 (100)	6 (86)	8 (89)	22 (92)	10 (100)	9 (100)	7 (88)	26 (96)
Febrile neutropenia	**34 (67)**	5 (63)	4 (57)	8 (89)	17 (71)	8 (80)	4 (44)	5 (63)	17 (63)
Diarrhea	**27 (53)**	4 (50)	4 (57)	4 (44)	12 (50)	6 (60)	7 (78)	2 (25)	15 (56)
Platelet count decreased	**22 (43)**	7 (88)	4 (57)	4 (44)	15 (63)	3 (30)	2 (22)	2 (25)	7 (26)
Anemia	**19 (37)**	4 (50)	2 (29)	4 (44)	10 (42)	4 (40)	3 (33)	2 (25)	9 (33)
Nausea	**19 (37)**	4 (50)	3 (43)	3 (33)	10 (42)	4 (40)	2 (22)	3 (38)	9 (33)
Neutrophil count decreased	**18 (35)**	6 (75)	3 (43)	3 (33)	12 (50)	3 (30)	2 (22)	1 (13)	6 (22)
Constipation	**18 (35)**	5 (63)	2 (29)	2 (22)	9 (38)	5 (50)	2 (22)	2 (25)	9 (33)

- Safety profile of ziftomenib in combination with intensive chemotherapy was similar to that reported for newly diagnosed AML patients treated with 7+3 alone[1]
- Rate of TEAEs was consistent across escalating doses of ziftomenib

[1]Lin et al. *Blood Adv* 2021 Mar 23;5(6):1719-1728 (NCT01696084).
Data cutoff: Oct 1, 2024. TEAE, treatment-emergent adverse event.

Safety and Tolerability of Ziftomenib in Combination with 7+3 in 1L AML (N=51)

Grade ≥3 TEAEs in ≥10% of All Patients

TEAEs, n (%)	All Patients (N=51)	*NPM1*-m 200 mg (n=8)	*NPM1*-m 400 mg (n=7)	*NPM1*-m 600 mg (n=9)	*NPM1*-m Total (n=24)	*KMT2A*-r 200 mg (n=10)	*KMT2A*-r 400 mg (n=9)	*KMT2A*-r 600 mg (n=8)	*KMT2A*-r Total (n=27)
Grade ≥3	**46 (90)**	8 (100)	6 (86)	8 (89)	**22 (92)**	10 (100)	8 (89)	6 (75)	**24 (89)**
Febrile neutropenia	**30 (59)**	5 (63)	4 (57)	8 (89)	**17 (71)**	7 (70)	3 (33)	3 (38)	**13 (48)**
Platelet count decreased	**21 (41)**	7 (88)	4 (57)	3 (33)	**14 (58)**	3 (30)	2 (22)	2 (25)	**7 (26)**
Anemia	**18 (35)**	4 (50)	2 (29)	3 (33)	**9 (38)**	4 (40)	3 (33)	2 (25)	**9 (33)**
Neutrophil count decreased	**18 (35)**	6 (75)	3 (43)	3 (33)	**12 (50)**	3 (30)	2 (22)	1 (13)	**6 (22)**
White blood cell count decreased	**13 (26)**	3 (38)	2 (29)	2 (22)	**7 (29)**	2 (20)	3 (33)	1 (13)	**6 (22)**
Sepsis	**7 (14)**	2 (25)	0	2 (22)	**4 (17)**	1 (10)	1 (11)	1 (13)	**3 (11)**
Pneumonia	**6 (12)**	1 (13)	2 (29)	0	**3 (13)**	2 (20)	0	1 (13)	**3 (11)**

Ziftomenib in Combination with 7+3-related Adverse Events of Interest

- One case of Gr3 differentiation syndrome (*NPM1*-m 600 mg); successfully managed and patient remained on treatment
- No ziftomenib-associated QTc prolongation
- No dose-limiting toxicities (DLTs) at any dose level

Data cutoff: Oct 1, 2024. TEAE, treatment-emergent adverse event.

Clinical Activity in All Response-Evaluable[a] 1L Patients (N=46)

- Historically, only 33% of 7+3 treated newly diagnosed Adverse-Risk AML patients achieve CRc, with a median overall survival of ~6 months[1-2]

		NPM1-m				*KMT2A*-r			
Response, n (%)	**All Patients (N=46)**	**200 mg (n=8)**	**400 mg (n=7)**	**600 mg (n=8)**	**Total (n=23)**	**200 mg (n=10)**	**400 mg (n=9)**	**600 mg (n=4)**	**Total (n=23)**
CRc	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
ORR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CRh	0	0	0	0	0	0	0	0	0
CRi	0	0	0	0	0	0	0	0	0
MLFS	0	0	0	0	0	0	0	0	0
PR	0	0	0	0	0	0	0	0	0
NR	3 (7)	0	0	0	0	0	3 (33)	0	3 (13)
NE	1 (2)	0	0	0	0	1 (10)	0	0	1 (4)
MRD negativity, n/N[b]	**28/37 (76)**	8/8 (100)	4/6 (67)	4/7 (57)	**16/21 (76)**	5/8 (63)	5/6 (83)	2/2 (100)	**12/16 (75)**

[a]Patients who have ≥1 response assessment or who had died.
[b]Among CRc responders tested for MRD per local assay (NGS, RT-qPCR, FISH, flow cytometry).

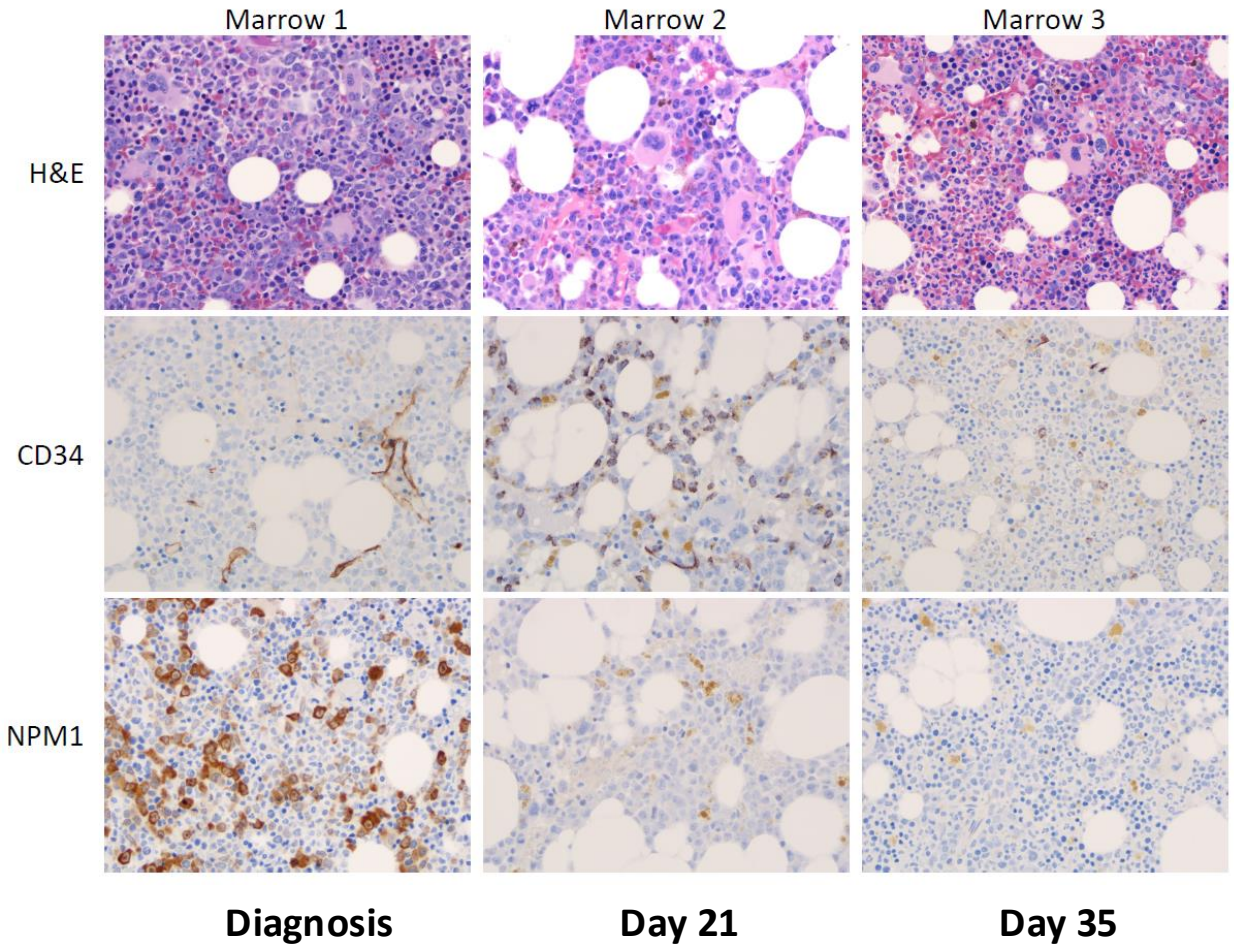
1. Lin et al. *Blood Adv* 2021 Mar 23;5(6):1719-1728. 2. Lancet et al. *Blood* 2014 May 22;123(21):3239-46.
Data cutoff: Oct 1, 2024. Per ELN 2022: CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; FISH, fluorescence in situ hybridization; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NGS, next-generation sequencing; NR, no response; PR, partial remission; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

Case Study

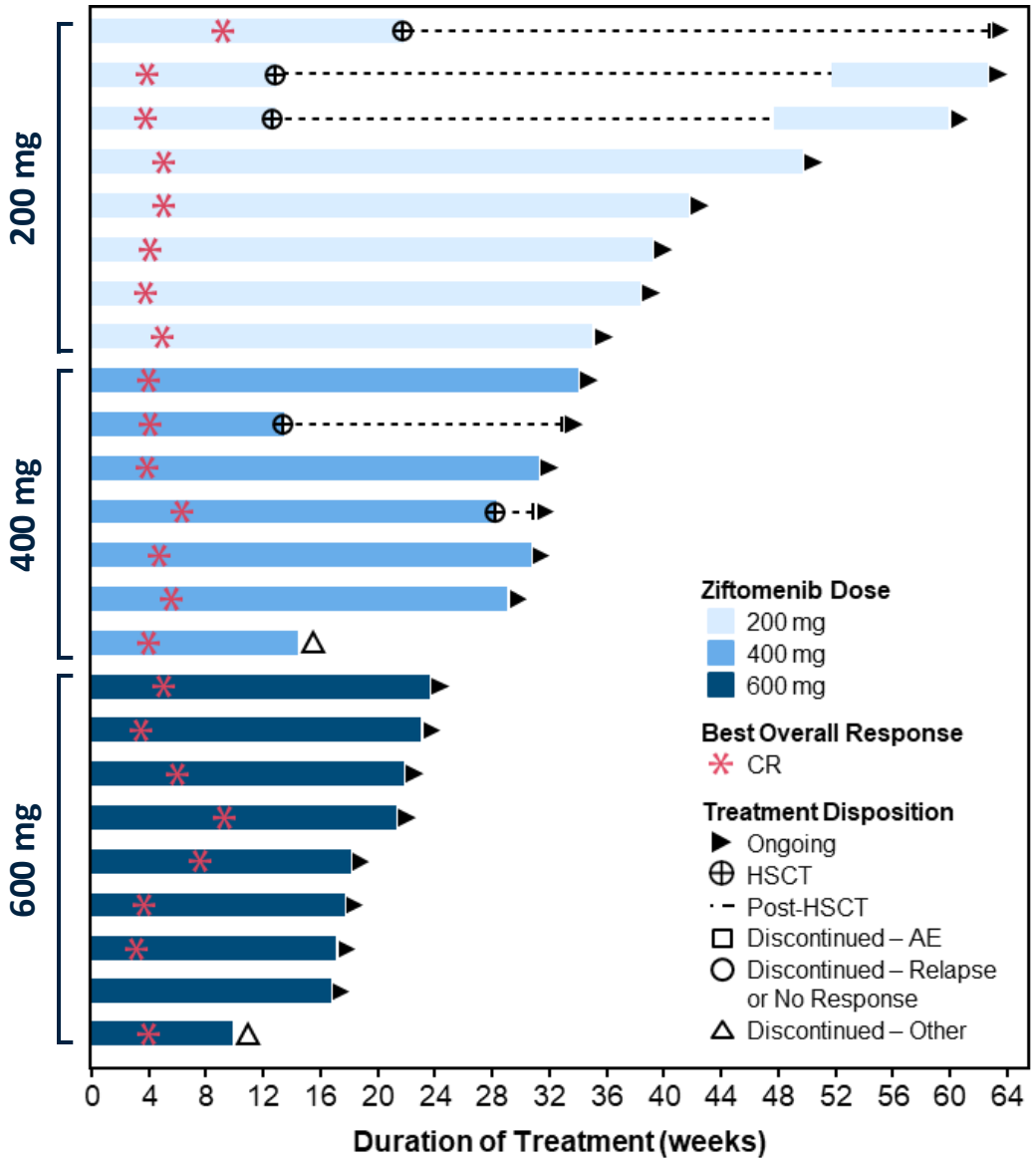
60-yr-old Female with Newly Diagnosed *NPM1*-m AML Treated with Ziftomenib and 7+3

- **Screening marrow**: blasts 8%, $CD34^{-}$ $NPM1^{+}$ AML
- **Day 21 marrow**: 30% morphologic blasts, but now $CD34^{+}$ $NPM1^{-}$ (IHC)
- **Days 22–24**: Platelet count recovering, decision to hold off salvage therapy and repeat marrow at Day 35
- **Day 35 marrow:** $NPM1^{-}$ (IHC), blasts 1%

- **Key considerations:**
  - **Distinguish refractory disease from differentiating/regenerating blasts**
  - **Allow time for count recovery and re-assess bone marrow, especially when clinical picture suggests otherwise (eg, change in blast immunophenotype, recovering counts, high CR rate)**



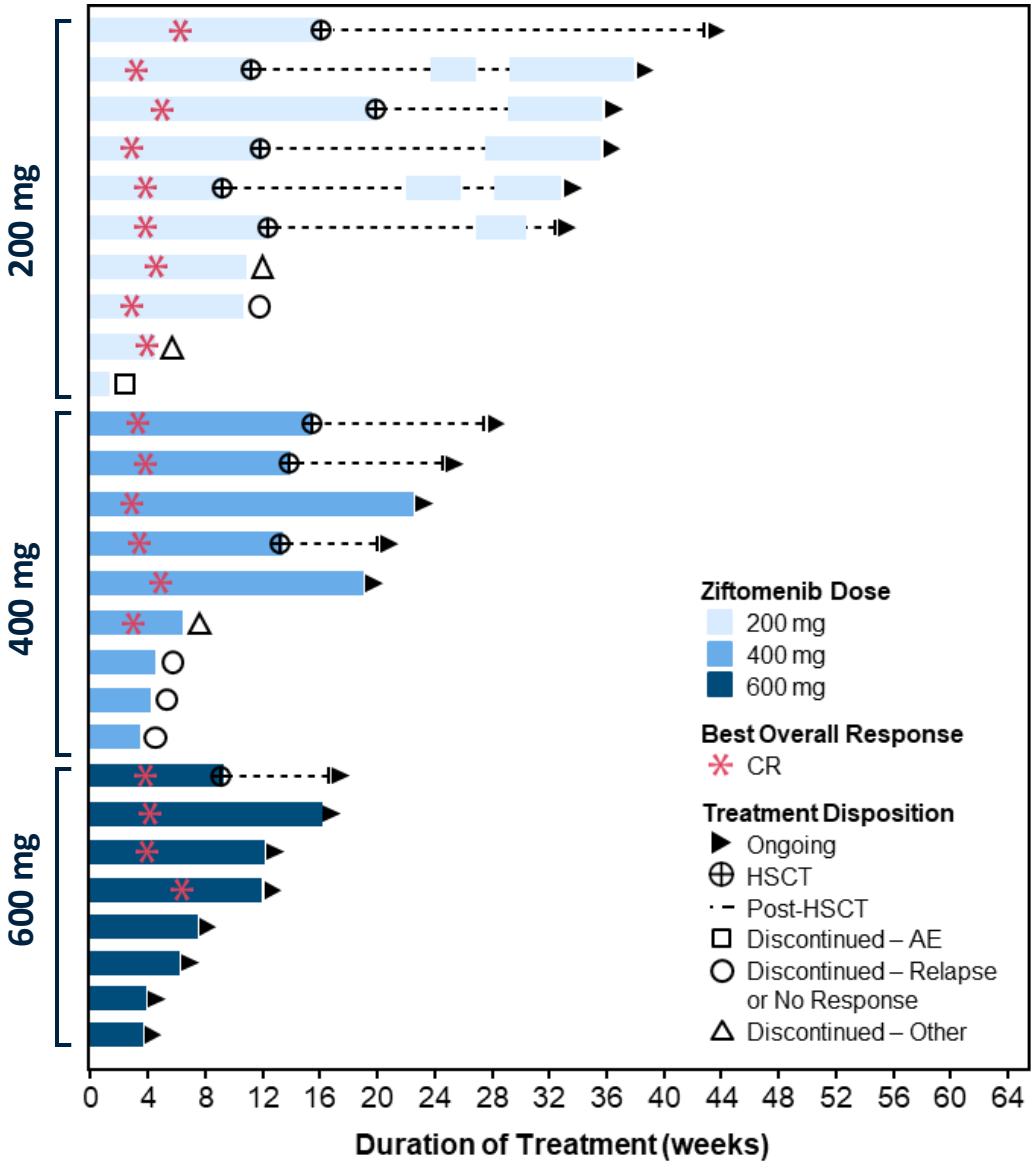
Duration of Treatment & Preliminary Clinical Outcomes in *NPM1*-m 1L AML



- For *NPM1*-m, after a median follow-up of 31 weeks (range 17–63):
  - Median duration of CR was **not reached**
  - Median OS was **not reached**
  - 5 *NPM1*-m patients received HSCT (200 mg n=3, 400 mg n=2). Thus far, 2 went onto ziftomenib maintenance
  - No discontinuations due to AE or relapse
  - **100% (24/24) patients remained alive**

Data cutoff: Oct 1, 2024.
AE, adverse event; CR, complete remission; HSCT, hematopoietic stem cell transplant.

Duration of Treatment & Preliminary Clinical Outcomes in *KMT2A*-r 1L AML



- For *KMT2A*-r, after a median follow-up of 19 weeks (range 2–43):
  - Median duration of CR was **not reached**
  - Median OS was **not reached**
  - 10 *KMT2A*-r patients received HSCT (200 mg n=6, 400 mg n=3, 600 mg n=1). Thus far, 5 went onto ziftomenib maintenance
  - **96% (26/27) patients remained alive**

Data cutoff: Oct 1, 2024.
AE, adverse event; CR, complete remission; HSCT, hematopoietic stem cell transplant.

ANC and Platelet Recovery in CRc Responders

Median (range)	*NPM1*-m + *KMT2A*-r		
	200 mg n=17	400 mg n=13	600 mg n=12
Days to ANC ≥0.5x10^9/L, Cycle 1	32 (20–40)	27 (20–40)	28 (19–38)
Days to ANC ≥1.0x10^9/L, Cycle 1	33 (21–62)	28 (20–40)	28 (20–48)
Days to Platelets ≥50x10^9/L, Cycle 1	28 (15–62)	26 (15–40)	26 (18–48)
Days to Platelets ≥100x10^9/L, Cycle 1	32 (20–62)	26 (18–40)	28 (20–48)

- Higher ziftomenib doses did not impact or delay neutrophil and platelet count recovery

Data cutoff: Oct 1, 2024. ANC, absolute neutrophil count; CRc, composite complete response.

Conclusions

- **In the ongoing KOMET-007 study, ziftomenib combined with cytarabine and daunorubicin (7+3) was well tolerated across all dose levels in patients with newly diagnosed adverse-risk *NPM1*-m and *KMT2A*-r AML**
  - No DLTs or ziftomenib-associated QTc prolongation were reported
  - On-target DS occurred in 2% (n=1, Gr3), successfully managed and patient remained on treatment
  - Higher ziftomenib doses did not impact or delay neutrophil and platelet count recovery
- **Robust clinical activity was demonstrated in newly diagnosed *NPM1*-m and *KMT2A*-r AML**
  - CR: 100% for *NPM1*-m, 83% for *KMT2A-r* patients
    - MRD negativity: 76% for *NPM1*-m, 75% for *KMT2A*-r patients
  - 100% (24/24) of *NPM1*-m and 96% (26/27) *KMT2A*-r patients remained alive (median follow-up of 31 and 19 weeks, respectively)
- **Taken together, these data support the continued advancement of ziftomenib in combination with intensive chemotherapy in all newly diagnosed *NPM1*-m and *KMT2A*-r AML patients, with or without adverse-risk**
  - Given encouraging clinical activity and the lack of impact associated with increasing ziftomenib dose and TEAEs (including DS, QTc prolongation or myelosuppression), the Phase 1b dose expansion is investigating 600 mg ziftomenib-based combinations in all newly diagnosed *NPM1*-m and *KMT2A*-r AML patients

KOMET-017: Phase 3 Ziftomenib Pivotal 1L Combination

Expected to start in mid-2025

- **Randomized registration-enabling Phase 3 trial in both fit and unfit 1L AML to initiate in 2025**
  - Includes two independently powered Phase 3, randomized, double-blind, placebo-controlled studies
  - Populations: **Adult 1L AML with *NPM1*-m or *KMT2A*-r**
    - Non-intensive therapy: Ziftomenib + VEN/Aza combination
    - Intensive therapy: Ziftomenib and 7+3 combination

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