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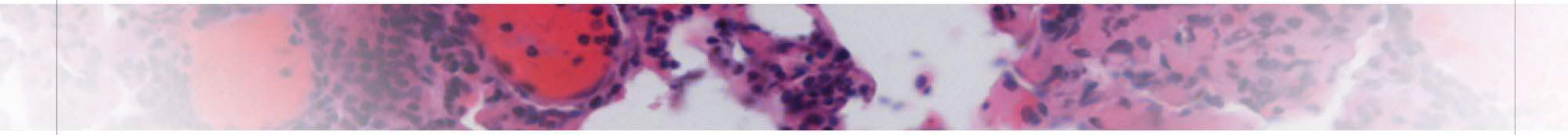


# Ziftomenib in Combination with Venetoclax and Azacitidine in Newly Diagnosed *NPM1*-m Acute Myeloid Leukemia: Phase 1b Results from KOMET-007

**Gail J. Roboz, MD**[1], Eunice S. Wang, MD[2], Amir T. Fathi, MD[3], Harry Erba, MD, PhD[4], Keith W. Pratz, MD[5], Guru Subramanian Guru Murthy, MD, MS[6], Leonard C. Alsfeld, MD[7], James S. Blachly, MD[8], Kiran Naqvi, MD[9], Ghayas C. Issa, MD[10], Ayman Qasrawi, MD[11], Stephen A. Strickland, MD[12], Neil D. Palmisiano, MDMS[13], Jessica K. Altman, MD[14], Cecilia Arana Yi, MD[15], Grerk Sutamtewagul, MD[16], Yazan F. Madanat, MD[17], Suresh Kumar Balasubramanian, MD[18], Christine M. McMahon, MD[19], Hongling Zhang, MS[20], Tianle Chen, PhD[20], Marcie Riches, MD[20], Daniel Corum, PhD[20], Mollie Leoni, MD[20], Amer M. Zeidan, MBBS, MHS[21]

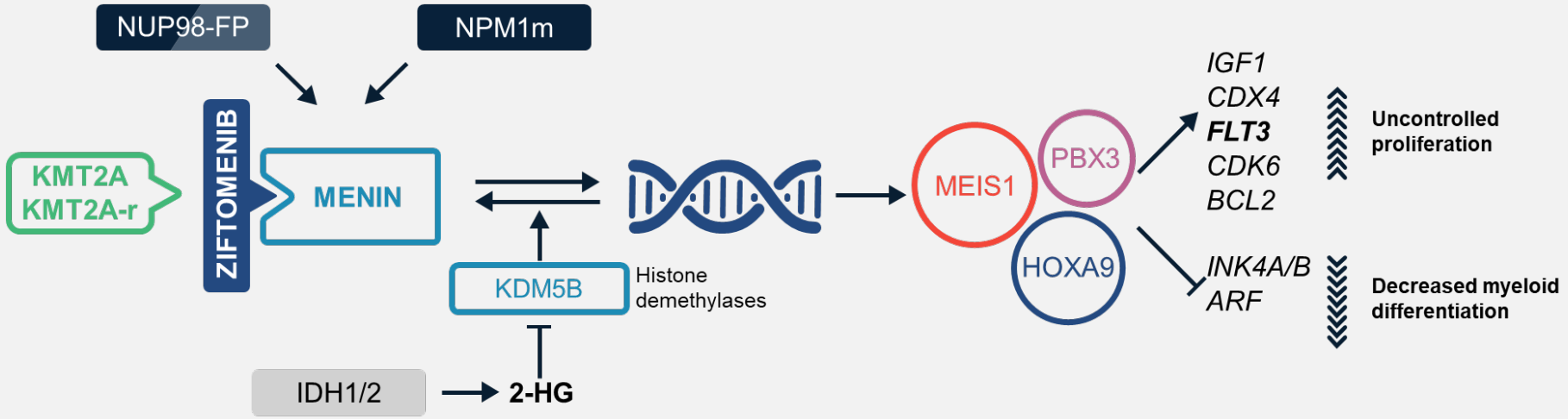
[1]Weill Cornell Medicine and The New York Presbyterian Hospital, New York, NY; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA; [4]Duke Cancer Institute, Durham, NC; [5]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [6]Froedtert & Medical College of Wisconsin, Milwaukee, WI; [7]Ochsner MD Anderson Cancer Center, New Orleans, LA; [8]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [9]Chao Family Comprehensive Cancer Center, University of California Irvine Health, Orange, CA; [10]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [11]Department of Internal Medicine, University of Kentucky, Lexington, KY; [12]SCRI at TriStar Centennial, Nashville, TN; [13]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [14]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; [15]Division of Hematology and Oncology, Mayo Clinic, Phoenix, AZ; [16]University of Iowa Health Care, Holden Comprehensive Cancer Center, Iowa City, IA; [17]The University of Texas Southwestern Medical Center, Dallas, TX; [18]Karmanos Cancer Institute, Wayne State University, Detroit, MI; [19]Anschutz Medical Campus, Division of Hematology, University of Colorado School of Medicine, Aurora, CO; [20]Kura Oncology, Inc., San Diego, CA; [21]Yale University and Yale Comprehensive Cancer Center, New Haven, CT

*Presented at the 67th American Society of Hematology (ASH) Annual Meeting and Exposition on December 6–9, 2025 in Orlando, FL* **#766**

# Ziftomenib Targets the Menin Pathway, a Foundational Target in AML

- *NPM1* mutations drive leukemogenesis in ~30% of AML[1,2]
- **Ziftomenib** is a potent, highly selective, oral menin inhibitor with clinical activity as both monotherapy and in combination for adults with *NPM1*-m AML[3,4]
- Ziftomenib monotherapy was approved for R/R *NPM1*-m AML by the US FDA on November 13, 2025
- **KOMET-007** (NCT05735184) is an ongoing, global, dose-escalation (phase 1a) and expansion (phase 1b) study of ziftomenib in combination with venetoclax/azacitidine (Ven/Aza), Ven alone, or cytarabine/daunorubicin (7+3) with or without quizartinib in newly diagnosed and relapsed/refractory *NPM1*-m or *KMT2A*-r AML

## Ziftomenib Mechanism of Action[5–14]

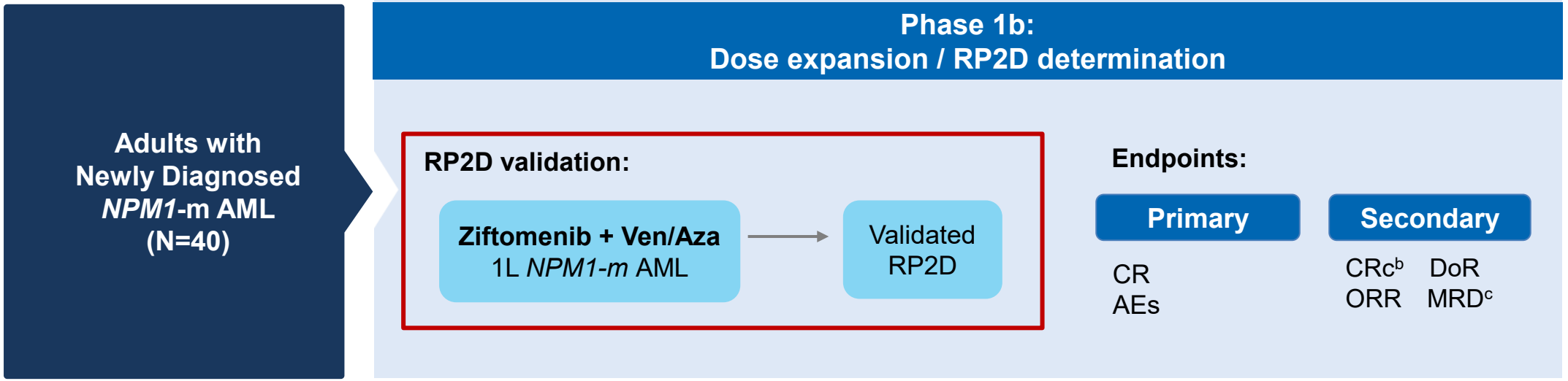



**1.** Papaemmanuil E et al. *N Engl J Med*. 2016;374(23):2209–21. **2.** Issa GC et al. *Leukemia*. 2021;35:2482–95. **3.** Wang ES et al. *Lancet Oncol*. 2024;25(10):1310–24. **4.** Zeidan AM et al. *Blood*. 2024 Nov 5;144(Suppl_1):214. **5.** Collins CT and Hess JL. *Curr Opin Hematol*. 2016;23(4)354–61. **6.** Lu R et al. *Cancer Cell*. 2016;30(1):92–107. **7.** Ferreira HJ et al. *Oncogene*. 2016;35(23):3079-82. **8.** Jeong M et al. *Nat Genet*. 2014;46(1):17-23. **9.** Wang GG et al. *Blood*. 2005;106(1):254–64. **10.** Chowdhury R et al. *EMBO Rep*. 2011;12(5):463–9. **11.** Schmidt L et al. *Leukemia*. 2019;33(7):1608–19. **12.** Xu H et al. *Cancer Cell*. 2016;30(6):863-78. **13.** Brunetti L et al. *Cancer Cell*. 2018;34(3):499–512. **14.** Wang XQD et al. *Cancer Discov*. 2023;13(3):724–45

AML, acute myeloid leukemia; R/R, relapsed/refractory; US FDA, U.S. Food and Drug Administration

# KOMET-007: Ongoing Phase 1 Combination Trial of Ziftomenib in Newly Diagnosed AML[a]

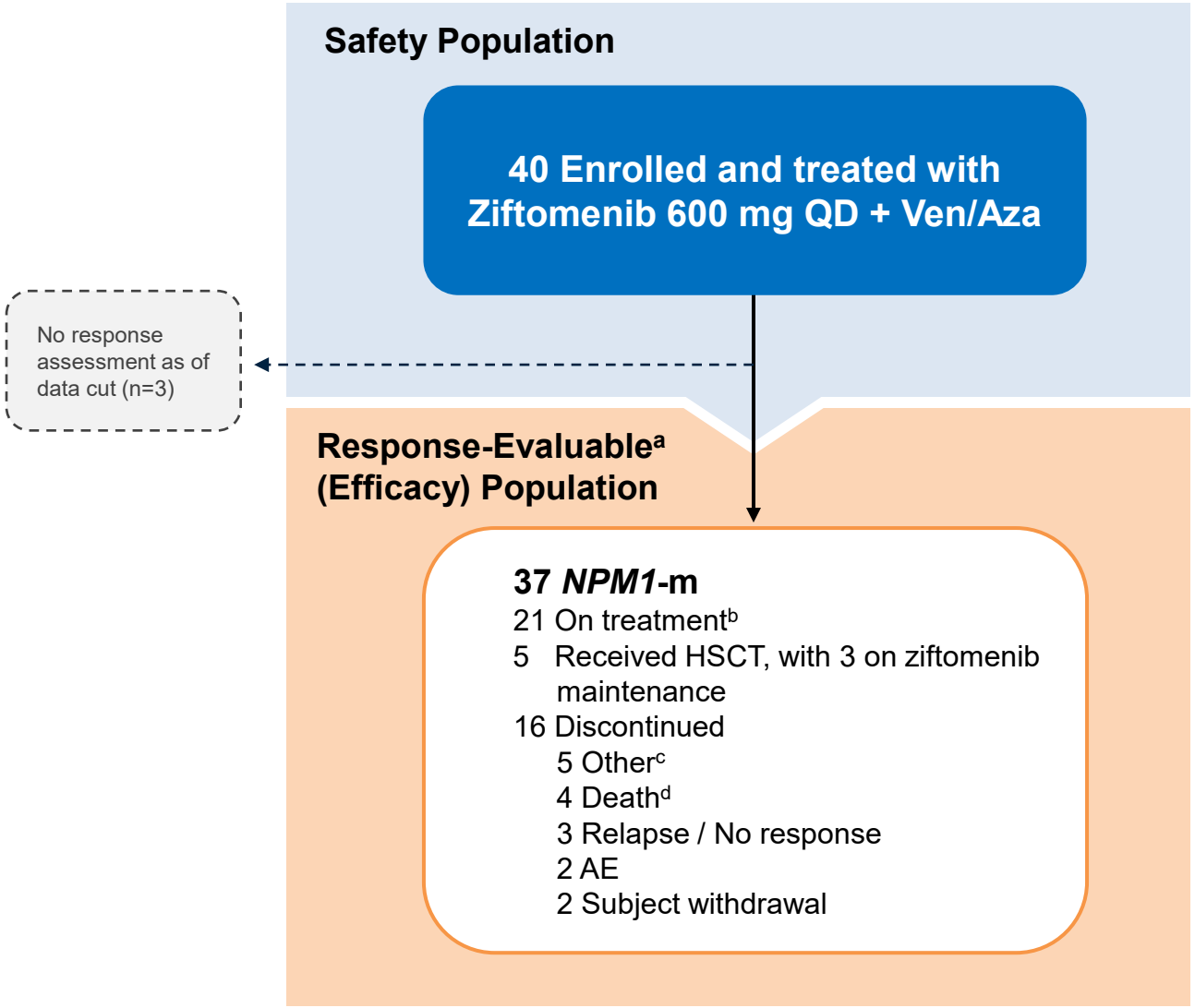
## Ziftomenib + Ven/Aza Combination (NCT05735184)




- Ziftomenib dosing started on Cycle 1 Day 8 and was administered continuously thereafter
- Ven was administered per label in 28-day cycles, with adjustments to Ven dosing and cycle length based on blast clearance in Cycle 1 bone marrow biopsy, performed between Days 14–28
- Aza was administered on Cycle 1 Days 1–7
- Patients were treated with ongoing cycles of triplet therapy based on protocol-mandated bone marrow biopsy results
- **Here we present the first safety and clinical activity results in patients with newly diagnosed *NPM1*-m AML from phase 1b treated with ziftomenib 600 mg in combination with Ven/Aza**

[a]Patients with *NPM1*-m AML from this cohort were included in the current analysis. [b]CR with full, partial, or incomplete hematologic recovery; [c]*NPM1* MRD was performed by central next-generation sequencing with $5x10^{-5}$ sensitivity
1L, first-line; AE, adverse event; CR, complete remission; CRc, composite complete remission; DoR, duration of response; MRD, measurable residual disease; ORR, objective response rate; RP2D, recommended phase 2 dose

# KOMET-007: Safety and Efficacy Populations: Newly Diagnosed AML




- As of Sep 24, 2025, 40 patients with newly diagnosed *NPM1*-m AML were enrolled and treated with ziftomenib 600 mg orally once daily + Ven/Aza
- Median follow-up was **26.1 weeks** (range 1.6–54.1)
- 70% (26/37) of patients were still on-study and 55% (21/37) were still receiving ziftomenib

[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: patient decision for hospice / close to home (n=2), non-compliance (n=1), moved to transplant on local maintenance protocol (n=1), physician decision (n=1). [d]Deaths included: sepsis (n=3), acute respiratory failure (n=1)

Data cutoff: Sep 24, 2025. HSCT, hematopoietic stem cell transplant; QD, once daily

# Baseline Characteristics: Newly Diagnosed AML

| n (%) | *NPM1*-m, 600 mg (N=40) |
|---|---|
| **Median age, years (range)** | 75 (53–93) |
| **Female** | 21 (53) |
| **Race** | |
| White | 31 (78) |
| Non-White / Other | 5 (13) |
| Unknown / Not reported | 4 (10) |
| **ECOG PS** | |
| 0 | 1 (3) |
| 1 | 16 (40) |
| 2 | 23 (58) |
| **Selected co-mutations[a]** | 26 (65) |
| *FLT3* | 14 (35) |
| *IDH1/2* | 9 (23) |
| **Therapy-related AML** | 0 (0) |

[a]Co-mutations can be co-occurring

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

# Safety and Tolerability of Ziftomenib with Ven/Aza: Newly Diagnosed AML

## TEAEs in ≥25% of Patients

| n (%) | All TEAEs (N=40) | Ziftomenib-Related TEAEs (N=40) |
|---|---|---|
| **Any Grade** | **40 (100)** | **25 (63)** |
| Nausea | 16 (40) | 9 (23) |
| Vomiting | 16 (40) | 4 (10) |
| Diarrhea | 16 (40) | 5 (13) |
| Fatigue | 16 (40) | 8 (20) |
| Thrombocytopenia[a] | 15 (38) | 8 (20) |
| Neutropenia[b] | 15 (38) | 9 (23) |
| Leukopenia[c] | 12 (30) | 5 (13) |
| Constipation | 12 (30) | 2 (5) |
| Edema peripheral | 11 (28) | 2 (5) |
| Anemia | 10 (25) | 5 (13) |
| Aspartate aminotransferase increased | 10 (25) | 7 (18) |
| Decreased appetite | 10 (25) | 6 (15) |

- Ziftomenib's safety profile in combination with Ven/Aza appeared similar to that reported for newly diagnosed AML patients treated with Ven/Aza alone[1]

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

**1.** DiNardo CD et al. *N Engl J Med* 2020;383:617–39

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

# Safety and Tolerability of Ziftomenib with Ven/Aza: Newly Diagnosed AML

## Grade ≥3 TEAEs in ≥10% of Patients

| n (%) | All Grade ≥3 TEAEs (N=40) | Grade ≥3 Ziftomenib-Related TEAEs (N=40) |
|---|---|---|
| **Grade ≥3** | **34 (85)** | **16 (40)** |
| Neutropenia[a] | 15 (38) | 8 (20) |
| Thrombocytopenia[b] | 11 (28) | 7 (18) |
| Leukopenia[c] | 10 (25) | 4 (10) |
| Anemia | 8 (20) | 5 (13) |
| Febrile neutropenia | 5 (13) | 1 (3) |
| Sepsis | 5 (13) | 1 (3) |
| Lymphocytopenia[d] | 4 (10) | 1 (3) |
| Pneumonia | 4 (10) | 0 (0) |

## Ziftomenib-Related AEs of Interest

- 1 (3%) case of differentiation syndrome (grade 2) successfully resolved with protocol-specified mitigation, and patient resumed ziftomenib
- 1 (3%) case of investigator-assessed QTc prolongation (grade 3) occurred in setting of concomitant significant electrolyte abnormalities; event resolved with electrolyte repletion, and patient successfully resumed ziftomenib

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

# Clinical Activity[a] of Ziftomenib with Ven/Aza: Newly Diagnosed AML

| n (%) | *NPM1*-m, 600 mg (N=37) |
|---|---|
| **CRc** | 32 (86) |
| Median time to first CRc, weeks (range) | 3.4 (2.4–9.6) |
| **ORR** | 33 (89) |
| CR | 27 (73) |
| CRh | 2 (5) |
| CRi | 3 (8) |
| MLFS | 1 (3) |
| PR | 0 (0) |
| **NR** | 1 (3) |
| **NE[b]** | 3 (8) |

- CR/CRh rates by co-mutated status were consistent with overall CR/CRh response rates:
  - 77% (10/13) for *FLT3* and 89% (8/9) for *IDH1/2*

[a]In patients with ≥1 response assessment or had died. [b]Post-baseline response assessment not done (n=3) at time of data cutoff

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

# Molecular MRD Negativity in CRc Responders: Newly Diagnosed AML

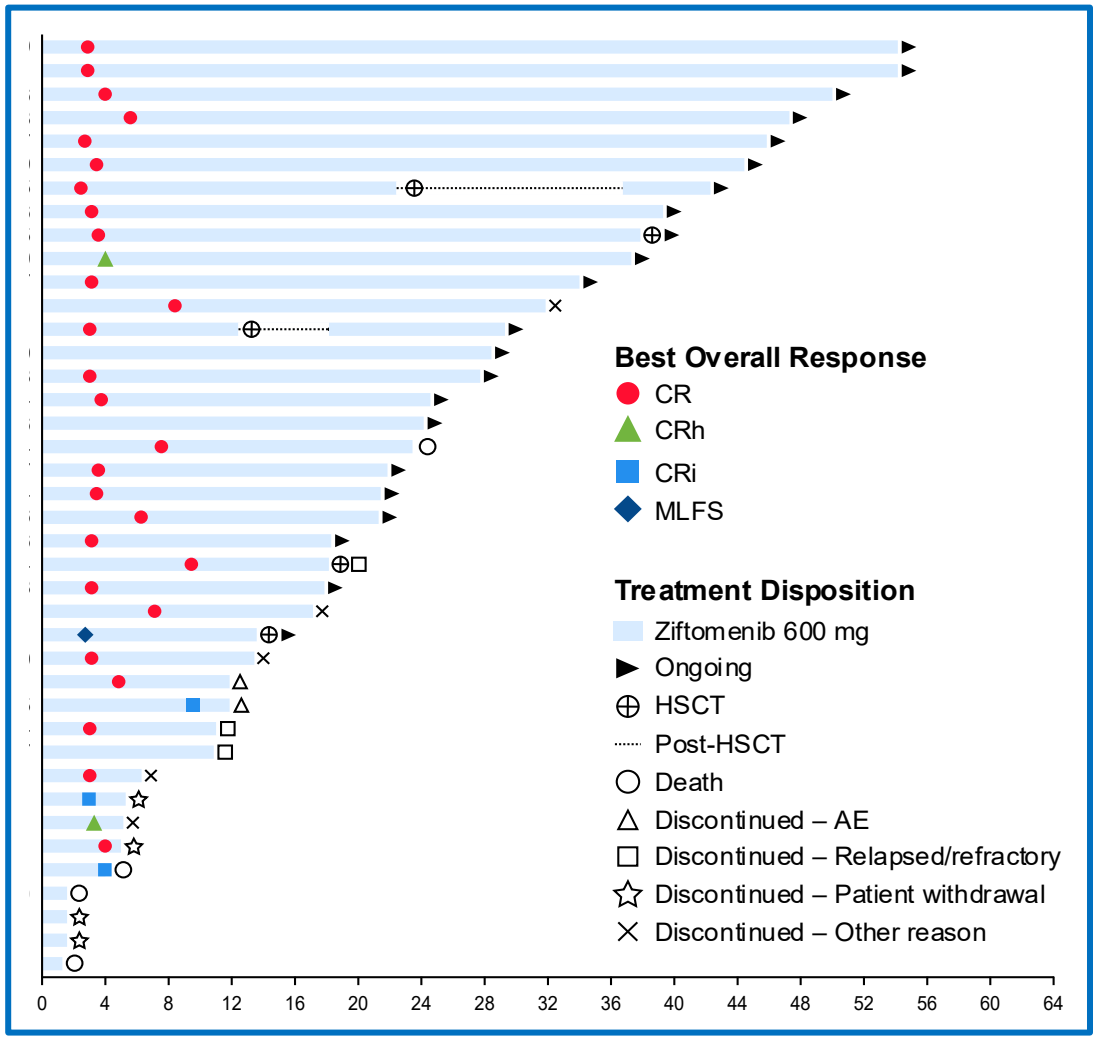
| n/N (%) | Central MRD (Threshold ≤0.1%) | Central MRD (Threshold ≤0.01%) |
|---|---|---|
| **MRD negativity rate[a]** | 17/25 (68) | 11/25 (44) |
| Median time to first MRD negativity, weeks (range) | 9.4 (4.9–22.9) | 9.6 (8.4–22.9) |
| **Timing of MRD negativity[b]:** | | |
| By Cycle 1 | 1/17 (6) | 0 |
| By Cycle 2 | 12/17 (71) | 7/11 (64) |
| By Cycle 3 | 16/17 (94) | 10/11 (91) |
| By Cycle 4[c] | 17/17 (100) | 11/11 (100) |

[a]*NPM1* MRD was performed among tested CRc responders by central next-generation sequencing with 0.005% sensitivity; protocol-defined threshold ≤0.01% was considered meaningful. [b]Among CRc responders who achieved MRD-negativity. [c]Four patients who received less than 4 cycles of therapy were just above the 0.01% MRD threshold at time of analysis; MRD assessments are ongoing

Data cutoff: Sep 24, 2025. MRD, measurable residual disease

# Duration of Treatment and Clinical Outcomes: Newly Diagnosed AML

***NPM1*-m**




After a median follow-up of 26.1 weeks (range 1.6–54.1):

- Median duration of CR was **not reached**[a]
- Median OS was **not reached**[a]
- 5 *NPM1*-m patients underwent HSCT, and 3 went onto ziftomenib maintenance
- 68% (27/40) of patients remained alive and continued on-study[b]

[a]Among response-evaluable patients; [b]Patients on-treatment or in long-term follow-up

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: Newly Diagnosed AML

| Median (range) | *NPM1*-m, 600 mg (N=32)[a] |
|---|---|
| **Days to ANC recovery ≥0.5 × $10^9$/L** | 36 (1–69) |
| **Days to ANC recovery ≥1.0 × $10^9$/L** | 37 (1–69) |
| **Days to platelet count recovery ≥50 × $10^9$/L** | 24 (0–84) |
| **Days to platelet count recovery ≥100 × $10^9$/L** | 30 (20–77) |

- Times to neutrophil and platelet count recovery were comparable to those for Ven/Aza alone[1–3]

[a]Subset of patients who reached cutoff

**1.** Gutman JA et al. *Haematologica.* 2023;108(10):2616–25. **2.** Li X et al. *Invest New Drugs*. 2025;43(4):915–23. **3.** Rausch CR et al. *Cancer*. 2021;127(14):2489–99

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

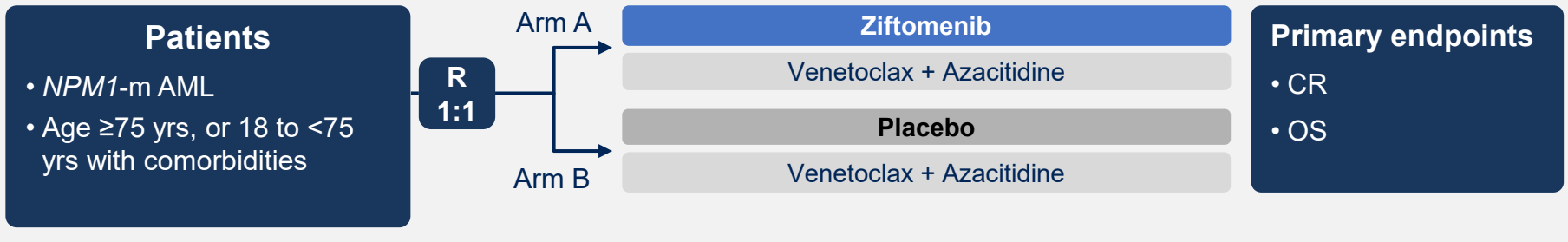
# Conclusions

- **In the ongoing KOMET-007 study, ziftomenib 600 mg QD combined with Ven/Aza showed high rates of durable morphologic and MRD-negative CR in newly diagnosed *NPM1*-m AML**
  - 86% CRc (73% CR), with 68% molecular CRc MRD-negativity
  - Median duration of CRc and median OS were not reached as of the data cutoff
- **The addition of ziftomenib to Ven/Aza did not result in increased toxicity**
  - Myelosuppression was as expected for Ven/Aza
  - Times to neutrophil and platelet count recovery were comparable to those for Ven/Aza alone
  - One case each of differentiation syndrome (grade 2) and investigator-assessed QTc (grade 3) were successfully managed and did not require discontinuation of ziftomenib
- **Taken together, these data support advancement of this ziftomenib-based combination in the ongoing KOMET-017 (NCT07007312) randomized phase 3 study in newly diagnosed *NPM1*-m AML**

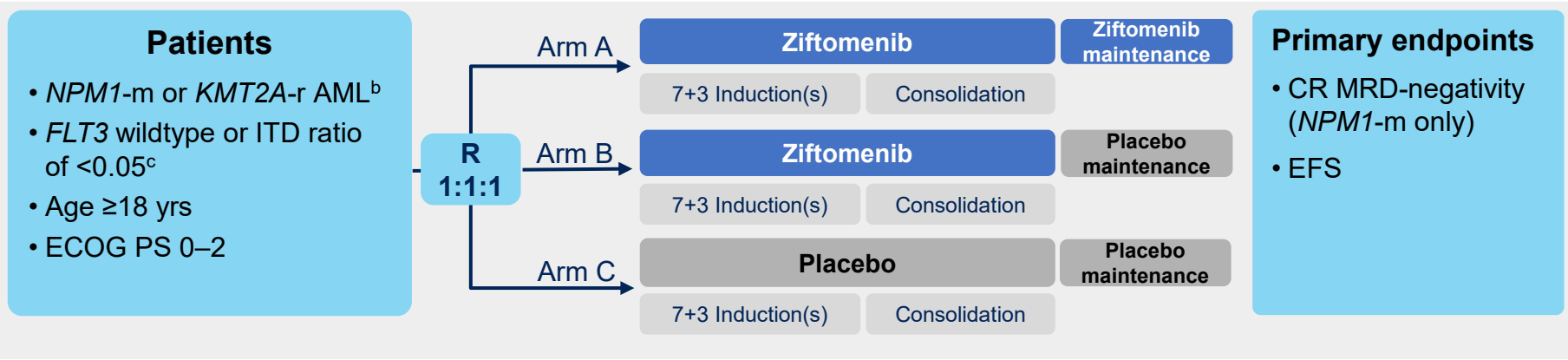
# KOMET-017: Phase 3 Ziftomenib Pivotal Newly Diagnosed Combination Studies

**Two independently powered, registration-enabling, randomized phase 3 studies in fit and unfit newly diagnosed AML (N=1300)**

## KOMET-017-NIC: Non-intensive therapy[a] – Ziftomenib + venetoclax/azacitidine combo




## KOMET-017-IC: Intensive therapy[a] – Ziftomenib and 7+3 combo




## Currently enrolling as of September 2025 (NCT07007312)

[a]HSCT allowed on both studies. [b]Excluding partial tandem duplication; [c]Unless ineligible for *FLT3*-targeted therapy

CR, complete remission; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; ITD, internal tandem duplication; MRD, measureable residual disease; NIC, non-intensive chemotherapy; OS, overall survival; R, randomized

# Acknowledgments


- We would like to thank all the patients, their families, and their caregivers, as well as the KOMET-007 study investigators and their study teams
- This study was sponsored by Kura Oncology, Inc., in partnership with Kyowa Kirin group
- Medical writing support was provided by Envision Pharma Group, with funding from Kura Oncology, Inc.