2025 ASCO ANNUAL MEETING

#6506

# Ziftomenib in Relapsed / Refractory (R/R) *NPM1*-mutant Acute Myeloid Leukemia (AML): Phase 1b/2 Clinical Activity and Safety Results from the Pivotal KOMET-001 Study

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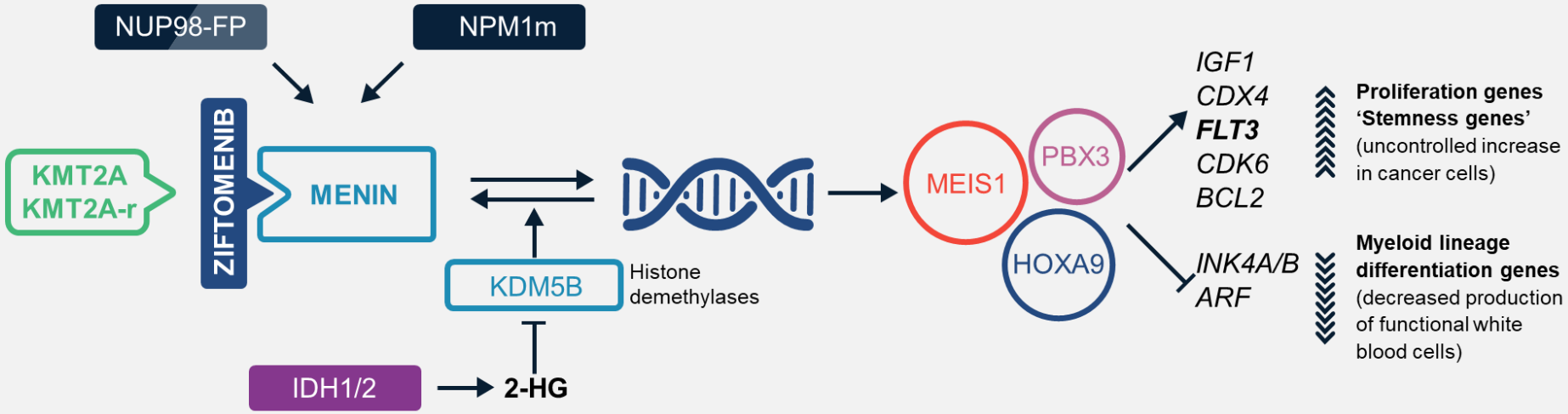
# Ziftomenib Targets the Menin Pathway, a Foundational Target in AML

- *NPM1*-m drives leukemogenesis in ~30% of AML[1]
- Despite current risk stratification, nearly half will have R/R disease within a year, after which outcomes are poor for high-risk patients with < 10% complete remission following venetoclax-based therapy[2-4]
- **Ziftomenib** – a potent, highly selective, oral, investigational menin inhibitor – has shown clinical activity as monotherapy and in combination for adults with R/R *NPM1*-mutant (*NPM1*-m) and *KMT2A*-rearranged (*KMT2A*-r) AML, with 600 mg QD as the recommended phase 2 monotherapy dose for *NPM1*-m AML[5]
- Here, we present the primary analysis for R/R *NPM1*-m patients treated with ziftomenib 600 mg QD in the pivotal KOMET-001 study (NCT04067336)

**Ziftomenib Mechanism of Action[6-15]**




1. Issa GC et al. *Leukemia.* 2021;3:2482-95; 2. Koschade SE et al. *Ann Hematol.* 2022;101(8):1703-10; 3. Zainaldin C et al. *Leuk Lymphoma.* 2022;63(13):3245-8; 4. Maiti A et al. *Haematologica.* 2021;106(3):894-8; 5. Wang ES et al. *Lancet Oncol.* 2024; 25(10):1310-24; 6. Collins CT, Hess JL. *Curr Opin Hematol.* 2016;23(4)354-61; 7. Lu R et al. *Cancer Cell.* 2016;30(1):92–107; 8. Ferreira HJ et al. *Oncogene.* 2016;35(23):3079-82; 9. Jeong M et al. *Nat Genet.* 2014;46(1):17-23; 10. Wang GG et al. *Blood.* 2005;106(1):254-64; 11. Chowdhury R 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 L et al. *Cancer Cell.* 2018; 34(3):499–512; 15. Wang XQD et al. *Cancer Discov.* 2023; 13(3):724-45.

# KOMET-001: Pivotal Trial of Ziftomenib Monotherapy in R/R *NPM1*-m AML

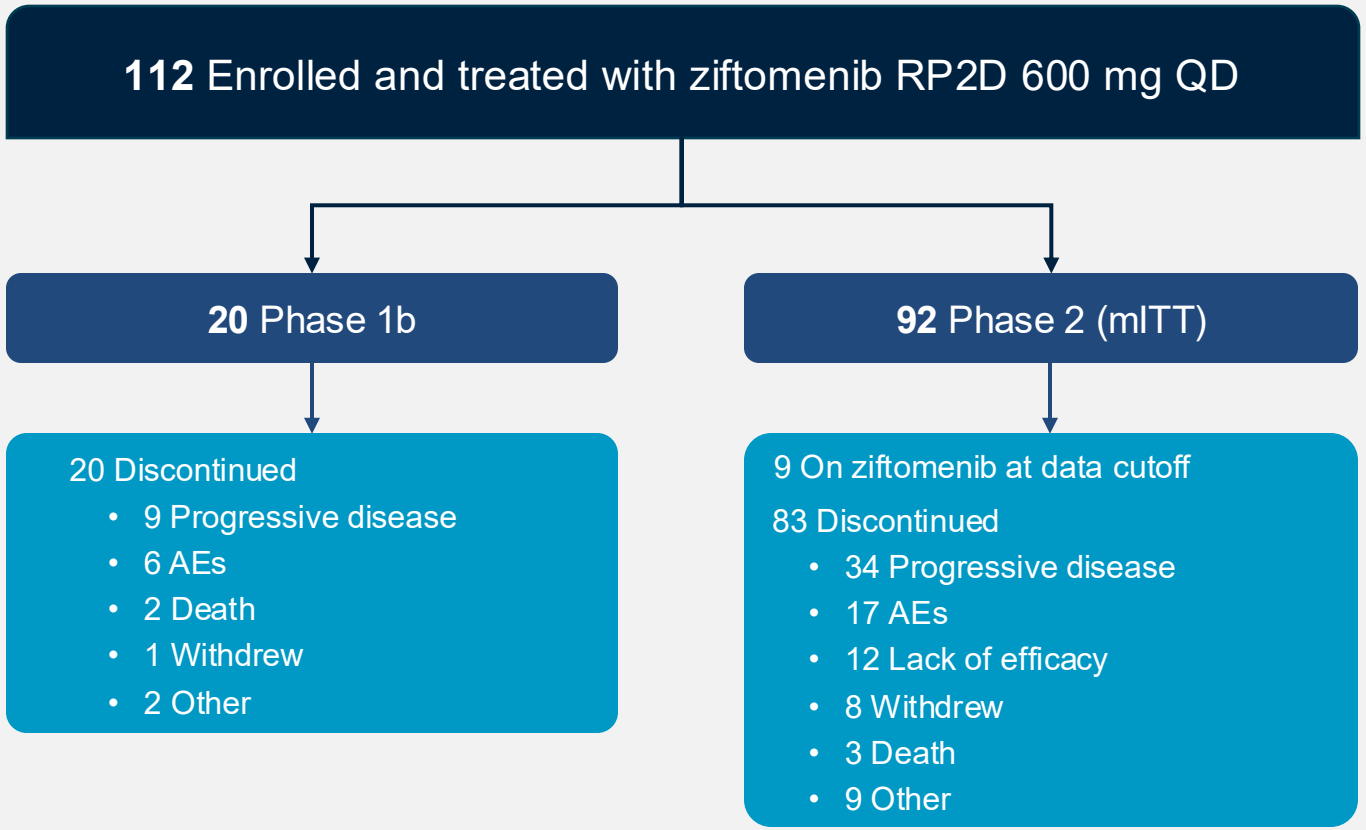
| Phase 1a Dose Escalation | Phase 1b Validation Cohorts | Phase 1b Expansion | Phase 2 Registration-Enabling |
|---|---|---|---|
| *Completed* | *Completed* | *Completed* | *Enrollment Completed* |
| 50 mg QD — 100 mg QD — 1000 mg QD | Cohort 1: 200 mg QD<br>Cohort 2: 600 mg QD | Expansion of 600 mg QD | 600 mg QD |
| *NPM1*-m, *KMT2A*-r, Other | *NPM1*-m or *KMT2A*-r | *NPM1*-m | *NPM1*-m |

## OBJECTIVES

| | | | |
|---|---|---|---|
| • Safety and tolerability<br>• Pharmacokinetics<br>• Early evidence of antitumor activity | • Safety and tolerability<br>• Pharmacokinetics<br>• Clinical activity | Continue enrollment of Phase 1b validation cohort(s) consistent with FDA's Project Optimus<br>• Safety and tolerability<br>• Pharmacokinetics<br>• Clinical activity | • **Primary endpoint:**<br>– CR/CRh<br>• **Key secondary endpoints:**<br>– Duration of CR/CRh<br>– CR/CRh MRD negativity<br>– Transfusion independence<br>– Adverse events |

CR/CRh, complete remission with full or partial hematologic recovery; *KMT2A*-r, *KMT2A*-rearranged; MRD, measurable residual disease; *NPM1*-m, *NPM1*-mutant; QD, once daily.

# KOMET-001 in R/R *NPM1*-m AML: Efficacy & Safety Populations




- Patients enrolled from January 26, 2023 to May 13, 2024
  - 40 Sites, 7 countries
- Pooled analyses: 112 patients (92 Phase 2 + 20 Phase 1b)

Data cutoff: Dec 20, 2024.

AE, adverse event; mITT, modified intention-to-treat; RP2D, recommended phase 2 dose; QD, once daily.

# Baseline Characteristics: R/R *NPM1*-m AML

| n (%) | Ziftomenib RP2D 600 mg QD<br>Phase 2<br>(N = 92) | Ziftomenib RP2D 600 mg QD<br>Pooled Phase 1b/2<br>(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<br>Phase 2<br>(N = 92) | Ziftomenib RP2D 600 mg QD<br>Pooled Phase 1b/2<br>(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.

- Baseline characteristics were similar between the phase 2 and pooled phase 1b/2 populations

Data cutoff: Dec 20, 2024.

ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; QD, once daily; RP2D, recommended phase 2 dose; TKD, tyrosine kinase domain.

# Response & Duration of Response: R/R *NPM1*-m AML

## Primary Phase 2 endpoint was met (*P*-value = 0.0058)* vs. 12% historical control rate[1]

| n (%) | Ziftomenib RP2D 600 mg QD | |
|---|---|---|
| | Phase 2 (N = 92) | 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)** |

For Phase 2 patients, after a median follow-up of 4.1 months (range, 0.1–19.7):

- Median time to CR/CRh: **2.8 months** (range, 1.0–15.0)
- Median time to ORR: **1.9 months** (range, 0.8–3.7)

*Based on primary analysis data cut (Oct 28, 2024).

[a]Stable disease/no response/clinical benefit/progressive disease/not evaluable.

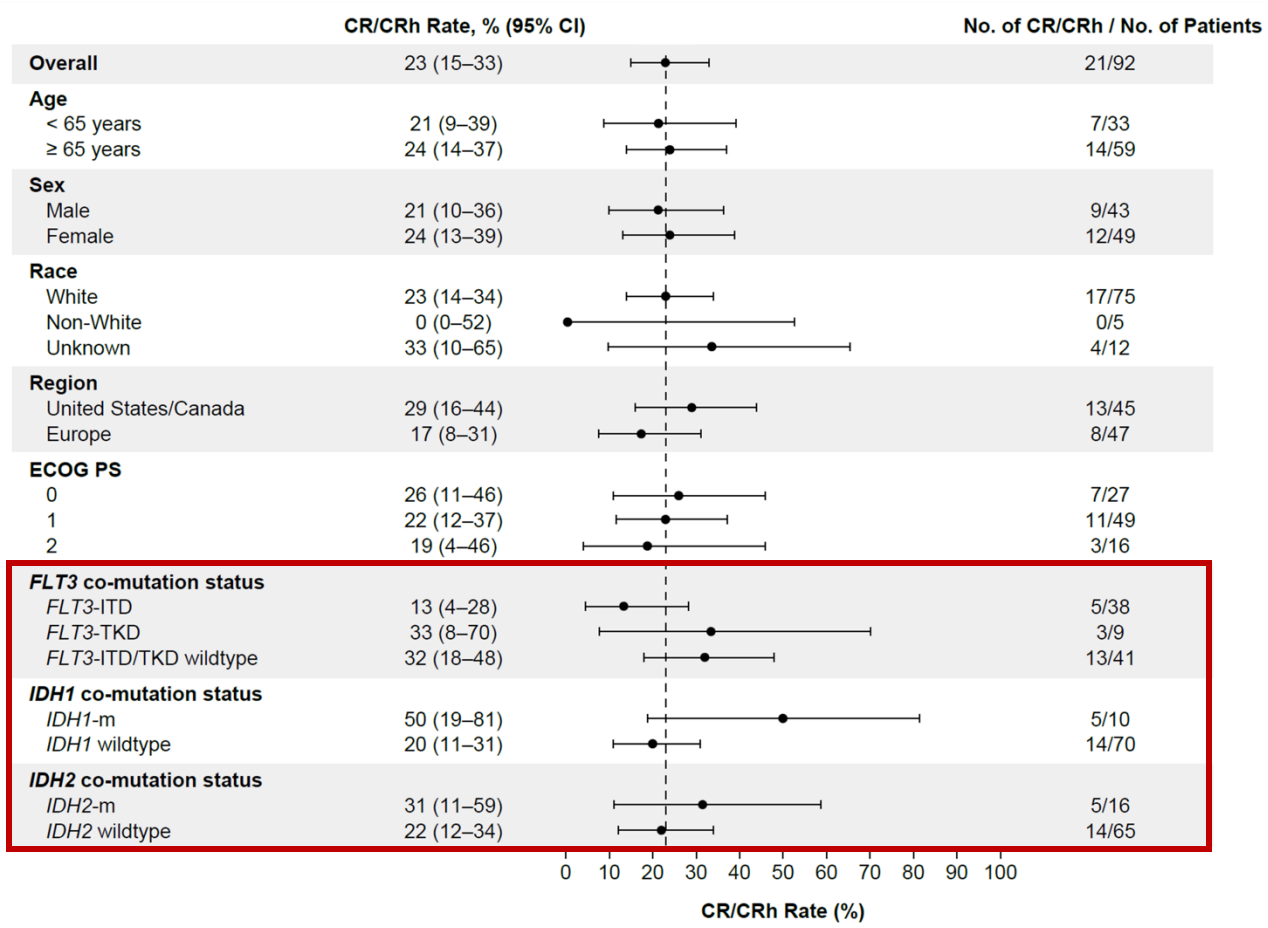
[b]Defined as the expected duration of response (area under the Kaplan-Meier curve, up to the time point when ≥ 10% of patients remain at risk).

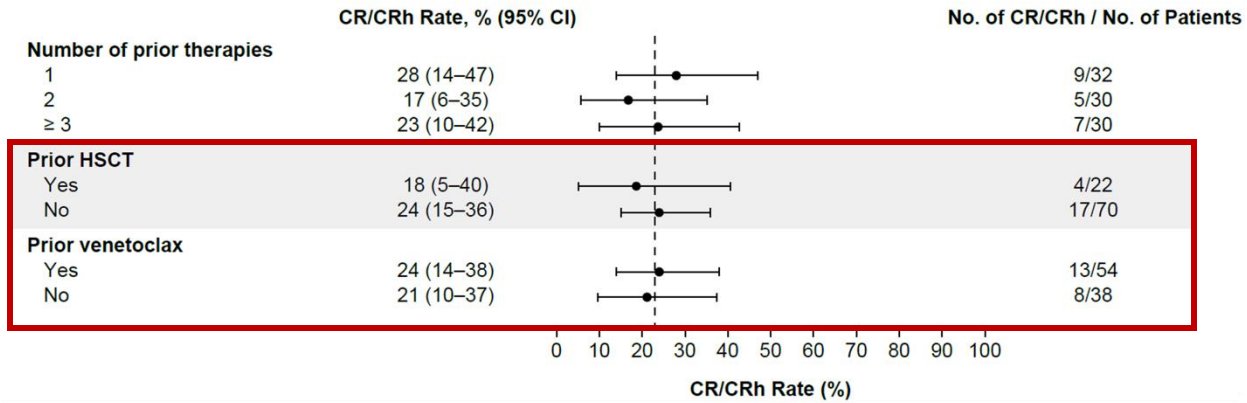
[c]Among CR/CRh responders evaluated for MRD (centrally tested).

Data cutoff: Dec 20, 2024.

1. Smith CC et al. *Blood Adv*. 2022;6(7):2144-55. CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia free state; MRD, measurable residual disease; ORR, overall response rate; PR, partial response; QD, once daily; RP2D, recommended phase 2 dose.

# Comparable CR/CRh Across Pre-specified Subgroups: R/R *NPM1*-m AML




- Comparable CR/CRh rates across pre-specified subgroups, regardless of prior HSCT, venetoclax, or *FLT3/IDH* co-mutations

Data cutoff: Dec 20, 2024.

CR/CRh, complete remission with full or partial hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

# Transfusion Independence: R/R *NPM1*-m AML

## Additional benefit beyond CR/CRh

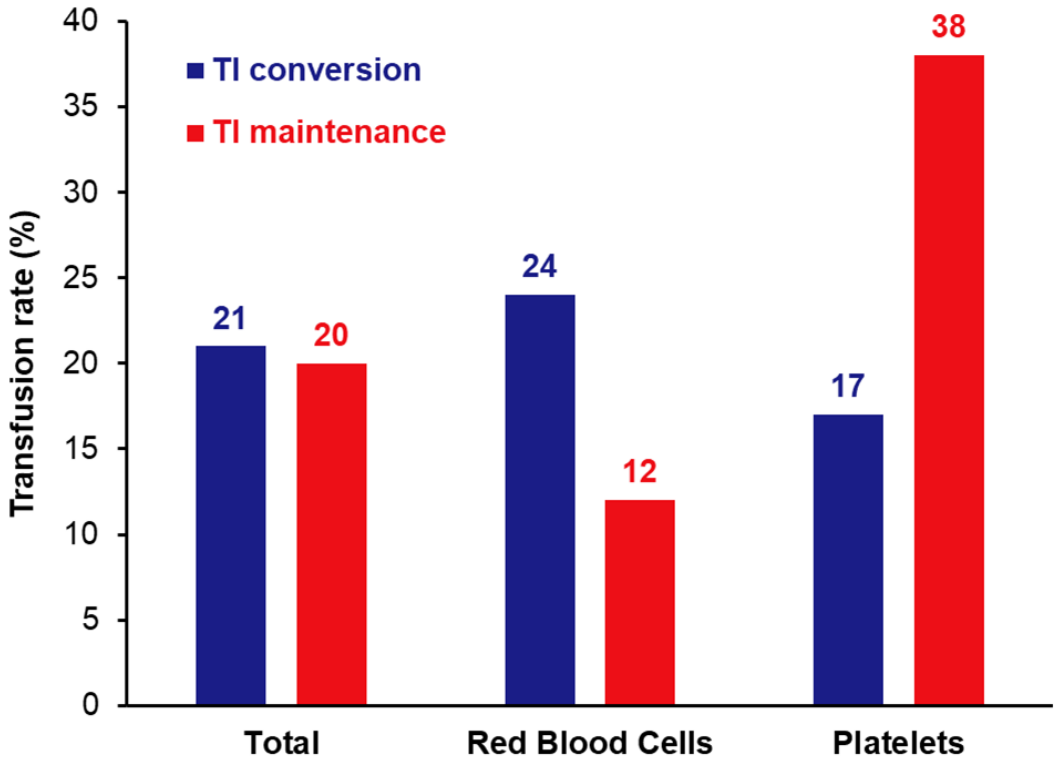
| | Ziftomenib RP2D 600 mg QD Phase 2 (N = 92) |
|---|---|
| **Total post-baseline transfusion independence** | |
| Transfusion conversion (TD to TI) rate[a], n/N (%) | 17/82 (21) |
| 95% CI[b] | 13–31 |
| Maintenance of transfusion independence (TI to TI) rate[c], n/N (%) | 2/10 (20) |
| 95% CI[b] | 3–56 |
| **Post-baseline transfusion of red blood cells** | |
| Transfusion conversion (TD to TI) rate[a], n/N (%) | 18/75 (24) |
| 95% CI[b] | 15–35 |
| Maintenance of transfusion independence (TI to TI) rate[c], n/N (%) | 2/17 (12) |
| 95% CI[b] | 2–36 |
| **Post-baseline transfusion of platelets** | |
| Transfusion conversion (TD to TI) rate[a], n/N (%) | 12/71 (17) |
| 95% CI[b] | 9–28 |
| Maintenance of transfusion independence (TI to TI) rate[c], n/N (%) | 8/21 (38) |
| 95% CI[b] | 18–62 |

[a]Transfusion conversion rate was defined as the number of patients who were TD at baseline but became TI post-baseline (ie, n) divided by the total number of patients who were TD at baseline.

[b]CI was calculated using the exact method based on binomial distribution.

[C]Transfusion maintenance rate was defined as the number of patients who were TI at baseline and remained TI post-baseline (ie, n) divided by the total number of patients who were TI at baseline.

Post-baseline transfusion period was defined as the 29 days post-first dose of ziftomenib until last dose prior to any new anti-cancer treatment (HSCT).

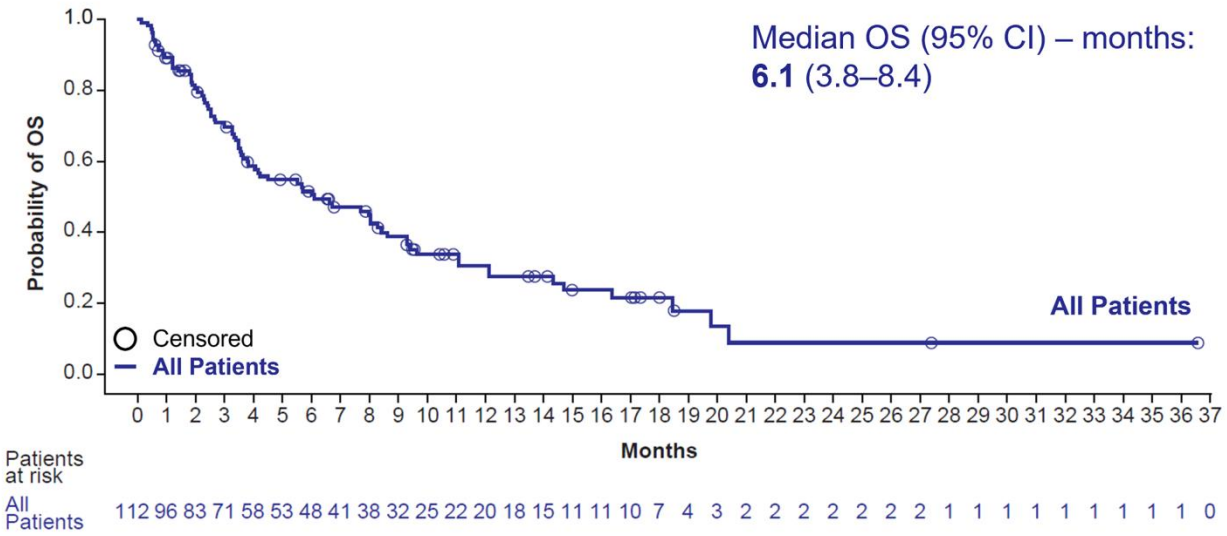



Data cutoff: Dec 20, 2024.

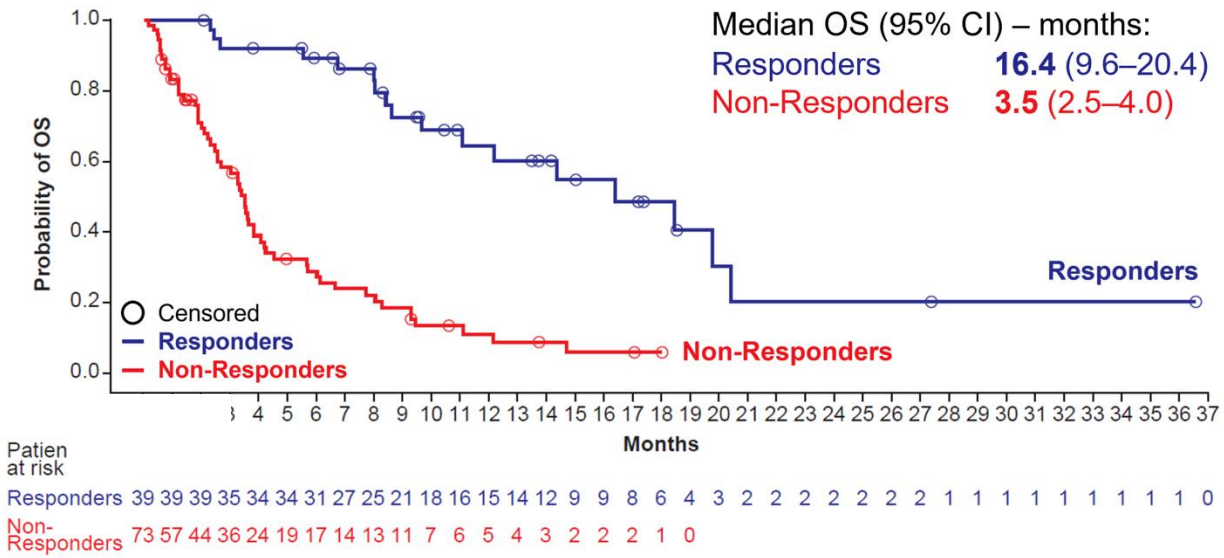
HSCT, hematopoietic stem cell transplantation; QD, once daily; RP2D, recommended phase 2 dose; TD, transfusion dependent; TI, transfusion independent.

# Overall Survival: R/R *NPM1*-m AML

## All Patients (Pooled Phase 1b/2)




## Responders* vs. Non-Responders




- Median OS: **6.1 months** (95% CI, 3.8–8.4)
- Note: 24 patients remained alive on-study, with 9 patients on-treatment

*Responders included CRc, MLFS, and PR.

Data cutoff: Dec 20, 2024. CRc, composite complete remission; MLFS, morphologic leukemia free state; OS, overall survival; PR, partial response.

# Safety & Tolerability of Ziftomenib in R/R *NPM1*-m AML (Safety Population)

## Treatment-Emergent AEs in ≥ 20% of All 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 AE** | 92 (100) | 86 (93) | 112 (100) | 105 (94) |
| **Hematologic AEs** | | | | |
| Anemia | 20 (22) | 18 (20) | 25 (22) | 23 (21) |
| Febrile neutropenia | 24 (26) | 24 (26) | 25 (22) | 25 (22) |
| Thrombocytopenia | 18 (20) | 18 (20) | 22 (20) | 22 (20) |
| **Nonhematologic AEs** | | | | |
| Diarrhea | 27 (29) | 1 (1) | 36 (32) | 5 (4) |
| Nausea | 23 (25) | 1 (1) | 31 (28) | 1 (1) |
| Hypokalemia | 22 (24) | 12 (13) | 29 (26) | 13 (12) |
| **Differentiation syndrome** | **23 (25)** | **14 (15)[a]** | **27 (24)** | **15 (13)[a]** |
| Pruritus | 21 (23) | 0 | 26 (23) | 0 |
| Peripheral edema | 23 (25) | 0 | 25 (22) | 0 |
| Pneumonia | 19 (21) | 13 (14) | 24 (21) | 17 (15) |

[a]No patients had Grade 4–5 differentiation syndrome.

*All 3 patients were on additional medications associated with QTc prolongation: 2 patients had electrolyte abnormalities and 1 patient had prior diagnosis of atrial fibrillation.

Ziftomenib was well tolerated, with a safety profile consistent with previous studies,[1,2] including:

- Low rates of ziftomenib-related myelosuppression
- No clinically significant QTc prolongation:
  - 3 (3%) Patients*: 1 Gr2, 2 Gr3 (all investigator-assessed)
- Differentiation syndrome: 15 (13%) Gr3; no Gr4–5 events

Data cutoff: Dec 20, 2024.

1. Wang ES et al. *Lancet Oncol.* 2024; 25(10):1310-24. 2. Fathi AT et al. *Blood*. 2024;144(Suppl_1):2880.

AE, adverse event; QD, once daily; QTc, corrected QT interval; RP2D, recommended phase 2 dose.

# Safety & Tolerability of Ziftomenib in R/R *NPM1*-m AML (Safety Population)

## Ziftomenib-Related AEs in ≥ 5% of All 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 patients had Grade 4–5 differentiation syndrome.

*All 3 patients were on additional medications associated with QTc prolongation: 2 patients had electrolyte abnormalities and 1 patient had prior diagnosis of atrial fibrillation.

Ziftomenib was well tolerated, with a safety profile consistent with previous studies,[1,2] including:

- Low rates of ziftomenib-related myelosuppression
- No clinically significant QTc prolongation:
  - 3 (3%) Patients*: 1 Gr2, 2 Gr3 (all investigator-assessed)
- Differentiation syndrome: 15 (13%) Gr3; no Gr4–5 events
- 3% Discontinuations due to ziftomenib-related AEs

Data cutoff: Dec 20, 2024.

1. Wang ES et al. *Lancet Oncol.* 2024; 25(10):1310-24. 2. Fathi AT et al. *Blood.* 2024;144(Suppl_1):2880.

AE, adverse event; QD, once daily; QTc, corrected QT interval; RP2D, recommended phase 2 dose.

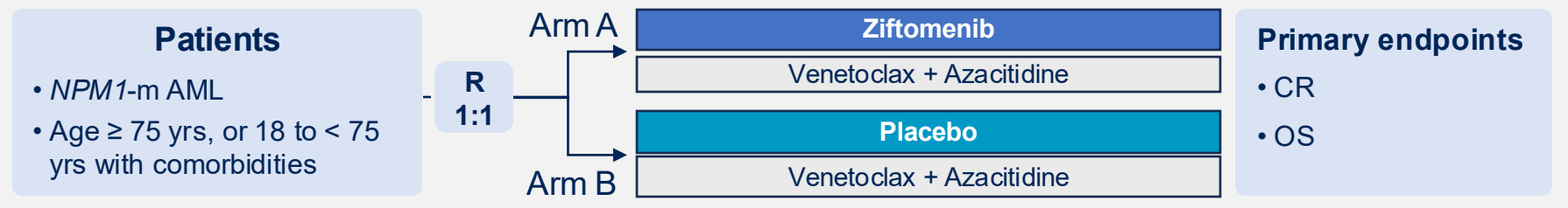
# Conclusions

- **In the pivotal KOMET-001 Phase 2 study, the primary endpoint was met**
  - Ziftomenib achieved clinically meaningful, MRD-negative responses in this heavily pretreated R/R *NPM1*-m AML population
  - Similar response rates were seen, regardless of prior therapies, including HSCT and venetoclax
- **Ziftomenib monotherapy was well tolerated with a safety profile consistent with previous studies**
  - Low rates of ziftomenib-related myelosuppression
  - 3% Ziftomenib-related discontinuations
  - No clinically significant QTc prolongation
  - Differentiation syndrome was managed with protocol-specified mitigation strategies; no Grade 4–5 DS events
- **NDA submitted for ziftomenib monotherapy as a new potential treatment option for R/R *NPM1*-m AML patients**
- **Ziftomenib combination studies are currently ongoing in both newly diagnosed and R/R AML (KOMET-007, KOMET-008)**

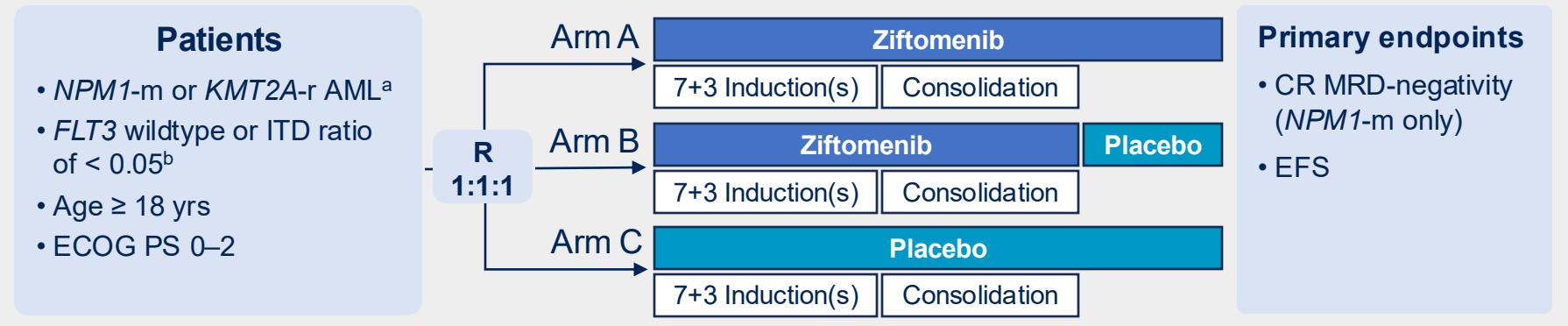
# KOMET-017: Phase 3 Ziftomenib Pivotal 1L Combination Studies

- **Two independently powered, registration-enabling, randomized Phase 3 studies in fit and unfit Newly Diagnosed AML**

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




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




[a]Excluding partial tandem duplication. [b]Unless ineligible for *FLT3*-targeted therapy.

**Expected to start in 2H 2025 (see EHA 2025 Trial-in-Progress abstract)**

CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ITD, internal tandem duplication; MRD, measurable residual disease; OS, overall survival.

# Acknowledgements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