S136

Ziftomenib combined with intensive induction chemotherapy (7+3) in newly diagnosed *NPM1*-m or *KMT2A*-r acute myeloid leukemia: Updated phase 1a/b results from KOMET-007

Harry Erba[1], Eunice S. Wang[2], Amir T. Fathi[3], Gail J. Roboz[4], Yazan F. Madanat[5], Stephen A. Strickland[6], Suresh Balasubramanian[7], James K. Mangan[8], Keith Pratz[9], Anjali Advani[10], Ivana Gojo[11], Jessica K. Altman[12], Marcello Rotta[13], Kiran Naqvi[14], Jorge Cortes[15], Mark Juckett[16], Leonard C. Alsfeld[17], James S. Blachly[18], Marina Kremyanskaya[19], Neil Palmisiano[20], Kalyan V. Nadiminti[21], Gary Schiller[22], Tara L. Lin[23], Mohamad Khawandanah[24], Michael W. Schuster[25], Talha Badar[26], Julie Mackey Ahsan[27], Tianle Chen[27], Marcie Riches[27], Daniel Corum[27], Mollie Leoni[27], and Amer M. Zeidan[28]

[1]Duke Cancer Institute, Durham, NC, USA; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Weill Cornell Medicine and The New York Presbyterian Hospital, New York, NY, USA; [5]University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]SCRI at TriStar Centennial, Nashville, TN, USA; [7]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [8]Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA; [9]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [10]Cleveland Clinic, Cleveland, OH, USA; [11]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [12]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA; [13]Colorado Blood Cancer Institute, Denver, CO, USA; [14]Chao Family Comprehensive Cancer Center, University of California Irvine Health, Orange, CA, USA; [15]Georgia Cancer Center, Augusta, GA, USA; [16]Department of Hematology, University of Minnesota, Minneapolis, MN, USA; [17]Ochsner MD Anderson Cancer Center, New Orleans, LA, USA; [18]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [19]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [20]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [21]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI, USA; [22]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [23]The University of Kansas Cancer Center, Kansas City, KS, USA; [24]University of Oklahoma Health Sciences Center, Stephenson Cancer Center, Oklahoma, OK, USA; [25]Stony Brook University Hospital Cancer Center, Stony Brook, NY, USA; [26]Mayo Clinic, Jacksonville, FL, USA; [27]Kura Oncology, Inc., San Diego, CA, USA; [28]Yale University and Yale Cancer Center, New Haven, CT, USA

EHA2025
Congress
June 12-15 | Milan, Italy

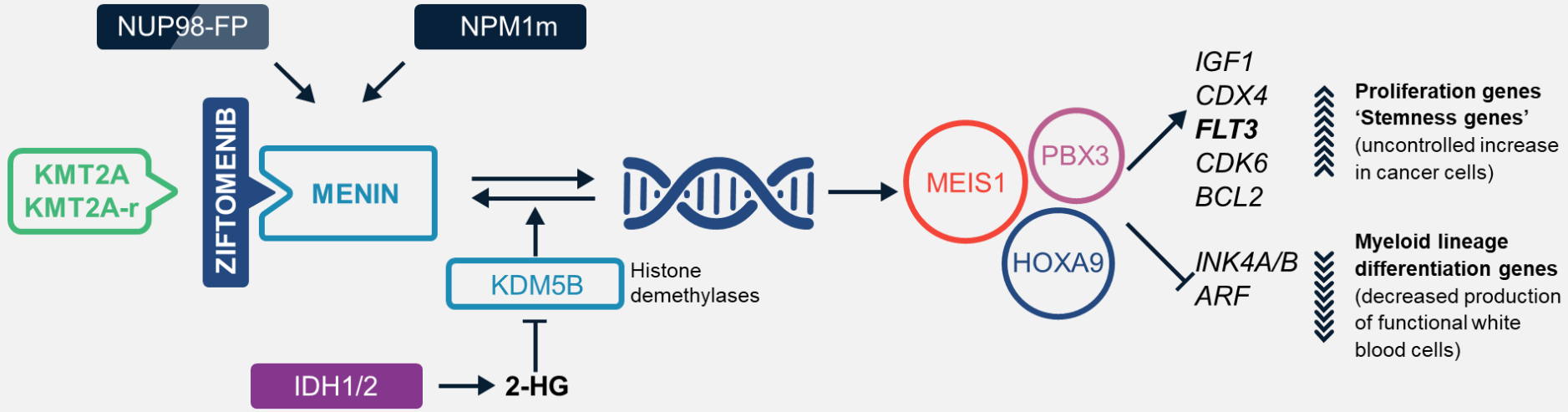
Presenter Disclosures

Agios (Leadership, Consulting/Advisory, Speakers' Bureau, Institutional Research Funding); AbbVie (Honoraria, Consulting/Advisory, Institutional Research Funding, Chair of Independent Review Committee for VIALE A and VIALE C); Stemline (Consulting/Advisory); Servier (Consulting/Advisory, Speakers' Bureau, Institutional Research Funding);
Schrodinger (Consulting/Advisory); Pfizer (Consulting/Advisory); Novartis (Consulting/Advisory, Speakers' Bureau, Institutional Research Funding); MacroGenics (Consulting/Advisory, Institutional Research Funding);
Kura Oncology (Consulting/Advisory, Institutional Research Funding); Jazz (Consulting/Advisory, Speakers' Bureau);
Incyte (Consulting/Advisory); Immunogen (Consulting/Advisory); Glycomimetics (Consulting/Advisory, Institutional Research Funding, Steering Committee Member); Genentech (Consulting/Advisory);
Daiichi Sankyo (Consulting/Advisory, Institutional Research Funding); Celgene (Consulting/Advisory, Speakers' Bureau, Institutional Research Funding, Chair of Myeloid Neoplasms Repository Study);
BMS (Consulting/Advisory, Speakers' Bureau, Chair of Myeloid Neoplasms Repository Study);
Astellas (Consulting/Advisory); Sumitomo Pharma (Consulting/Advisory, Institutional Research Funding);
Syros (Consulting/Advisory); Takeda (Consulting/Advisory); Trillium (Consulting/Advisory);
ALX Oncology (Institutional Research Funding); Aptose (Institutional Research Funding);
Ascentage (Institutional Research Funding); Oryzon (Institutional Research Funding);
PTE (Institutional Research Funding); Taiho Oncology (Institutional Research Funding)

Ziftomenib Targets the Menin Pathway, a Foundational Target in AML

- *NPM1*-m and *KMT2A*-r drive leukemogenesis in ~35–40% of AML[1,2]
- **Ziftomenib** is a potent, highly selective, oral, investigational menin inhibitor with clinical activity as both monotherapy and in combination for adults with *NPM1*-m or *KMT2A*-r AML[3,4]
- KOMET-007 (NCT05735184) is an ongoing dose-escalation (phase 1a) and expansion (phase 1b) study of ziftomenib in combination with venetoclax/azacitidine, venetoclax alone, or cytarabine and daunorubicin (7+3) in *NPM1*-m or *KMT2A*-r AML

Ziftomenib Mechanism of Action[5-14]

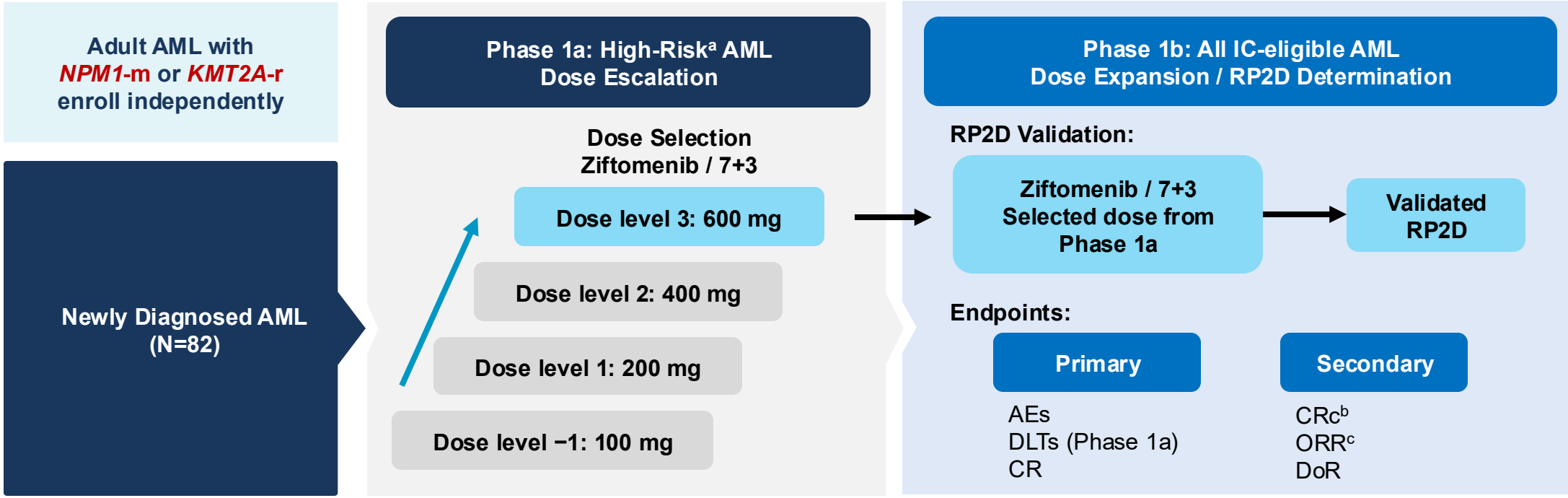


AML, acute myeloid leukemia.

1. Papaemmanuil et al. *N Engl J Med.* 2016;375:900-1; 2. Issa GC et al. *Leukemia.* 2021;3:2482-95; [3]Wang ES et al. *Lancet Oncol.* 2024;25(10):1310-24; [4]Zeidan AM et al. *Blood.* 2024;144(Suppl_1):214;
5. Collins and Hess. *Curr Opin Hematol.* 2016;23(4)354-61; 6. Lu et al. *Cancer Cell.* 2016;30(1):92-107; 7. Ferreira et al. *Oncogene.* 2016;35(23):3079-82; 8. Jeong et al. *Nat Genet.* 2014;46(1):17-23;
9. Wang et al. *Blood.* 2005;106(1):254-64; 10. Chowdhury et al. *EMBO Rep.* 2011;12(5):463-9; 11. Schmidt et al. *Leukemia.* 2019;33(7):1608-19; 12 Xu et al. *Cancer Cell.* 2016;30(6):863-78;
13. Brunetti et al. *Cancer Cell.* 2018; 34(3):499-512; 14. Wang et al. *Cancer Discov.* 2023; 13(3):724-45.

KOMET-007: Ongoing Combination Trial of Ziftomenib in Newly Diagnosed AML

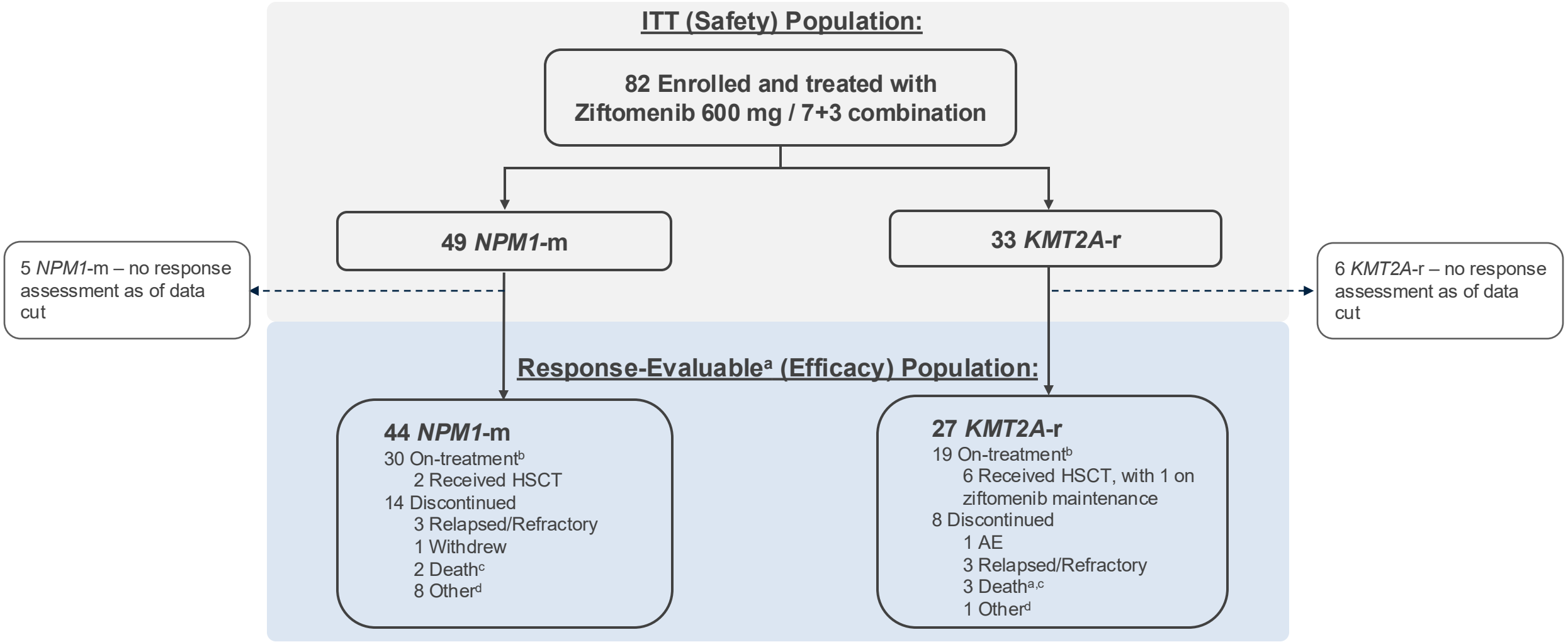
Ziftomenib / 7+3 Combination



- 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 updated safety and clinical activity in all newly diagnosed AML patients treated at the ziftomenib RP2D of 600 mg QD in combination with standard doses of 7+3 across phase 1a/b

[a]High-risk is defined as *KMT2A*-r AML, or *NPM1*-m with adverse-risk cytogenetics per ELN criteria, age ≥60 yrs and/or treatment-related AML regardless of age. [b]CR, CRh, or CRi. [c]CRc or MLFS.
AE, adverse event; CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; DLT, dose limiting toxicity; DoR, duration of remission; IC, intensive chemotherapy; MLFS, morphologic leukemia-free state; QD, once daily; ORR, objective response rate; RP2D, recommended phase 2 dose.

KOMET-007 in 1L AML: Safety & Efficacy Populations



[a]Patients who had ≥1 response assessment or who had died - one *KMT2A*-r patient had no response assessment and had died before the data cut (not evaluable). [b]Patients who had not discontinued ziftomenib as of the data cutoff date. [c]Deaths included: *NPM1*-m: ischemic enteritis (n=1), cerebral hemorrhage (n=1); *KMT2A*-r: bowel perforation (n=1), angioinvasive mucormycosis (n=1), sepsis (n=1). [d]Other reasons included: *NPM1*-m: physician decision (n=3), completed planned therapy (n=1), joint pain (n=1), planned for other maintenance study (n=2), patient decision (n=1); *KMT2A*-r: physician decision (n=1).
Data cutoff: Mar 21, 2025. AE, adverse event; ITT, intention-to-treat; HSCT, hematopoietic stem cell transplant.

Baseline Characteristics and Disposition: 1L AML (N=82)

	NPM1-m 600 mg (n=49)	*KMT2A*-r 600 mg (n=33)	All Patients 600 mg (N=82)
Median age, years (range)	60 (30–71)	43 (18–70)	56 (18–71)
Female, n (%)	25 (51)	18 (55)	43 (52)
Race, n (%)			
White	35 (71)	20 (61)	55 (67)
Non-White	14 (29)	13 (39)	27 (33)
ECOG PS 0–1, n (%)	43 (88)	31 (94)	74 (90)
Co-mutations, n (%)			
FLT3	6 (12)[a]	5 (15)[a]	11 (13)[a]
IDH1/2	13 (27)	2 (6)	15 (18)
Therapy-related AML, n (%)	2 (4)	8 (24)	10 (12)
Patients on-treatment, n (%)	35 (71)	25 (76)	60 (73)
Patients on-study[b], n (%)	47 (96)	29 (88)	76 (93)
Median follow-up, weeks (range)	24.9 (4.3–47.1)	15.7 (1.1–40.3)	18.4 (1.1–47.1)

[a]*FLT3*-ITD allelic ratio <0.05 (3 *NPM1*-m) or considered ineligible for FLT3 inhibitor (3 *NPM1*-m, 5 *KMT2A*-r).
[b]Patients on-treatment or in long-term follow-up.

Data cutoff: Mar 21, 2025.
ECOG PS, Eastern Cooperative Oncology Group performance status; ITD, internal tandem duplication.

Safety and Tolerability of Ziftomenib in Combination with 7+3 in 1L AML (N=82)

TEAEs in ≥25% of All Patients

n (%)	*NPM1*-m 600 mg (n=49)	*KMT2A*-r 600 mg (n=33)	All Patients 600 mg (N=82)
Any Grade	**46 (94)**	**31 (94)**	**77 (94)**
Febrile neutropenia	26 (53)	23 (70)	49 (60)
Diarrhea	22 (45)	17 (52)	39 (48)
Platelet count decreased	24 (49)	13 (39)	37 (45)
Pruritus	19 (39)	13 (39)	32 (39)
Nausea	18 (37)	8 (24)	26 (32)
Hypokalemia	16 (33)	10 (30)	26 (32)
Anemia	16 (33)	8 (24)	24 (29)
Stomatitis	12 (24)	12 (36)	24 (29)
Alanine aminotransferase increased	13 (27)	9 (27)	22 (27)
Constipation	15 (31)	6 (18)	21 (26)

- Ziftomenib safety profile in combination with intensive chemotherapy was similar to that reported for newly diagnosed AML patients treated with 7+3 alone[1]

Data cutoff: Mar 21, 2025.
1. Lin et al. *Blood Adv.* 2021;5(6):1719-28.
TEAE, treatment-emergent adverse event.

Safety and Tolerability of Ziftomenib in Combination with 7+3 in 1L AML (N=82)

Grade ≥3 TEAEs in ≥10% of All Patients

n (%)	*NPM1*-m 600 mg (n=49)	*KMT2A*-r 600 mg (n=33)	All Patients 600 mg (N=82)
Grade ≥3	**42 (86)**	**29 (88)**	**71 (87)**
Febrile neutropenia	25 (51)	20 (61)	45 (55)
Platelet count decreased	23 (47)	12 (36)	35 (43)
Anemia	16 (33)	8 (24)	24 (29)
Neutrophil count decreased	14 (29)	6 (18)	20 (24)
White blood cell count decreased	10 (20)	7 (21)	17 (21)
Sepsis	8 (16)	5 (15)	13 (16)
Lymphocyte count decreased	5 (10)	4 (12)	9 (11)

Grade ≥3 Ziftomenib-related Adverse Events of Interest

29 Patients (35%) had Grade ≥3 ziftomenib-related adverse events:

- Most common (≥10%) were febrile neutropenia (15%), decreased platelet count (15%), anemia (11%), and decreased neutrophil count (11%)
- 1 case of differentiation syndrome (*KMT2A*-r, Gr3), which was successfully managed
- 2 cases of investigator-assessed QTc prolongation (both *KMT2A*-r, Gr3)*

*Both patients were on other medications (posaconazole and/or piperacillin/tazobactam) at time of QT assessment.
Data cutoff: Mar 21, 2025.
QTc, QT corrected; TEAE, treatment-emergent adverse event.

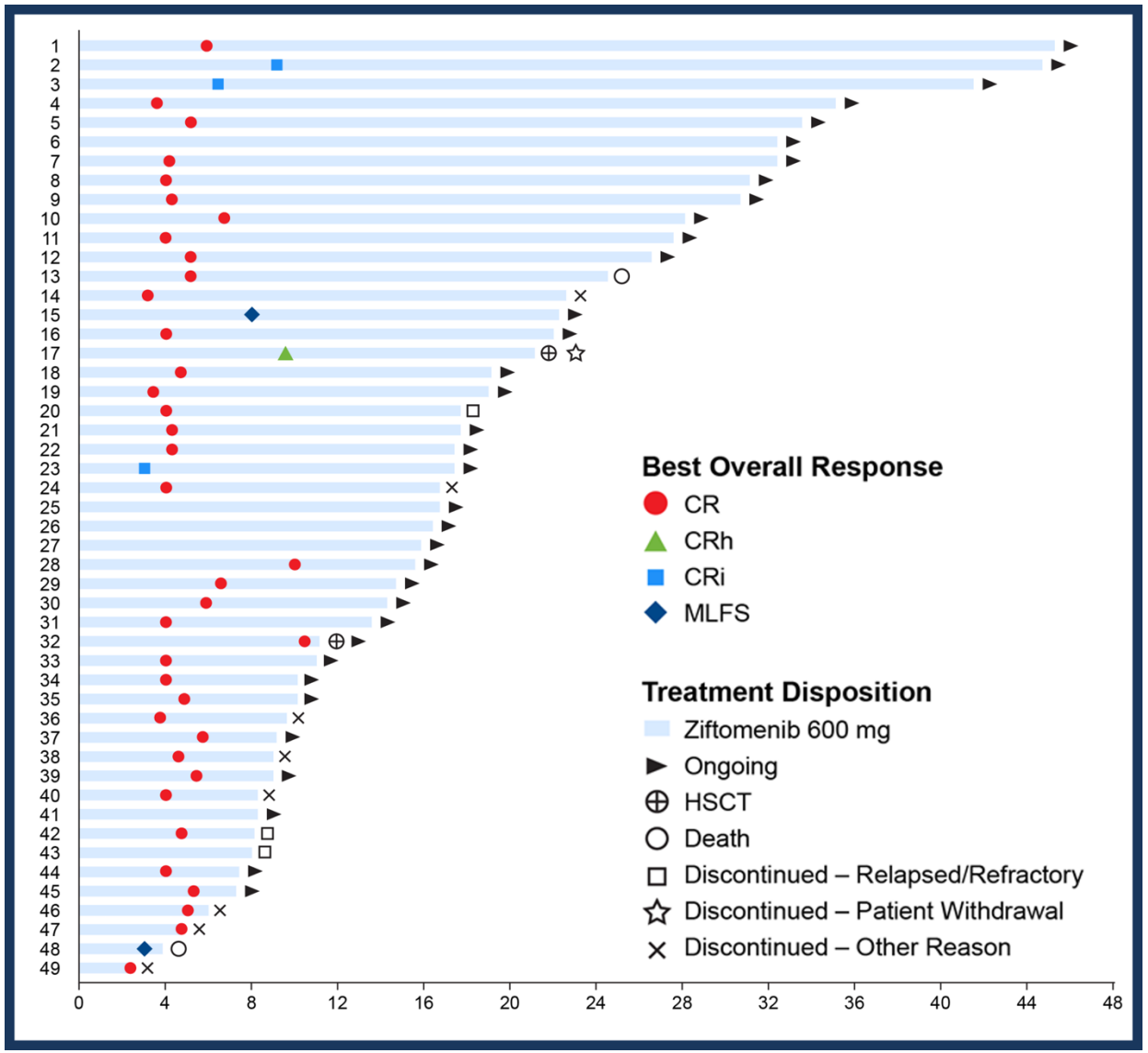
Clinical Activity in All Response-Evaluable[a] 1L Patients (N=71)

n (%)	*NPM1*-m 600 mg (n=44)	*KMT2A*-r 600 mg (n=27)	All Patients 600 mg (N=71)
CRc	**41 (93)**	**24 (89)**	**65 (92)**
ORR	**43 (98)**	**24 (89)**	**67 (94)**
CR	37 (84)	20 (74)	57 (80)
CRh	1 (2)	0	1 (1)
CRi	3 (7)	4 (15)	7 (10)
MLFS	2 (5)	0	2 (3)
PR	0	0	0
NR	1 (2)	2 (7)	3 (4)
NE	0	1 (4)	1 (1)
CR MRD-negativity, n/N (%)[b]	**24/34 (71)**	**14/16 (88)**	**38/50 (76)**
CRc MRD-negativity, n/N (%)[b]	**26/38 (68)**	**15/18 (83)**	**41/56 (73)**
Median time to CR MRD-negativity, weeks (range)	4.7 (2–17)	4.4 (3–12)	4.5 (2–17)
Median time to CRc MRD-negativity, weeks (range)	4.7 (2–17)	4.1 (3–12)	4.3 (2–17)

[a]Patients who had ≥1 response assessment or who had died.
[b]Among evaluable responders tested for MRD per local assay (NGS, RT-qPCR, FISH, flow cytometry). Preliminary central testing also shows concordance with local MRD-negative rates.

Data cutoff: Mar 21, 2025.
Per ELN 2022: CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; CRc, composite complete remission; FISH, fluorescence in situ hybridization; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NGS, next-generation sequencing; NR, no response; ORR, objective response rate; PR, partial remission; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

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

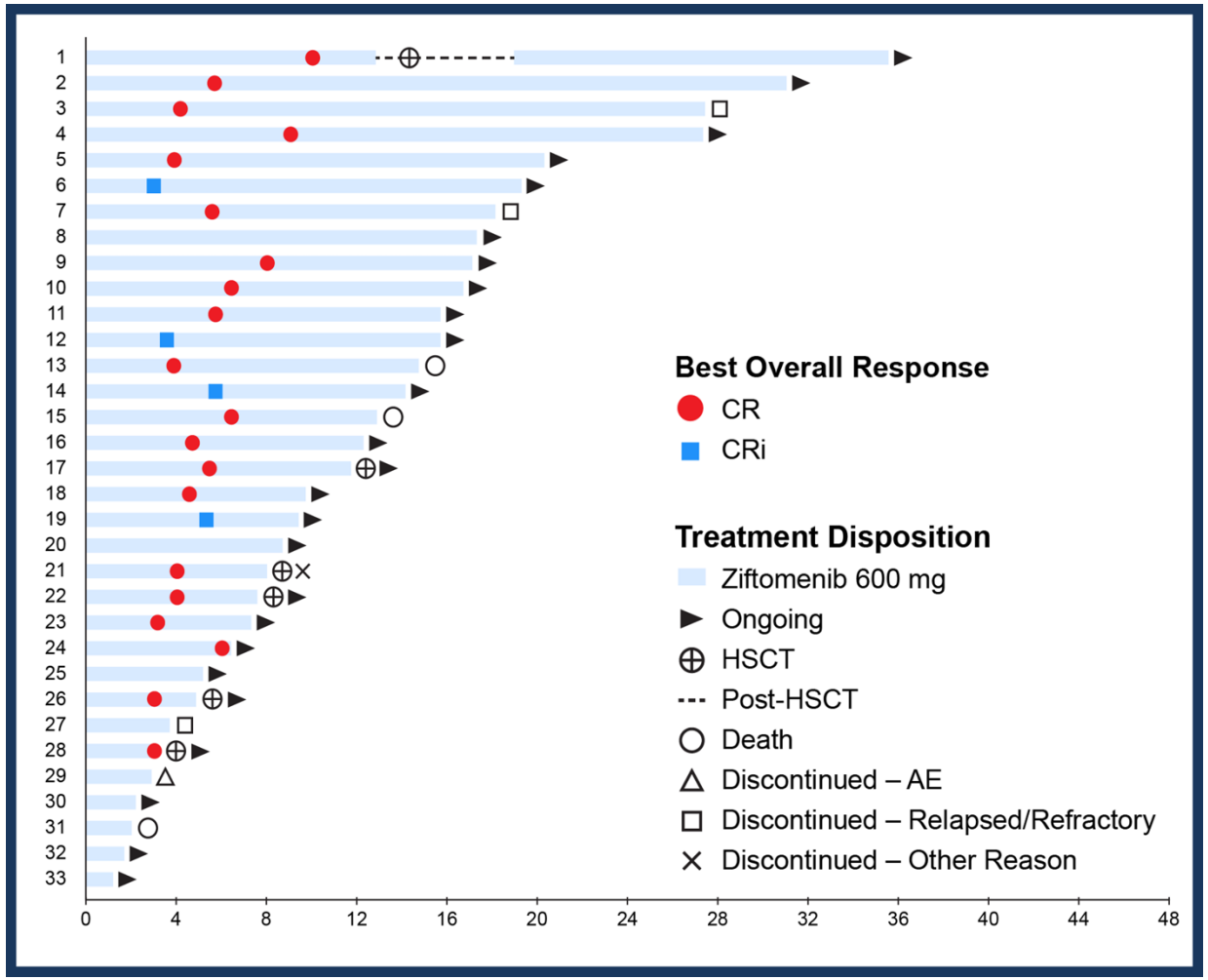


For *NPM1*-m, after a median follow-up of 24.9 weeks (range 4.3–47.1):

- Median duration of CR was **not reached**[a]
- Median OS was **not reached**[a]
- 2 *NPM1*-m patients received HSCT
- 3 Discontinuations due to relapse
- 96% (47/49) of patients remained alive and continued on-study[b]

Data cutoff: Mar 21, 2025.
[a]Among response-evaluable patients.
[b]Patients on-treatment or in long-term follow-up.
CR / CRh / CRi, complete remission with full / partial / incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphologic leukemia-free state; OS, overall survival.

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



For *KMT2A*-r, after a median follow-up of 15.7 weeks (range 1.1–40.3):

- Median duration of CR: **25.6 weeks (95% CI 8.3–not estimable)**[a] and follow-up continues
- Median OS was **not reached**[a]
- 6 *KMT2A*-r patients received HSCT. Thus far, 1 went onto ziftomenib maintenance
- 1 Discontinuation due to AE
- 88% (29/33) of patients remained alive and continued on-study[b]

Data cutoff: Mar 21, 2025.
[a]Among response-evaluable patients.
[b]Patients on-treatment or in long-term follow-up.
AE, adverse event; CR / CRi, complete remission with full / incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; OS, overall survival.

Neutrophil and Platelet Recovery in CRc Responders: 1L AML

Median days (range), Cycle 1	*NPM1*-m 600 mg (n=41)	*KMT2A*-r 600 mg (n=24)	All Patients 600 mg (n=65)
ANC ≥0.5 × 10^9/L	28 (19–66)	32 (20–63)	31 (19–66)
ANC ≥1.0 × 10^9/L	30.5 (20–88)	33 (20–63)	**32 (20–88)**
Platelets ≥50 × 10^9/L	27 (18–105)	31.5 (20–63)	27 (18–105)
Platelets ≥100 × 10^9/L	28 (20–105)	32 (20–63)	**29 (20–63)**

- Time to neutrophil and platelet recovery was comparable to that for intensive chemotherapy regimens[1,2]

Data cutoff: Mar 21, 2025.

1. Lancet JE et al. *J Clin Oncol.* 2018; 36(26):2684-92; 2. Erba HP et al. *Lancet.* 2023; 401(10388):1571-83.

ANC, absolute neutrophil count; CRc, composite complete remission.

Conclusions

- **In the ongoing KOMET-007 study, ziftomenib 600 mg QD combined with 7+3 was well tolerated, with a safety profile consistent with previous reports**
  - Low rates of ziftomenib-related cytopenia and no additional myelosuppression observed with the combination
    - Ziftomenib 600 mg QD did not delay neutrophil and platelet count recovery
  - 1 Case of Gr3 differentiation syndrome (*KMT2A*-r), which was successfully managed

- **Robust clinical activity with deep responses was demonstrated in newly diagnosed *NPM1*-m and *KMT2A*-r AML**
  - CRc: 93% for *NPM1*-m, 89% for *KMT2A*-r patients
    - CRc MRD negativity: 68% for *NPM1*-m at median of 4.7 weeks, 83% for *KMT2A*-r at median of 4.1 weeks
  - 96% (47/49) of *NPM1*-m and 88% (29/33) *KMT2A*-r patients remained alive and continued on-study (median follow-up of 25 and 16 weeks, respectively)

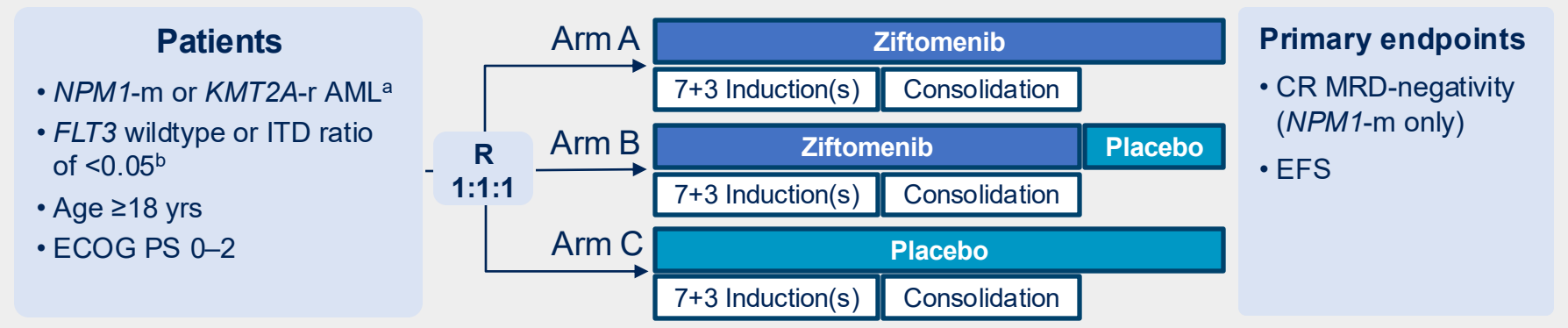
- **Taken together, these data support the phase 3 advancement of ziftomenib combination in newly diagnosed *NPM1*-m and *KMT2A*-r AML (KOMET-017)**

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 Zeidan AM et al. EHA 2025 Abstract #PB2573)

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

- **The patients, their families, and their caregivers**
- **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 Oxford PharmaGenesis, Inc., with funding from Kura Oncology, Inc.

Presentation can be accessed through this Quick Response (QR) code.