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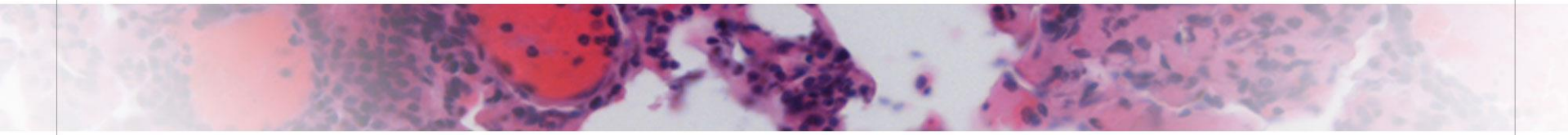

# Update on a Phase 1/2 First-in-Human Study of the Menin-KMT2A (MLL) Inhibitor Ziftomenib (KO-539) in Patients with Relapsed or Refractory Acute Myeloid Leukemia


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# *NPM1*-m and *KMT2A*(*MLL*)-r AML Represent a Significant Unmet Need No FDA-Approved Targeted Therapies Exist Today

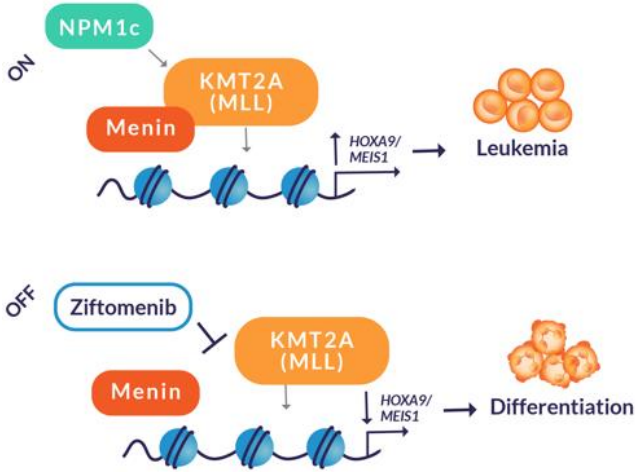
## *NPM1*-mutant AML

~30% AML

~**6,000** new cases annually in U.S.[1]

Adult patients with *NPM1*-m and select co-mutations and/or R/R disease are associated with poor prognosis[2]

**5-year Overall Survival ~50%**[3]



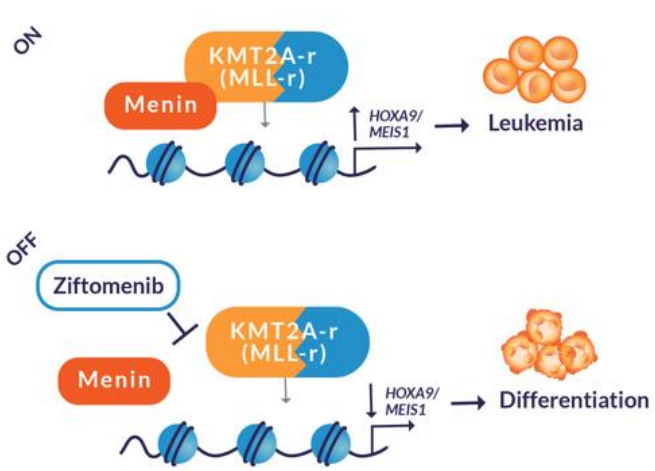

## *KMT2A*-rearranged AML

~5-10% AML

~**1,000-2,000** new cases annually in U.S.[1]

Adult patients with *KMT2A*-r have poor prognosis with high rates of resistance and relapse following SoC[4-5]

**5-year Overall Survival <20%**[4]



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# KOMET-001 Phase 1a Clinical Trial of Ziftomenib in Patients with Relapsed or Refractory (R/R) AML

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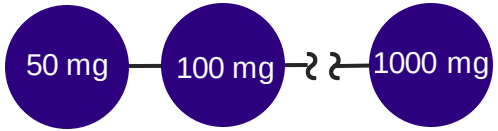
## Phase 1a Dose Escalation




## Phase 1b Validation Cohorts

Cohort 1: 200 mg

Cohort 2: 600 mg

## Phase 1b Expansion

Expansion of 600 mg

## OBJECTIVES

**Phase 1a**

Dose escalation in all-comer patients to establish maximum tolerated dose and/or RP2D

- Safety and tolerability
- Pharmacokinetics
- Early evidence of antitumor activity

**Phase 1b Validation Cohorts**

Enroll 2 genetically enriched cohorts to determine the optimal RP2D in line with FDA's Project Optimus

- Safety and tolerability
- Pharmacokinetics
- Antitumor efficacy

**Phase 1b Expansion**

Continue enrollment of phase 1b validation cohort(s) meeting go/no-go criteria

- Safety and tolerability
- Pharmacokinetics
- Antitumor efficacy

# Phase 1a Dose Escalation – Demographics

| Demographics | All Patients (N = 30) |
|---|---|
| Median age - n (Min, Max) | 65.5 (22, 85) |
| Male – n (%) | 17 (56.7) |
| ECOG PS 1 – n (%) | 19 (63.3) |
| ECOG PS 2 – n (%) | 6 (20.0) |
| *KMT2A*-r – n (%) | 10 (33.3) |
| *NPM1*-m – n (%) | 4 (13.3) |
| Non *KMT2A*-r/*NPM1*-m – n (%) | 16 (53.3) |
| Median no. of prior therapies - n (Min, Max) | 3.5 (1, 9) |
| Prior venetoclax – n (%) | 22 (73.3) |
| Prior SCT – n (%) | 7 (23.3) |

# Phase 1a Dose Escalation – Safety

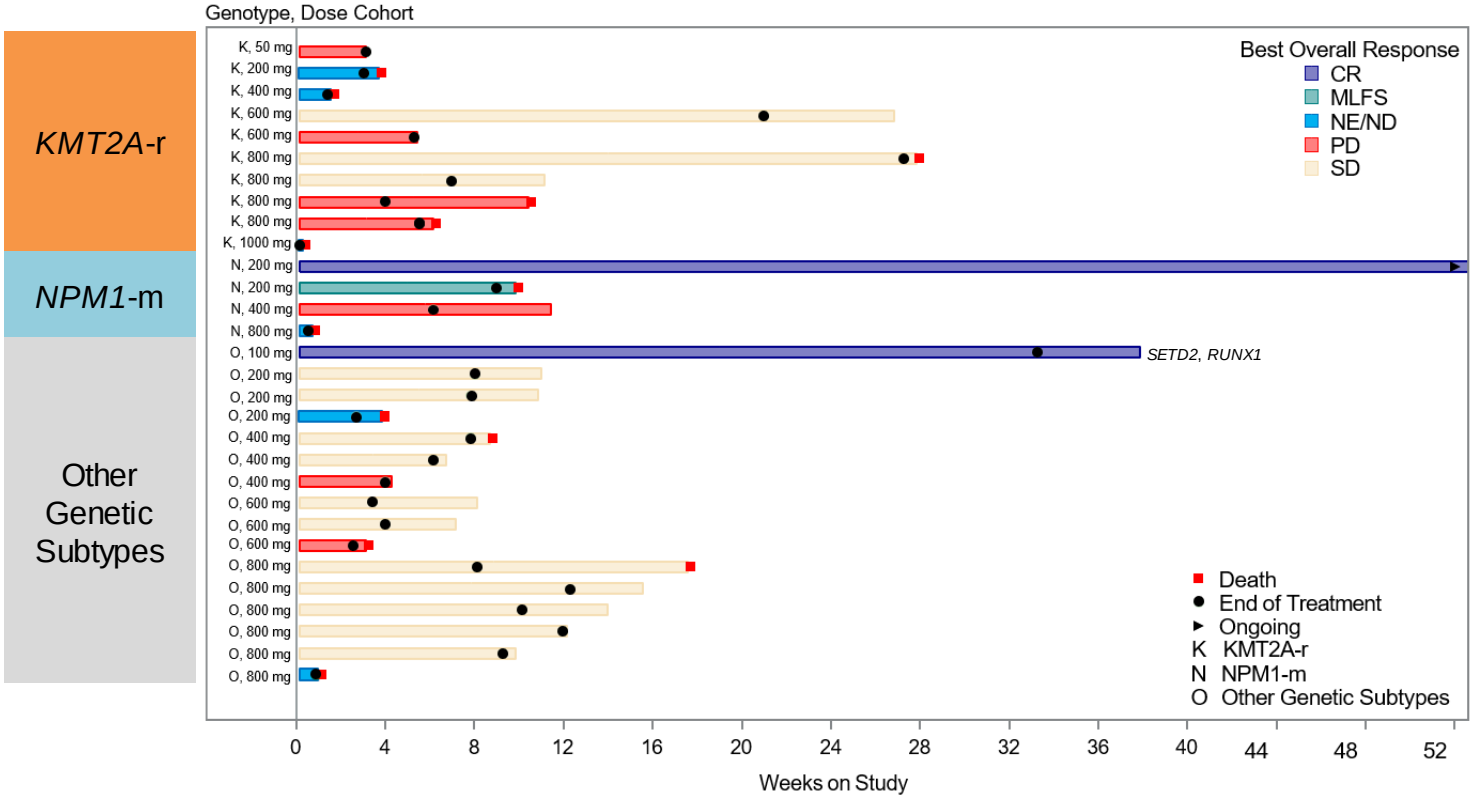
| ≥Gr3 TEAEs (All Causality) Preferred Term | 50 mg (N = 1) n (%) | 100 mg (N = 1) n (%) | 200 mg (N = 6) n (%) | 400 mg (N = 5) n (%) | 600 mg (N = 5) n (%) | 800 mg (N = 11) n (%) | 1000 mg (N = 1) n (%) |
|---|---|---|---|---|---|---|---|
| Anemia | 0 | 0 | 2 (33.3) | 1 (20.0) | 3 (60.0) | 2 (18.2) | 0 |
| Pneumonia | 1 (100.0) | 0 | 2 (33.3) | 1 (20.0) | 0 | 3 (27.3) | 0 |
| Thrombocytopenia | 0 | 0 | 1 (16.7) | 1 (20.0) | 3 (60.0) | 0 | 0 |
| Neutropenia | 0 | 1 (100.0) | 1 (16.7) | 0 | 0 | 3 (27.3) | 0 |
| Febrile neutropenia | 0 | 0 | 0 | 1 (20.0) | 1 (20.0) | 1 (9.1) | 0 |
| Decreased appetite | 0 | 0 | 2 (33.3) | 0 | 0 | 1 (9.1) | 0 |

No drug-induced QT/QTc prolongation reported

Two DLTs were reported:

- 400 mg cohort (pneumonitis, post-aspiration pneumonia)
- 1000 mg cohort (differentiation syndrome)
    - Per protocol, the DLT in first patient at 1000 mg resulted in de-escalation to 800 mg

# Ziftomenib Demonstrates Encouraging Early Clinical Activity in the Phase 1a, All Comer Population



# KOMET-001 Phase 1b Clinical Trial of Ziftomenib in Patients with Relapsed or Refractory (R/R) AML

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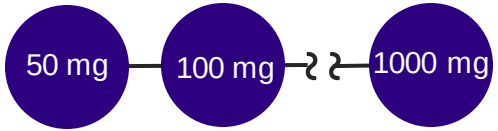
## Phase 1a Dose Escalation




## Phase 1b Validation Cohorts

Cohort 1: 200 mg

Cohort 2: 600 mg

## Phase 1b Expansion

Expansion of 600 mg

## OBJECTIVES

**Dose escalation in all-comer patients to establish maximum tolerated dose and/or RP2D**

- Safety and tolerability
- Pharmacokinetics
- Early evidence of antitumor activity

**Enroll 2 genetically enriched cohorts to determine the optimal RP2D in line with FDA's Project Optimus**

- Safety and tolerability
- Pharmacokinetics
- Antitumor efficacy

**Continue enrollment of phase 1b validation cohort(s) meeting go/no-go criteria**

- Safety and tolerability
- Pharmacokinetics
- Antitumor efficacy

# Phase 1b Baseline Characteristics, Demographics, and Disposition

| Demographics | 200 mg (N = 17) | 600 mg (N = 36) |
|---|---|---|
| Median age - n (Min, Max) | 49.0 (30, 79) | 54.5 (18, 86) |
| Male – n (%) | 7 (41.2) | 15 (41.7) |
| ECOG PS 1 – n (%) | 7 (41.2) | 22 (61.1) |
| *KMT2A*-r – n (%) | 13 (76.5) | 16 (44.4) |
| *NPM1*-m – n (%) | 4 (23.5) | 20 (55.6) |
| Median number of prior therapies - n (Min, Max) | 3.0 (1,11) | 3.0 (1,7) |
| Prior venetoclax – n (%) | 11 (64.7) | 22 (61.1) |
| Prior SCT – n (%) | 5 (29.4) | 8 (22.2) |
| *FLT3** – n (%) | 3 (17.6) (100% FLT3-ITD) | 7 (19.4) (57% FLT3-ITD) |
| *IDH1/2** – n (%) | 1 (5.9) | 7 (19.4) |

*Patient could have both *FLT3* and *IDH1/2*, and be counted in both co-mutation categories

| Disposition | 200 mg (N = 17) n (%) | 600 mg (N = 36) n (%) |
|---|---|---|
| Patients on Treatment | 0 | 10 (27.8) |
| Patients in Follow-Up | 1 (5.9) | 17 (47.2) |
| Reason for Treatment Discontinuation | | |
| Adverse Event** | 2 (11.8) | 4 (11.1) |
| Death | 4 (23.5) | 3 (8.3) |
| Disease progression (including Clinical) | 5 (29.4) | 11 (30.6) |
| Patients off Study | 16 (94.1) | 19 (52.8) |
| Reason for Study Discontinuation | | |
| Death | 14 (82.4) | 14 (38.9) |

Additional reasons for Treatment D/C include PI Decision, Receipt of Alt Tx, and Other.
Additional Reasons for Study D/C include Withdrawal by Subject and Other.
****No events were considered treatment related**

# Ziftomenib Demonstrates Encouraging Safety Profile and Tolerability in Phase 1b

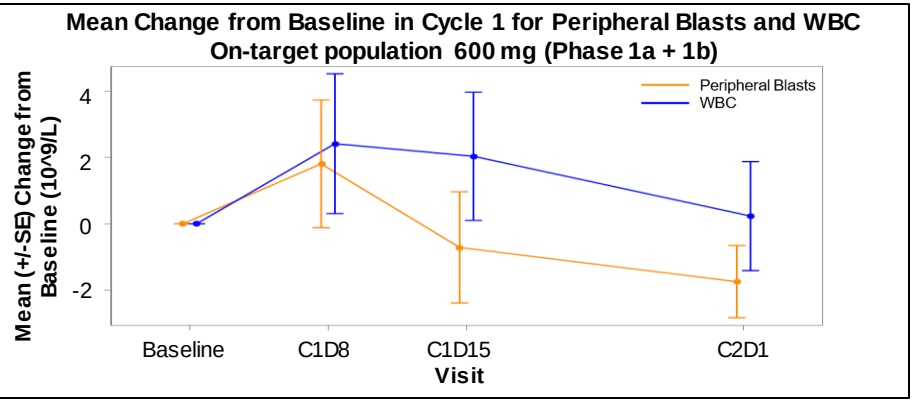
| ≥Gr 3 TEAEs Occurring in >10% Participants (Regardless of Causal Assessment) | 200 mg | 600 mg |
|---|---|---|
| *NPM1*-m | (N = 4) | (N = 20) |
| | 0 | 0 |
| *KMT2A*-r | (N = 13) | (N = 16) |
| Differentiation Syndrome | 4 (30.8) | 4 (25.0) |
| Febrile Neutropenia | 0 | 2 (12.5) |

# Characterization of Differentiation Syndrome (DS) with Ziftomenib

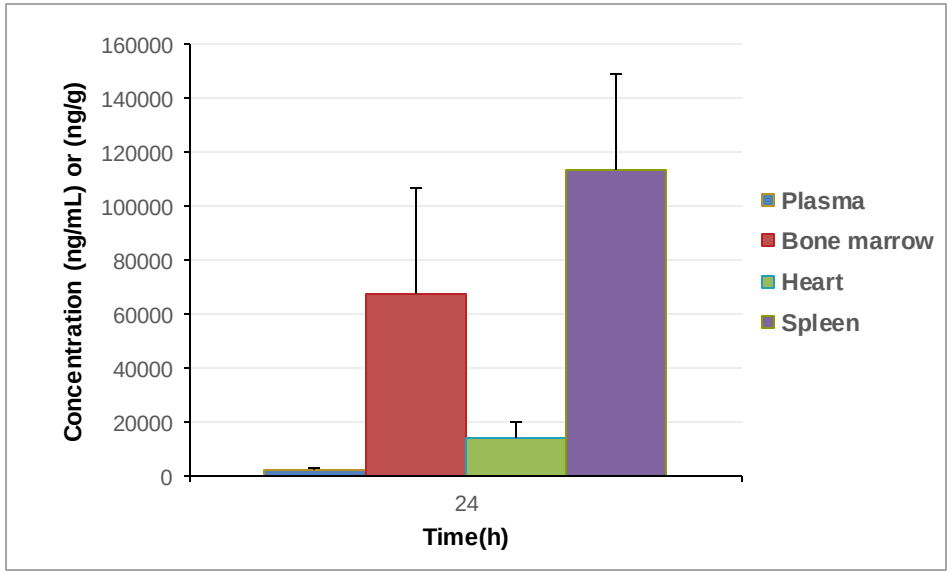
## Any Grade and ≥G3 DS in P1a/b population†

| | 200 mg N = 17, n (%) | 600 mg N = 36, n (%) |
|---|---|---|
| *NPM1*-m (all grades) | 0/4 (0) | 4/20 (20.0) |
| ≥ Gr3 | 0/4 (0) | 1/20 (5.0) |
| *KMT2A*-r (all grades) | 5/13 (38.5) | 6/16 (37.5) |
| ≥ Gr3 | 4/13 (30.8) | 4/16 (25.0) |

† Patients with DS event at 600 mg
ORR rate: 75% for *NPM1*-m; 16.7% for *KMT2A*-r




## Ziftomenib Accumulates in Tissues in Mice




Trough levels prior to dosing on Day 8 (repeat dosing)
Ziftomenib plasma protein binding >99%

# Ziftomenib Demonstrates Encouraging Antileukemic Activity at 600 mg

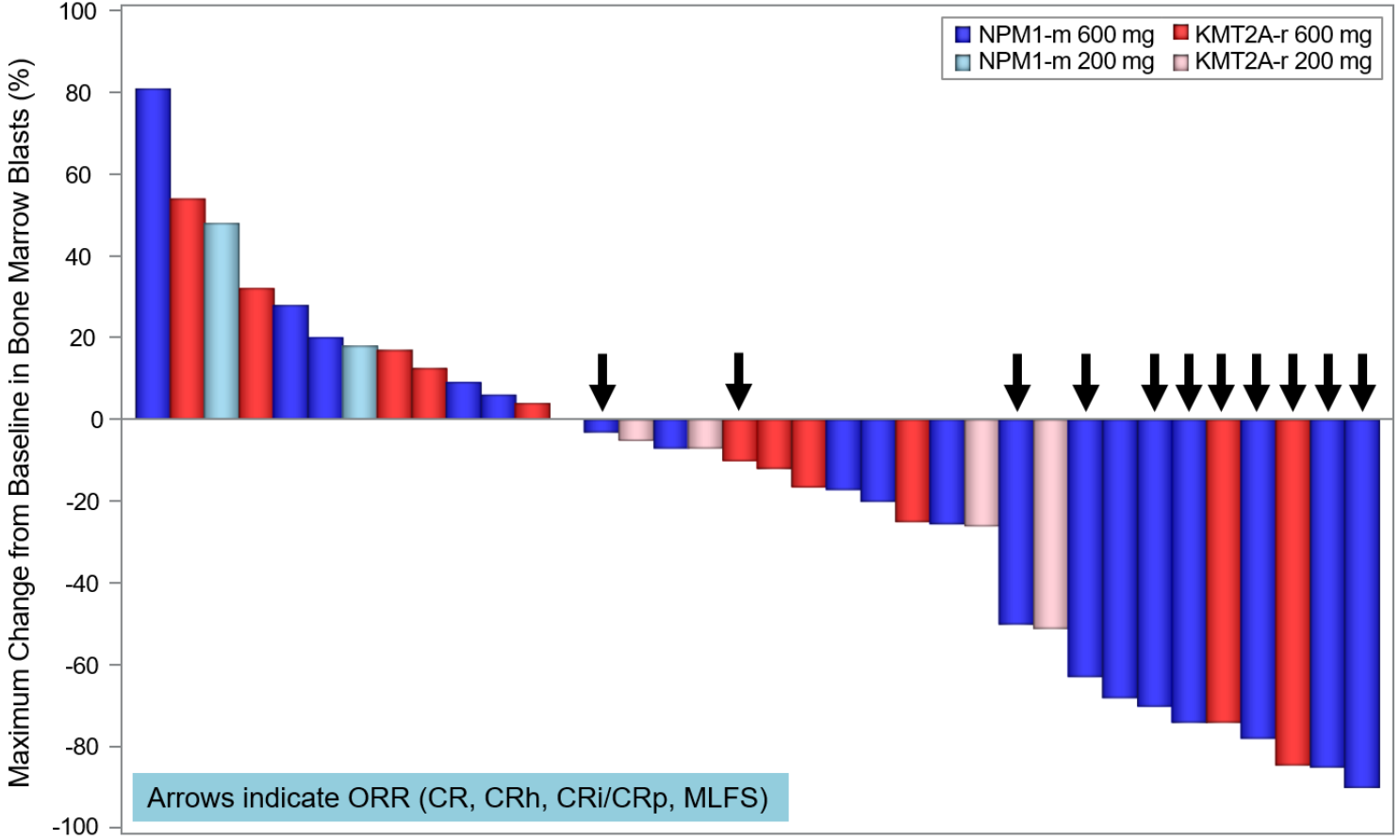
| Best Overall Response | 200 mg | 600 mg |
|---|---|---|
| ***NPM1*-m Phase 1a + 1b** | **(n=6)** | **(n=20)** |
| **CR** | **1 (16.7)** | **6 (30.0)** |
| CR/CRh | 1 (16.7) | 6 (30.0) |
| CRc | 1 (16.7) | 7 (35.0) |
| MRD negativity | 1 (100.0) | 3 (42.9)[1] |
| ORR | 2 (33.3) | 8 (40.0) |
| ***KMT2A*-r Phase 1a + 1b** | **(n=14)** | **(n=18)** |
| CR/CRh | 0 | 1 (5.6) |
| CRc | 0 | 2 (11.1) |
| MRD negativity | 0 | 2 (100.0) |
| ORR | 0 | 3 (16.7) |

- 2 pts had concurrent *IDH1/2*
- 2 pts had both *IDH1/2* and *FLT3-ITD/TKD*

*Of IDH*1/2 co-mutants (7), 57% experienced a CR

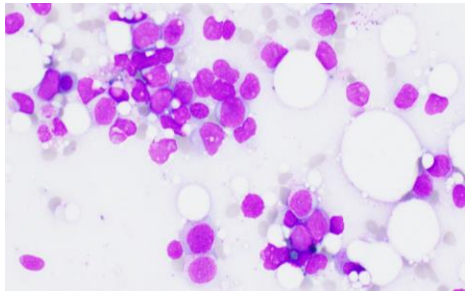
[1] MRD was assessed for 5/7 CRc patients; 3 of those 5 patients (60%) tested were MRD negative
CRc includes CR, CRh, CRi, CRp
ORR includes CR, CRh, CRi, CRp, MLFS

# Decreasing Bone Marrow Blast Counts Consistently Reported

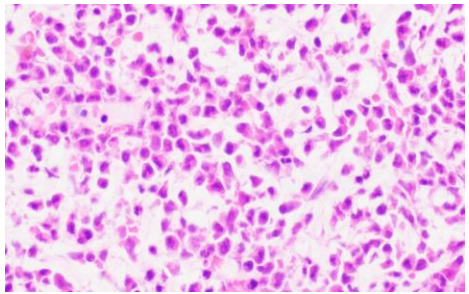


# Ziftomenib Causes Differentiation of *NPM1*-mutant Leukemia

| **Case Example: 61 yo male with *NPM1*-m, *FLT3-ITD*, and *IDH2* AML**<br>Baseline bone marrow blasts: 75% | |
|---|---|
| Prior therapies | 7+3, Midostaurin, HiDAC, gilteritinib |
| Initiated ziftomenib at 600 mg | |
| DS during C1 | Bone pain, ↓BP<br>WBC ↑58K |
| Response | • MLFS after Cycle 1<br>• CR after Cycle 3 |



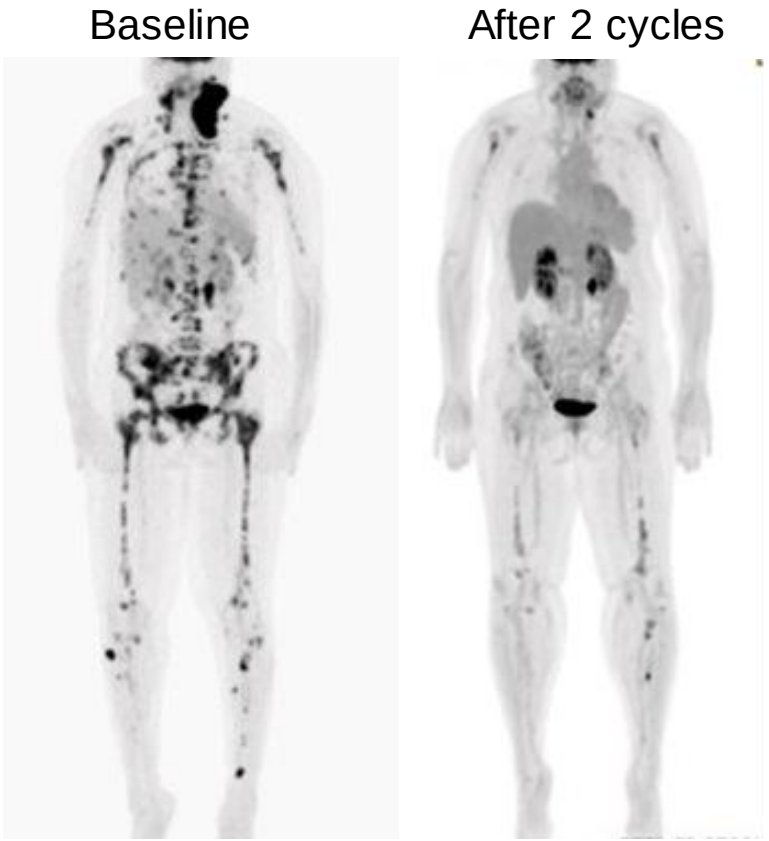
**Baseline Bone Marrow**
Cellular BM (40%) with 75% blasts consistent with relapsed AML



**Cycle 1 Day 28 ziftomenib**
Hypercellular BM (>95%) with striking granulocytic hyperplasia and <1% blasts

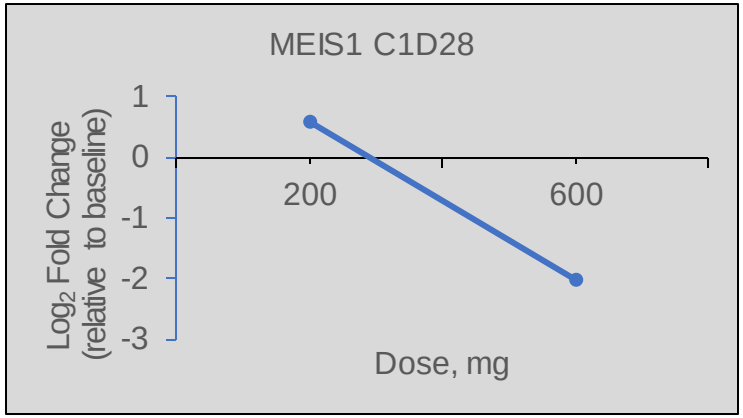
# Clinical Benefit: An Example of a *KMT2A*-r Non-Responder

| **Case Example: 47 yo female with *KMT2A-r, TERT,* and *BRAF* AML**<br>Baseline bone marrow blasts: 52% | |
|---|---|
| Prior therapies | ddAC + paclitaxel, CPX-35, SCT, Aza, FLAG Ida-ven, DLI, RT - gums |
| Initiated ziftomenib at 200 mg | |
| DS during C1 | Muscle and EMD pain, ↑temp, ↓BP, WBC ↑ 5.2 |
| Response | • Bone marrow blasts 2% end of Cycle 2<br>• Best overall response of SD due to residual EMD |



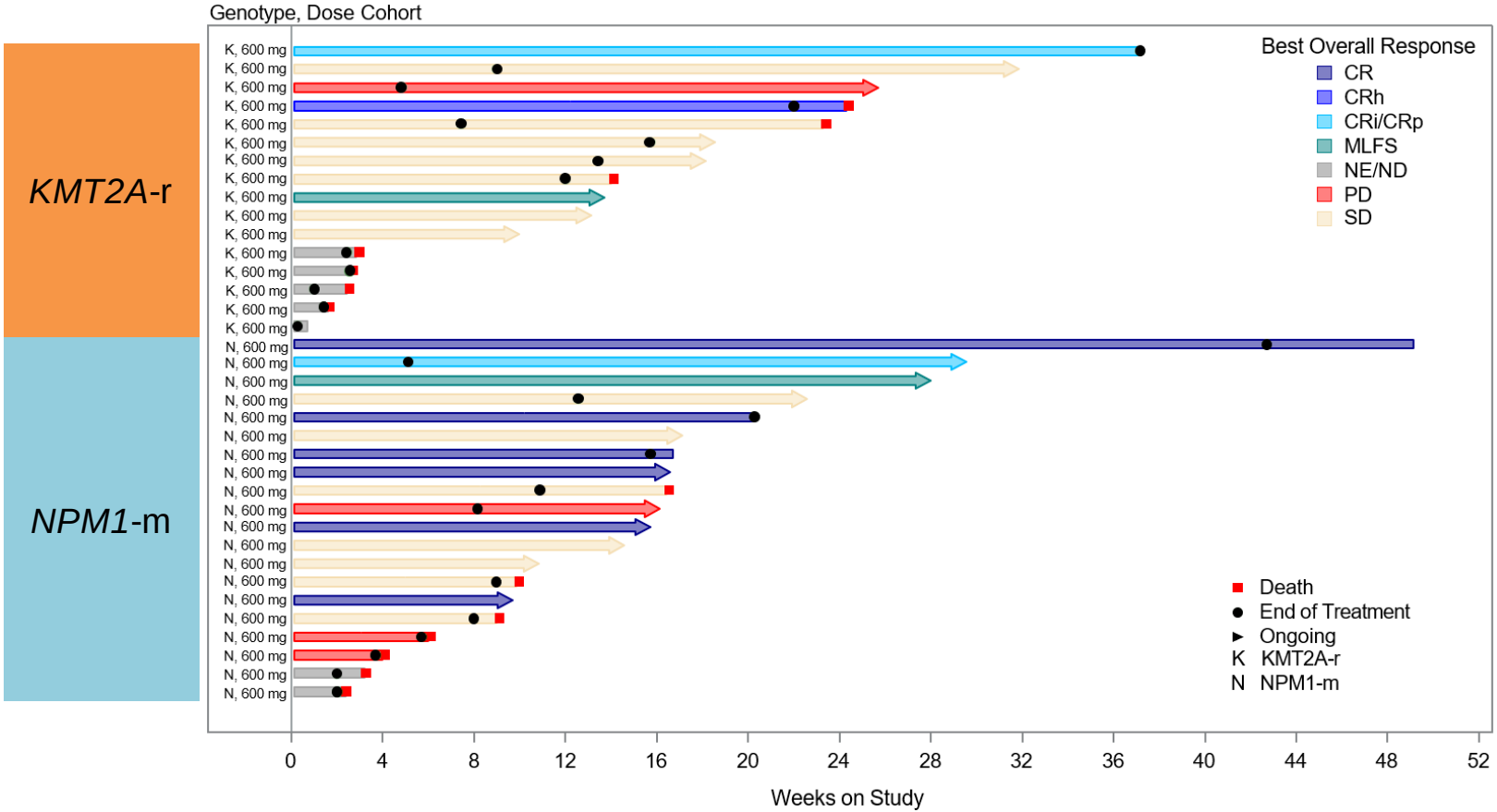
# Pharmacokinetic/Pharmacodynamic Analyses Support 600 mg Dosing

- Dose-dependent increases in exposure support 600 mg vs 200 mg dose




- *MEIS1* expression at C1D28 was 6-fold lower in patients dosed at 600 mg vs 200 mg
  - *HOXA9*, *HOXA10*, *MEF2C* were also 2- to 6-fold lower relative to baseline
- Target gene expression at 800 mg did not provide evidence of further knockdown

# Ziftomenib 600 mg Demonstrates Optimal Clinical Benefit



# Acknowledgements


- The patients, their families, and caregivers
- The study investigators and their study teams
- The study is sponsored by Kura Oncology, Inc.

# Conclusions

**Ziftomenib demonstrates an encouraging safety profile and tolerability**

- Reported events most often consistent with features and manifestations of underlying disease
  - No evidence of drug-induced QTc prolongation
  - Differentiation syndrome, an on-target effect, manageable with mitigation strategy

**Clinical activity of Ziftomenib monotherapy is optimal at the 600 mg dose**

- Favorable *NPM1*-m benefit/risk balance with pronounced activity and 30% CR rate (n=20)
- High levels of ziftomenib tissue penetration likely drive clearance of extramedullary disease

**Monotherapy data supportive of combination strategies**

- No predicted adverse drug-drug interactions
- Optimization of *KMT2A*-r benefit/risk planned via rational combination strategies, to maximize patients' time on treatment
- Oral, QD dosing allows for convenient administration and combination with standards of care