Activity, tolerability and resistance profile of the menin inhibitor ziftomenib in adults with relapsed or refractory *NPM1*-mutated AML

Amir T. Fathi[1], Eunice S. Wang[2], Ghayas C. Issa[3], Jessica K. Altman[4], Pau Montesinos[5], Stephane DeBotton[6], Roland Walter[7], Kristen Pettit[8], Stephen Strickland[9], Mrinal Patnaik[10], Marina Kremyanskaya[11], Maria R. Baer[12], James Foran[13], Gary Schiller[14], Lionel Ades[15], Mael Heiblig[16], Celine Berthon[17], Jolanta Grembecka[8], Tomasz Cierpicki[8], Bradley Clegg[8], Pierre Peterlin[18], Eduardo Rodriguez Arboli[19], Olga Salamero Garcia[20], Cristina Papayannidis[21], Kun Nie[22], Julie Mackey[22], Marilyn Tabachri[22], Daniel Corum[22], Mollie Leoni[22], Stephen Dale[22], Harry P. Erba[23]

[1]Massachusetts General Hospital, Boston, MA; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [3]MD Anderson Cancer Center, Houston, TX; [4]Northwestern University-Robert H. Lurie Comprehensive Cancer Center, Chicago IL; [5]Hospital Universitari i Politècnic La Fe, Valencia, Spain; [6]Institut Gustave Roussy Service d'Hématologie Clinique, Paris, France; [7]Fred Hutchinson Cancer Research Center, Seattle, WA; [8]University of Michigan, Ann Arbor, MI; [9]Sarah Cannon Research Institute, Nashville, TN; [10]Mayo Clinic-Minnesota, Rochester, MN; [11]Mount Sinai-PRIME, New York, NY; [12]University of Maryland-Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; [13]Mayo Clinic-Florida, Jacksonville, FL; [14]UCLA Medical Center, Los Angeles, CA; [15]Hospital Saint-Louis, Paris, France; [16]Centre Hospitalier Lyon Sud, Lyon, France; [17]Centre Hospitalo-Universitaire Lille, Lille, France; [18]CHU de Nantes-Hôtel-Dieu, Nantes, France; [19]Hospitales Universitarios Virgen del Rocío, Sevilla, Spain; [20]Hospital Universitari Vall d'Hebron-Institut de Recerca (VHIR), Barcelona, Spain; [21]IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy; [22]Kura Oncology, Inc., San Diego, CA; [23]Duke Cancer Institute, Durham, NC

Disclosures

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NPM1-Mutant AML is a Large Genetic Subset[1] with a High Unmet Need

NPM1-mutant AML

~6,000 new cases annually in the U.S.[2]

5-year Overall Survival ~50%[3]

Adult patients with *NPM1*-mutant AML and select co-mutations and/or relapsed/refractory disease have a poor prognosis[1]

Median overall survival is suboptimal[4]

Second Line — 7.8 mo.

Third Line — 5.3 mo.

Fourth Line — 3.5 mo.

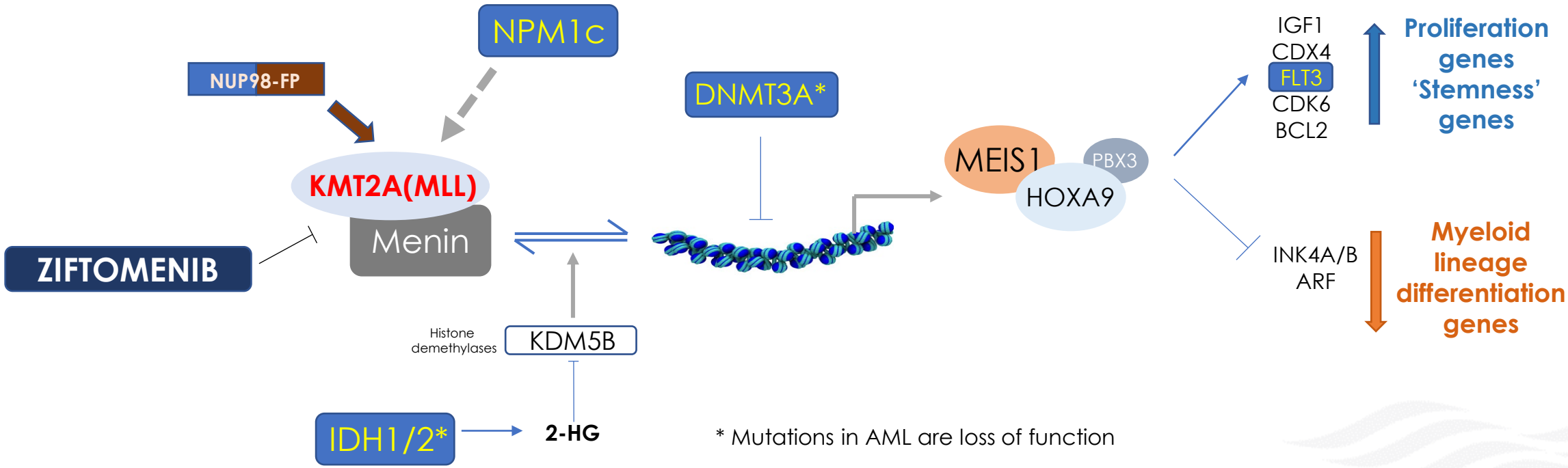
No FDA-approved *NPM1*-m specific targeted therapies exist today in AML

AML, acute myeloid leukemia; *NPM1*-m, nucleophosmin1 mutant; OS, overall survival; R/R, relapsed/refractory.

1. Döhner et al. *Blood* 2017;129(4):424-47; 2. SEER statistics for AML in the US, accessed April 2020; 3. Angenendt L, et al. *J Clin Oncol* 2019;37(29):2632-42; 4. Issa G, et al. *Blood Adv* 2023;7(6):933-42.

Ziftomenib Targets the Menin-KMT2A Pathway, a Foundational Target in AML

- *NPM1*-m and *KMT2A*-r drive overexpression of *HOXA9/MEIS1* genes, critical for transformation to AML
- KMT2A(MLL) sits upstream from major AML targets (*i.e.*, *FLT3*, *IDH1/2*, *DNMT3A*)
- KMT2A(MLL)-dependent genes contribute to therapeutic resistance and relapse to current therapies
- Menin inhibition downregulates HOXA9/MEIS1, leading to differentiation of leukemic blasts



KMT2A = lysine[K]-specific methyltransferase 2; MEIS1 = meis homeobox 1; MLL-mixed lineage leukemia; NPM1-c = cytoplasmic localization of nucleophosmin-1

1. Lu et al. *Cancer Cell* 2016;30(1):92–107; 2. Ferreira et al. *Oncogene* 2016;35(23):3079-82; 3. Jeong et al. *Nat. Genet* 2014;46(1):17-23; 4. Wang et al. *Blood* 2005;106(1):254–64; 5. Chowdhury et al. *EMBO Rep* 2011;12(5):463-9; 6. Schmidt et al. *Leukemia* 2019;33(7):1608-19; 7. Xu et al. *Cancer Cell* 2016;30(6):863-78; 8. Collins & Hess. *Curr Opin Hematol* 2016;23(4):354-61; 9. Brunetti et al. *Cancer Cell* 2018; 34(3):499–512.

KOMET-001 Phase 1/2 Study of Ziftomenib in R/R AML

Phase 1a Dose Escalation	Phase 1b Validation Cohorts	Phase 1b Expansion	Phase 2 Registration-Enabling
Completed	***Completed***	***Completed***	***Ongoing***
50 mg QD — 100 mg QD — 1000 mg QD	**Cohort 1: 200 mg QD** **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
• Pharmacokinetics
• Early evidence of clinical activity
	• Safety and tolerability
	• Pharmacokinetics
	• Clinical activity
		Continue enrollment of Phase 1b validation cohort(s) consistent with FDA's Project Optimus
		• Safety and tolerability
		• Pharmacokinetics
		• Clinical activity
			• Primary endpoint:
			  • CR/CRh
			• Secondary endpoints:
			  • Duration of CR/CRh
			  • Transfusion independence
			  • CR/CRh MRD negativity
			  • Adverse events

CR, complete remission; CRh, complete remission with partial hematological recovery; FDA, United States Food and Drug Administration; MRD, measurable residual disease; R/R, relapsed/refractory; RP2D, recommended phase 2 dose.

Baseline Patient Characteristics

Demographics	600 mg, n = 20
Age, median (min, max), y	**70.5 (22, 86)**
Male, n (%)	6 (30)
ECOG PS 0, n (%)	3 (15)
PS 1	14 (70)
PS 2	3 (15)
Number of prior therapies, median (min, max)	**3 (1,10)**
Prior venetoclax, n (%)	13 (65)
Prior SCT, n (%)	4 (20)
Co-mutations, n (%)	
FLT3 [1]	6 (30)
IDH1/2 [1]	8 (40)
Co-mutations with both *FLT3* and *IDH1/2*	4 (20)

Disposition	600 mg, n = 20
Patients in follow-up, n (%)	**7 (35)**
Reason for treatment discontinuation, n (%)	
Adverse event (not study drug-related) [2]	5 (25)
Death	1 (5)
Disease progression (including clinical)	9 (45)
All other reasons [3]	5 (25)
Patients off study, n (%)	**13 (65)**
Reason for study discontinuation, n (%)	
Death	13 (65)

[1]Patient could have both *FLT3* and *IDH1/2* and be counted in both co-mutation categories.
[2]These adverse events leading to discontinuation were not considered study drug related.
[3]Additional reasons for treatment discontinuation include physician decision, receipt of alternative anticancer treatment, withdrawal by subject, and other.

12-April-2023 Data Cut

Phase 1b Safety and Tolerability of Ziftomenib in R/R *NPM1*-m AML

≥ 20% Treatment-Emergent Adverse Events, n (%)	*NPM1*-m, n = 20
Patients with TEAEs (All Grades)	**19 (95)**
Diarrhea	9 (45)
Hypokalemia	8 (40)
Nausea	6 (30)
Anemia	6 (30)
Back pain	6 (30)
Epistaxis	5 (25)
Patients with TEAEs (≥ Grade 3)	**17 (85)**
Anemia	5 (25)
Thrombocytopenia	4 (20)

≥ 20% Treatment-Related Adverse Events, n (%)	*NPM1*-m, n = 20
Patients with TRAEs (All Grades)	**12 (60)**
Nausea	4 (20)
Differentiation Syndrome	4 (20)
Patients with TRAEs (≥Grade 3)	**6 (30)**
N/A	

- **No reports of drug-induced QTc prolongation**
- **1 report of grade 3 differentiation syndrome**
  - **manageable with mitigation strategy**
- **Other reports of DS Grade ≤ 2**

Adverse event are listed by preferred term. TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

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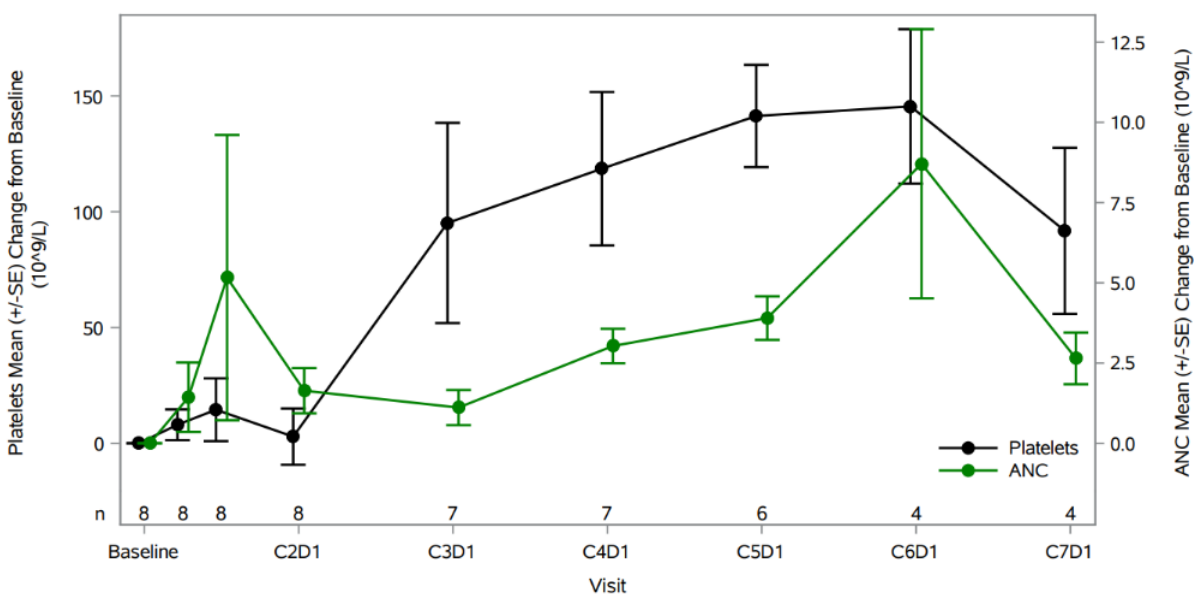
Ziftomenib Demonstrates Encouraging Clinical Activity

Best Overall Response	n (%)
Complete remission rate (CR)	**7 (35)**
CRc rate (CR+CRh+CRi)	8 (40)
Overall response rate (CR+CRh+CRi+MLFS)	9 (45)
CR	7 (35)
CRh	0
CRi	1 (5)
MLFS	1 (5)

33% CR co-*FLT3*m (N=6)
50% CR co-*IDH*m (N=8)

Mean Change in Platelets and ANC for CRc up to C7D1



- Co-mutations in *FLT3* and *IDH1/2* did not affect chances of response to single agent ziftomenib
- 1 patient achieved CRi, proceeded to HSCT, and achieved and remains in CR
- Median time to first response: 51 days

HSCT, hematopoietic stem cell transplantation; MLFS, morphological leukemia-free state

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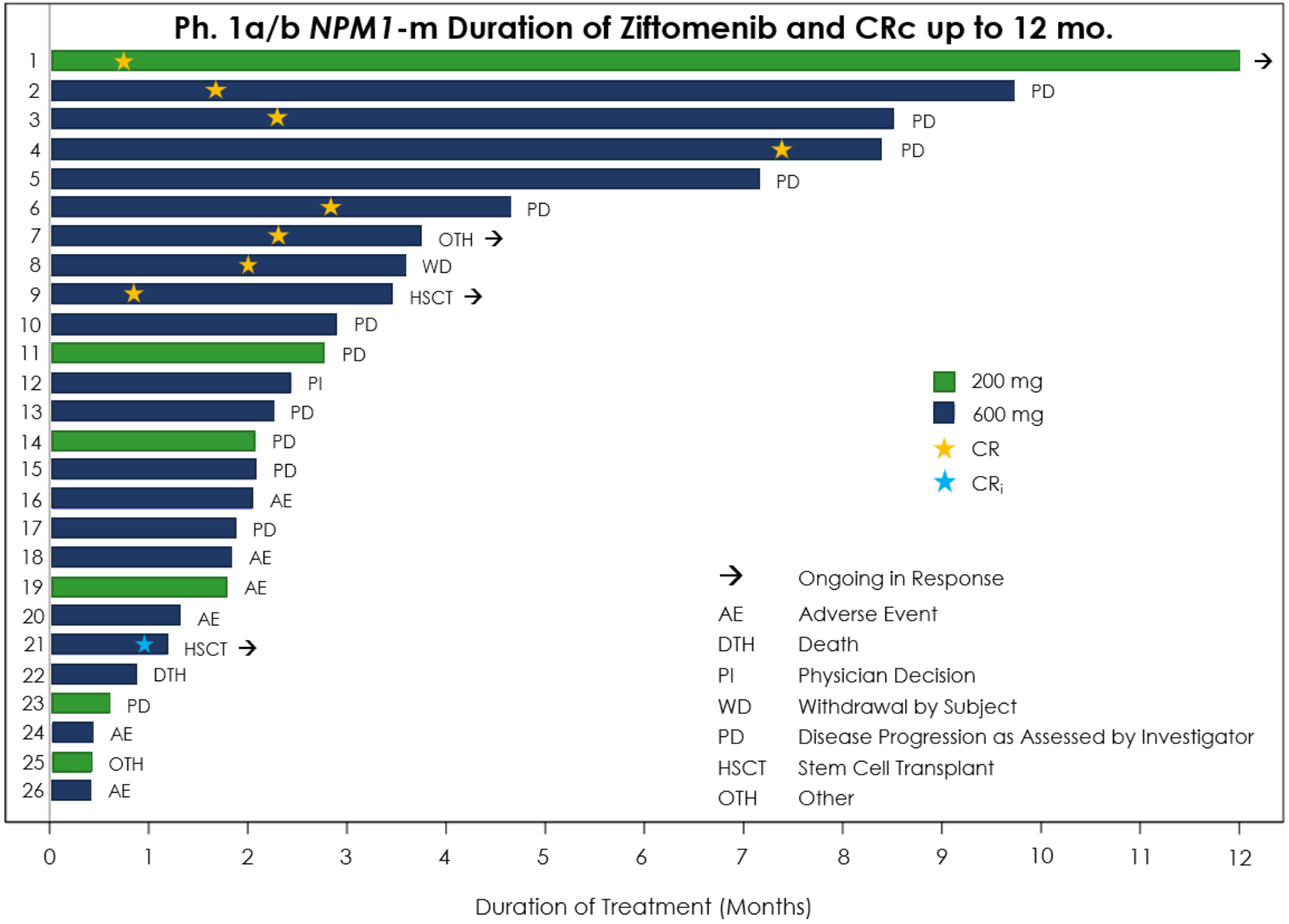
Ziftomenib Monotherapy Drives Durable Responses

- Median DoR **8.2 months** (95% CI: 1.0 to Not Evaluable) with a median follow up time of 8.8 months

- Patient 1 remained on ziftomenib in CR (MRD-) into Cycle 36

- Patients 9 and 21 proceeded to HSCT
  - Patient 9 remains in complete response on ziftomenib for post-HSCT maintenance
  - Patient 21 remains in complete response



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Ziftomenib Clears Measurable Residual Disease (MRD), Including Sub-Clones

Local MRD Analysis[1]

- 67% of patients (4 of 6) achieving CRc were MRD-negative[2]

Ongoing Central MRD Analysis, by NGS (Representative Patients)[3]

Subject 1: Prior Tx with midostaurin	*NPM1*	*FLT3*-TKD	*IDH1*
	Variant Allele Frequency (%)		
C1 D28	33	33	35
C5 D28	Not detected	Not detected	Not detected

Subject 2: Prior Tx with midostaurin and gilteritinib	*NPM1*	FLT3-ITD	*IDH2*
	Variant Allele Frequency (%)		
C1 D28	47	91	46
C4 D28	0.37	0.87	0.41

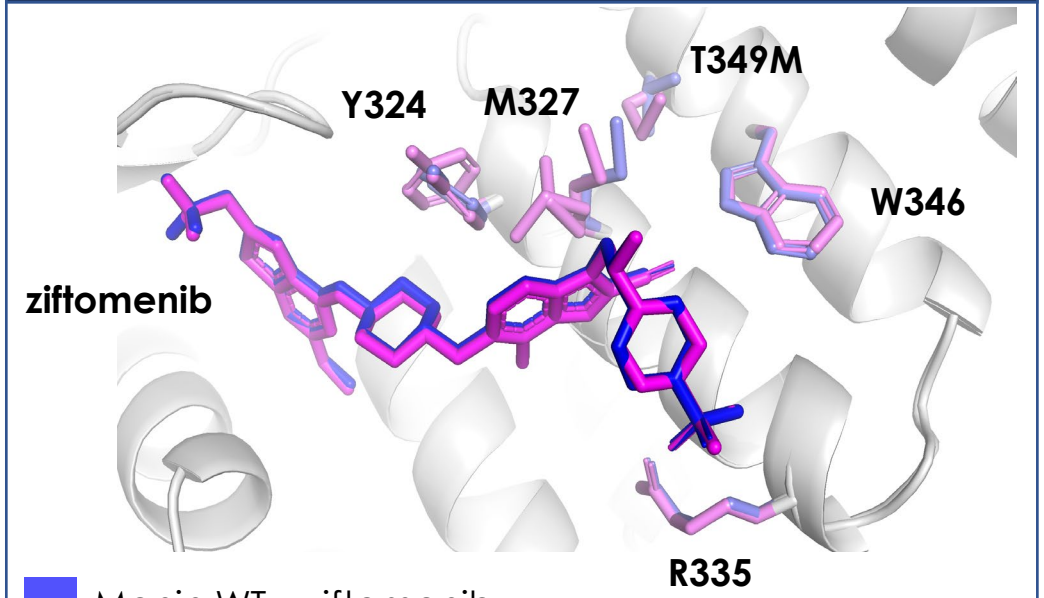
[1]4 patients by multiparameter flow cytometry (MFC), 1 patient by NGS, 1 patient RT-qPCR.
[2]6 of 8 patients who achieved CRc were tested for MRD status (local MRD test).
[3]Mutations detected in MyMRD NGS (Invivoscribe, San Diego, CA).
CRc is defined as achieving best overall response of any of the following: CR, CRh, CRi (including CRp). MRD, measurable residual disease. NGS, Next Generation Sequencing.

12-April-2023 Data Cut

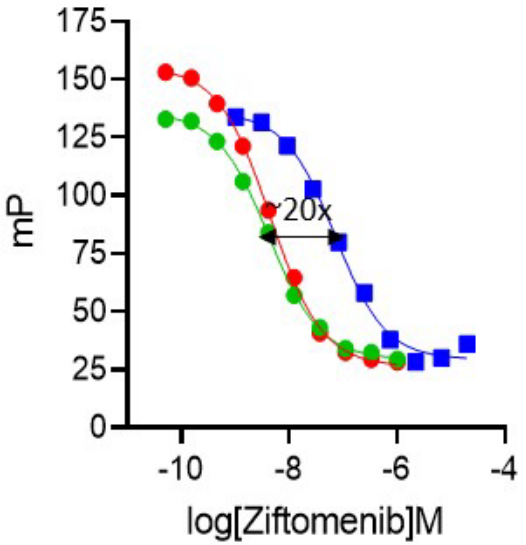
Ziftomenib Active Against Known Menin Gatekeeper Mutations

- No major conformational changes observed in Menin^{T349M} vs. wild-type (WT) protein
- M327 and Y324 side chains adopt new conformations in Menin^{T349M} but do not affect ziftomenib binding
- Binding affinity of ziftomenib is reduced for Menin^{M327I} but unaffected for Menin^{T349M}
  - Per Armstrong lab[1], ziftomenib also retains activity against Menin^{G331R}
- Ziftomenib retains activity against 2 of 3 known *MEN1* mutant loci

Crystal structure of ziftomenib binding to menin



Inhibitory activity of ziftomenib

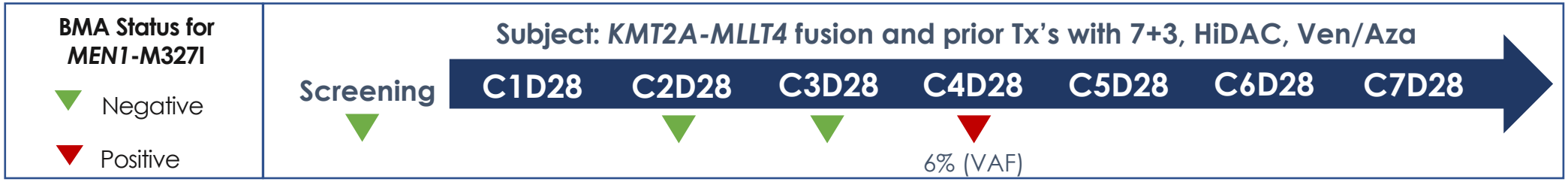


IC50 (WT)	4.1 nM
IC50 (M327I)	71 nM
IC50 (T349M)	4.4. nM

[1]Perner et al. Abstract #3457 presented at *AACR* April 14-19, 2023, Orlando, FL.

Ziftomenib Appears Less Susceptible to Observed Mutations Associated with Resistance to Menin Inhibition

- Following reports of *MEN1* resistance mutations with another menin inhibitor[1], an analysis of KOMET-001 identified 1 of 29 subjects (3.4%) with the resistance mutation (MEN1-M327I) acquired while on ziftomenib[2]



- *MEN1* mutant RNA was not detected in 13 of 13 other subjects who received ≥ 2 cycles of ziftomenib and had best response of SD or PD, suggesting that progression or lack of response in these subjects is not due to *MEN1* mutations
- Ziftomenib's ability to target MEN1 harboring G331R or T349M mutations may in part explain the low frequency of *MEN1* resistance mutations detected in KOMET-001 subjects
- Further analysis is underway to continue to characterize mechanisms of menin resistance

[1]Perner et al. *Nature* 2023; 615(7954):913-19.
[2]MEN1 mutant transcripts detected from serial analysis of bone marrow aspirate (BMA) of patients treated with at least 1 cycle of ziftomenib using RNA NGS

Conclusions

- Ziftomenib demonstrates significant clinical activity with 45% ORR (35% CR rate) and lack of myelosuppression, with maintained count recovery in heavily pretreated R/R *NPM1*-m AML
- Durable remissions with MRD clearance of foundational *NPM1-m* and other key co-mutations, including *FLT3 ITD/TKD* and *IDH1/2*, observed with ziftomenib monotherapy
- Resistance mutations have developed infrequently and ziftomenib retains activity against common menin gatekeeper mutations
- Ziftomenib is well tolerated, with no drug induced QTc and manageable DS; the lack of predicted adverse drug-drug interactions is supportive of combination approaches
- The pivotal KOMET-001 trial is currently recruiting patients with R/R *NPM1*-m AML
- KOMET-007 Phase 1 is open for enrollment (NCT05735184), studying ziftomenib in combination with existing intensive chemotherapy (IC) and non-intensive chemotherapy (NIC) standards of care (SOC) in newly diagnosed and R/R *NPM1*-m or *KMT2A*-r AML

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