Activity, Tolerability and Resistance Profile of the Menin Inhibitor Ziftomenib in Adults with Relapsed or Refractory NPM1-Mutated AML

Cristina Papayannidis, MD, PhD

ROMA,
23-25 Ottobre 2023
Marriott Park Hotel
Disclosures

Cristina Papayannidis, MD, PhD

• No Disclosures
Adult patients with NPM1-mutant AML and select co-mutations and/or relapsed/refractory disease have a poor prognosis. 

- **NPM1-mutant AML**
  - ~6,000 new cases annually in the U.S. 
  - 5-year Overall Survival ~50% 

Median overall survival is suboptimal:

- **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

---

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

* Mutations in AML are loss of function

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

**Phase 1a Dose Escalation**
- Completed
- 50 mg QD
- 100 mg QD
- 1000 mg QD

**Phase 1b Validation Cohorts**
- Completed
- Cohort 1: 200 mg QD
- Cohort 2: 600 mg QD

**Phase 1b Expansion**
- Completed
- Expansion of 600 mg QD

**Phase 2 Registration-Enabling**
- Ongoing
- 600 mg QD

**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

<table>
<thead>
<tr>
<th>Age, median (min, max), y</th>
<th>70.5 (22, 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>ECOG PS 0, n (%)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>PS 1</td>
<td>14 (70)</td>
</tr>
<tr>
<td>PS 2</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Number of prior therapies, median (min, max)</td>
<td>3 (1,10)</td>
</tr>
<tr>
<td>Prior venetoclax, n (%)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Prior SCT, n (%)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Co-mutations, n (%)</td>
<td></td>
</tr>
<tr>
<td>FLT3 ¹</td>
<td>6 (30)</td>
</tr>
<tr>
<td>IDH1/2 ¹</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Co-mutations with both FLT3 and IDH1/2</td>
<td>4 (20)</td>
</tr>
</tbody>
</table>

### Disposition

<table>
<thead>
<tr>
<th>Patients in follow-up, n (%)</th>
<th>7 (35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for treatment discontinuation, n (%)</td>
<td></td>
</tr>
<tr>
<td>Adverse event (not study drug-related) ²</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Disease progression (including clinical)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>All other reasons ³</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Patients off study, n (%)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Reason for study discontinuation, n (%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>13 (65)</td>
</tr>
</tbody>
</table>

¹Patient could have both FLT3 and IDH1/2 and be counted in both co-mutation categories.

²These adverse events leading to discontinuation were not considered study drug related.

³Additional reasons for treatment discontinuation include physician decision, receipt of alternative anticancer treatment, withdrawal by subject, and other.
### Phase 1b Safety and Tolerability of Ziftomenib in R/R NPM1-m AML

#### ≥ 20% Treatment-Emergent Adverse Events, n (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with TEAEs (All Grades)</th>
<th>Patients with TEAEs (≥ Grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPM1-m, n = 20</td>
<td>NPM1-m, n = 20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (45)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8 (40)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (30)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (30)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (30)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5 (25)</td>
<td>4 (20)</td>
</tr>
</tbody>
</table>

#### ≥ 20% Treatment-Related Adverse Events, n (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with TRAEs (All Grades)</th>
<th>Patients with TRAEs (≥ Grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPM1-m, n = 20</td>
<td>NPM1-m, n = 20</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (20)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Differentiation Syndrome</td>
<td>4 (20)</td>
<td>4 (20)</td>
</tr>
</tbody>
</table>

- 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
Ziftomenib Demonstrates Encouraging Clinical Activity

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission rate (CR)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>CRc rate (CR+CRh+CRi)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Overall response rate (CR+CRh+CRi+MLFS)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>CR</td>
<td>7 (35)</td>
</tr>
<tr>
<td>CRh</td>
<td>0</td>
</tr>
<tr>
<td>CRi</td>
<td>1 (5)</td>
</tr>
<tr>
<td>MLFS</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

• 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

Mean Change in Platelets and ANC for CRc up to C7D1

[Graph showing mean change in platelets and ANC up to C7D1]

33% CR co-FLT3m (N=6)
50% CR co-IDHm (N=8)
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

12-April-2023 Data Cut
Zifotinenib Clears Measurable Residual Disease (MRD), Including Sub-Clones

Local MRD Analysis

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

Ongoing Central MRD Analysis, by NGS (Representative Patients)

<table>
<thead>
<tr>
<th>Subject 1: Prior Tx with midostaurin</th>
<th>NPM1</th>
<th>FLT3-TKD</th>
<th>IDH1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 D28</td>
<td>33</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>C5 D28</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject 2: Prior Tx with midostaurin and gilteritinib</th>
<th>NPM1</th>
<th>FLT3-ITD</th>
<th>IDH2</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 D28</td>
<td>47</td>
<td>91</td>
<td>46</td>
</tr>
<tr>
<td>C4 D28</td>
<td>0.37</td>
<td>0.87</td>
<td>0.41</td>
</tr>
</tbody>
</table>

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.

1 Mutations detected in MyMRD NGS (Invivoscribe, San Diego, CA).
26 of 8 patients who achieved CRc were tested for MRD status (local MRD test).
3 Mutations detected in MyMRD NGS (Invivoscribe, San Diego, CA).
Ziftomenib Active Against Known Menin Gatekeeper Mutations

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

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Mutant & IC\textsubscript{50} (nM) \\
\hline
WT & 4.1 \\
M327I & 71 \\
T349M & 4.4 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{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

\(^2\)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
Acknowledgements

• The patients, their families, and caregivers
• The study investigators and their study teams:
  - Centre Hospitalier Lyon-Sud
  - CHU de Lille
  - CHU de Nantes - Hôtel Dieu
  - Duke Cancer Institute
  - Fred Hutchinson Cancer Center
  - Gustave Roussy
  - Hôpital Saint Louis
  - Hospital Clínic de Barcelona
  - Hospital Universitari i Politècnic La Fe
  - Hospital Universitario Central de Asturias
  - Hospital Universitari Vall d’Hebron
  - Hospital Universitario Virgen del Rocío
  - Indiana University
  - IRCCS Azienda Ospedaliero Universitaria di Bologna
  - Massachusetts General Hospital
  - Mayo Clinic-Florida
  - Mayo Clinic-Rochester
  - MD Anderson Cancer Center
  - MD Anderson Cancer Center – Madrid
  - Mount Sinai
  - Northwestern University
  - Roswell Park
  - UCLA
  - University of Maryland
  - University of Michigan
  - UPMC-Pittsburgh
  - Vanderbilt University

• The study is sponsored by Kura Oncology, Inc.
Author List

Amir T. Fathi¹, Eunice S. Wang², Ghayas C. Issa³, Jessica K. Altman⁴, Pau Montesinos⁵, Stephane DeBotton⁶, Roland Walter⁷, Kristen Pettit⁸, Stephen Strickland⁹, Mrinal Patnaik¹⁰, Marina Kremyanskaya¹¹, Maria R. Baer¹², James Foran¹³, Gary Schiller¹⁴, Lionel Ades¹⁵, Mael Heiblig¹⁶, Celine Berthon¹⁷, Jolanta Grembecka⁸, Tomasz Cierpiki⁸, Bradley Clegg⁸, Pierre Peterlin¹⁸, Eduardo Rodriguez Arbolí¹⁹, Olga Salamero Garcia²⁰, Cristina Papayannidis²¹, Kun Nie²², Julie Mackey²², Marilyn Tabachri²², Daniel Corum²², Mollie Leoni²², Stephen Dale²², Harry P. Erba²³

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