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


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Disclosures

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- Consulting: Agios, Celgene/BMS, Astellas, Daiichi Sankyo, Takeda, Kura, Amgen, Pfizer, Seattle Genetics, AbbVie, and Genentech; Research support: Celgene/BMS and Agios
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.
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

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

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

**Phase 1b**
- **Validation Cohorts**
  - Completed
  - Cohorts: 200 mg QD, 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

<table>
<thead>
<tr>
<th>Demographics</th>
<th>600 mg, n = 20</th>
<th>Disposition</th>
<th>600 mg, n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (min, max), y</strong></td>
<td>70.5 (22, 86)</td>
<td><strong>Patients in follow-up, n (%)</strong></td>
<td>7 (35)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>6 (30)</td>
<td><strong>Reason for treatment discontinuation, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ECOG PS 0, n (%)</strong></td>
<td>3 (15)</td>
<td>Adverse event (not study drug-related)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>PS 1</td>
<td>14 (70)</td>
<td>Death</td>
<td>1 (5)</td>
</tr>
<tr>
<td>PS 2</td>
<td>3 (15)</td>
<td>Disease progression (including clinical)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Number of prior therapies, median (min, max)</td>
<td>3 (1,10)</td>
<td>All other reasons</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Prior venetoclax, n (%)</td>
<td>13 (65)</td>
<td><strong>Patients off study, n (%)</strong></td>
<td>13 (65)</td>
</tr>
<tr>
<td>Prior SCT, n (%)</td>
<td>4 (20)</td>
<td><strong>Reason for study discontinuation, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Co-mutations, n (%)</td>
<td></td>
<td>Death</td>
<td>13 (65)</td>
</tr>
<tr>
<td>FLT3</td>
<td>6 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1/2</td>
<td>8 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-mutations with both FLT3 and IDH1/2</td>
<td>4 (20)</td>
<td></td>
<td></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

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

<table>
<thead>
<tr>
<th>≥ 20% Treatment-Related Adverse Events, n (%)</th>
<th>NPM1-m, n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TRAEs (All Grades)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Differentiation Syndrome</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Patients with TRAEs (≥ Grade 3)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>N/A</td>
<td></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

12-April-2023 Data Cut
Ziftomenib Demonstrates Encouraging Clinical Activity

**Best Overall Response**

<table>
<thead>
<tr>
<th>Response Type</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.

**Mean Change in Platelets and ANC for CRc up to C7D1**

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

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

**Ph. 1a/b NPM1-m Duration of Ziftomenib and CRc up to 12 mo.**

- Duration of Treatment (Months)
- Phases: PD, CR, CR1, PI, AE, OTH, DTH, HSCT
- Stages: 1-26
- **200 mg**, **600 mg**
- Ongoing in Response: AE, PI, AE, OTH, AE
- Death: OTH
- Withdrawal by Subject: OTH
- Disease Progression as Assessed by Investigator: OTH
- Stem Cell Transplant: OTH
- Other: OTH

12-April-2023 Data Cut
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)\(^3\)

<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>Variant Allele Frequency (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>Variant Allele Frequency (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>

\(^1\) 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 lab¹, 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

- Ziftomenib interacts with Menin WT and Menin$^{T349M}$

### Inhibitory activity of ziftomenib

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

¹Perner 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\(^2\)

<table>
<thead>
<tr>
<th>BMA Status for MEN1-M327I</th>
<th>Screening</th>
<th>Subject: KMT2A-MLLT4 fusion and prior Tx’s with 7+3, HiDAC, Ven/Aza</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼ Negative</td>
<td>C1D28</td>
<td>C2D28 C3D28 C4D28 C5D28 C6D28 C7D28</td>
</tr>
<tr>
<td>▼ Positive</td>
<td></td>
<td>6% (VAF)</td>
</tr>
</tbody>
</table>

- 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.