Mutant Isocitrate Dehydrogenase (mIDH) Inhibitors, Enasidenib or Ivosidenib, in Combination with Azacitidine (AZA): Preliminary Results of a Phase 1b/2 Study in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

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**IDH1 AND IDH2 MUTATIONS**

- **IDH** mutations occur in ~20% of patients (pts) with AML
  - Higher prevalence with increased pt age
  - Enriched in certain molecularly and karyotypically defined populations (eg, normal karyotype, mutant-\(NPM1\) AML)
    - Most (~85%) occur in diploid or +8 de novo AML
- “Hot-Spot” mutations in enzymatic active site
  - **IDH1-R132**, **IDH2-R140** or **IDH2-R172**
- Often considered “founder mutations”
  - **IDH** mutations are ancestral in 20% of **IDH1** cases and 35% of **IDH2** cases
- Can be acquired at time of progression
  - 10-15% of AML from MDS
  - 20-25% of AML from MPN

2HG ACCUMULATION

• IDH1/2 mutations lead to 2HG accumulation; the oncometabolite 2HG competitively inhibits enzymes that utilize αKG as a substrate
  – αKG is a substrate for >60 αKG-dependent dioxygenases

• 2HG-induced oncogenic activities are thought to include:
  A and B: Differentiation block via inhibition of TET family enzymes and histone demethylases, yielding hypermethylated DNA and histones
  C: BCL2 dependence via inhibition of Cyt C Oxidase in electron transport chain leading to lowered apoptotic threshold
  D: Altered hypoxic response via dysregulated HIF-1α

**Mutant-IDH (mIDH) inhibitors**

- Enasidenib (IDHIFA®; CC-90007/AG-221) and ivosidenib (AG-120) are oral, small-molecule inhibitors of mIDH2 and mIDH1 proteins, respectively.
- In pts with mIDH2 R/R AML, enasidenib monotherapy associated with 40.3% overall response rate (ORR), complete remission (CR) rate of 19.3%, and median overall survival (OS) of 9.3 months\(^1\).
- Updated outcomes with investigational ivosidenib monotherapy in pts with mIDH1 AML to be presented at ASH (Abstract #725).
  - ORR for pts with mIDH1 R/R AML was 41.6% and CR rate was 21.6%.

**Azacitidine (AZA)**

- AZA reduces DNA methylation by inhibiting DNA methyltransferases.
- AZA monotherapy prolonged OS vs conventional care regimens (CCR) in older pts with newly diagnosed (ND) AML (10.4 vs 6.5 months; \(P=0.101\)),\(^2\) including in the subgroup of pts with AML-MRC (\(P=0.0264\))\(^3\).

**mIDH inhibitors + AZA**

- mIDH inhibitors + AZA showed synergistic effects on releasing differentiation block in mIDH leukemia models in vitro\(^4\).
- We report initial results of the phase 1b portion of an ongoing phase 1b/2 study of mIDH inhibitors + AZA combinations in pts with mIDH1 or mIDH2 ND-AML (NCT02677922).

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**KEY ELIGIBILITY CRITERIA**

- Newly diagnosed AML
- Age ≥18
- Ineligible for intensive chemotherapy
- Pts with antecedent hematologic disorders allowed but prior HMA excluded

**PHASE 1B (3+3 DESIGN)**

- mIDH1
  - Dose-finding*: Ivosidenib + AZA
    - n=7
  - Expansion: Ivosidenib + AZA
    - n=15†

- mIDH2
  - Dose-finding*: Enasidenib + AZA
    - n=6

**PHASE 2 (2:1 RANDOMIZATION)**

- Enasidenib
  - 100mg QD + SC AZA
    - n=66

- Monotherapy
  - SC AZA
    - n=33

SC AZA 75mg/m²/day x 7 days/ 28-day cycle (all study phases)

**PRIMARY ENDPOINTS:**
- Recommended combination dose (RCD); safety

**KEY SECONDARY ENDPOINTS:**
- Overall response rate
- PK/PD
- QOL outcomes

**PRIMARY ENDPOINT:**
- Overall response rate

**KEY SECONDARY ENDPOINTS:**
- Safety
- Event-free survival
- Overall survival

*Dose finding for enasidenib or ivosidenib; AZA dose remained constant
†4 pts had enrolled in expansion as of data cutoff (1 Sep 2017); enrollment is now closed
ClinicalTrials.gov NCT02677922
AML, acute myeloid leukemia; AZA, azacitidine; IC, induction chemotherapy; ORR, overall response rate; QOL, quality of life; RCD, recommended combination dose
## BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

- 17 pts treated with enasidenib +AZA (n=6) or ivosidenib + AZA (n=11)
- At data cutoff (1-Sep-2017), 11 pts remained on-study (3 enasidenib, 8 ivosidenib)

<table>
<thead>
<tr>
<th></th>
<th>Enasidenib 100 mg + AZA (n=3)</th>
<th>Enasidenib 200 mg + AZA (n=3)</th>
<th>Combined Enasidenib + AZA (n=6)</th>
<th>Ivosidenib 500 mg + AZA (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>76 (69–79)</td>
<td>65 (64–67)</td>
<td>68 (64–79)</td>
<td>76 (72–88)</td>
</tr>
<tr>
<td>Age &lt;65, n (%)</td>
<td>0</td>
<td>1 (33)</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Age ≥65, n (%)</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>5 (83)</td>
<td>11 (100)</td>
</tr>
<tr>
<td><strong>Gender, n Male/Female</strong></td>
<td>1/2</td>
<td>1/2</td>
<td>2/4</td>
<td>5/6</td>
</tr>
<tr>
<td><strong>IDH2 mutation type, n (%)</strong></td>
<td>2 (67)</td>
<td>2 (67)</td>
<td>4 (67)</td>
<td>NA</td>
</tr>
<tr>
<td>R140</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>3 (50)</td>
<td>0</td>
</tr>
<tr>
<td>R172</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>1 (17)</td>
<td>5 (83)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td>0</td>
<td>1 (33)</td>
<td>1 (17)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>1</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>5 (83)</td>
<td>9 (82)</td>
</tr>
<tr>
<td><strong>Co-mutations, n (%)</strong></td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>3 (50)</td>
<td>0</td>
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<tr>
<td>FLT3-ITD / FLT3-TKD</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>1 (17)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>NPM1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (27)</td>
</tr>
<tr>
<td><strong>Cytogenetic risk, n (%)</strong></td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>6 (100)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>6 (100)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (9)</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL), median (range)</strong></td>
<td>9.8 (9.8–9.8)</td>
<td>9.7 (9.3–10.8)</td>
<td>9.8 (9.3–10.8)</td>
<td>9.1 (7.8–14.1)</td>
</tr>
<tr>
<td><strong>Platelets (10^9/L), median (range)</strong></td>
<td>141.5 (87–196)</td>
<td>42.0 (19–100)</td>
<td>87.0 (19–196)</td>
<td>55.5 (11–200)</td>
</tr>
<tr>
<td><strong>WBC (10^9/L), median (range)</strong></td>
<td>10.2 (0.8–19.6)</td>
<td>6.7 (1.3–19.2)</td>
<td>6.7 (0.8–19.6)</td>
<td>1.7 (0.6–15.4)</td>
</tr>
</tbody>
</table>

AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status score; NA, not applicable; WBC, white blood cell
### ENASIDENIB: TREATMENT-EMERGENT ADVERSE EVENTS

- Median enasidenib Tx cycles: 9 (range 1-13)
- Most common TEAEs (any grade): nausea, hyperbilirubinemia (n=4 each)
- Enasidenib-related TEAEs (any grade) in >1 pt: nausea (n=3), vomiting (2), hyperbilirubinemia (2)
- IDH-differentiation syndrome (IDH-DS) occurred in 1 pt in the enasidenib 200-mg arm

### Grade 3-4 treatment-emergent adverse events

<table>
<thead>
<tr>
<th></th>
<th>Enasidenib 100 mg + AZA (n=3)</th>
<th>Enasidenib 200 mg + AZA (n=3)</th>
<th>Enasidenib + AZA Total (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>2* (67)</td>
<td>2* (33)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1* (33)</td>
<td>1* (17)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>1* (33)</td>
<td>1* (17)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>1* (33)</td>
<td>1* (17)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>0</td>
<td>1 (33)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>WBC count decreased</td>
<td>0</td>
<td>1 (33)</td>
<td>1 (17)</td>
</tr>
<tr>
<td><strong>Non-hematological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1 (33)</td>
<td>1* (33)</td>
<td>2* (33)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Hemorrhoidal hemorrhage</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0</td>
<td>1 (33)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Embolism</td>
<td>0</td>
<td>1* (33)</td>
<td>1* (17)</td>
</tr>
</tbody>
</table>

*One event considered to be treatment-related
IVOSIDENIB: TREATMENT-EMERGENT ADVERSE EVENTS

- Median ivosidenib Tx cycles: 3.0 (1-13)
- Most common TEAEs (any grade): nausea (n=8), constipation (6), fatigue (5), diarrhea (4)
- Tx-related TEAEs (any grade) in >1 pt: nausea (n=6), fatigue (4)
- IDH-DS reported for 1 pt
- 1 death on-study (pneumonia; not considered Tx-related)

### Grade 3-4 treatment-emergent adverse events

<table>
<thead>
<tr>
<th></th>
<th>Ivosidenib 500 mg + AZA (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>2* (18)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1* (9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1* (9)</td>
</tr>
<tr>
<td><strong>Non-hematological</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1* (9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>1* (9)</td>
</tr>
<tr>
<td>IDH differentiation syndrome</td>
<td>1* (9)</td>
</tr>
<tr>
<td>Parainfluenza virus infection</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1 (9)</td>
</tr>
<tr>
<td>INR increased</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

*One event was considered to be treatment-related
OVERALL RESPONSE RATES


Enasidenib + AZA:

• ORR: 4 of 6
  – In the enasidenib 100 mg + AZA arm, 2 pts achieved CR
  – In the enasidenib 200 mg + AZA arm, 1 pt achieved PR and 1 had MLFS
    • 1 pt in the enasidenib 200 mg + AZA arm maintained SD on-study
    • 1 pt in the enasidenib 100 mg + AZA arm had PD

Ivosidenib 500 mg + AZA:

• ORR: 8 of 11
  – 4 pts achieved CR, 1 achieved CRi, 1 achieved PR, and 2 pts had MLFS
    • 3 pts maintained SD
Data cutoff: Sep 1, 2017
CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial remission; SD, stable disease
One additional patient was enrolled but did not have response data available at data cutoff.

Data cutoff: Sep 1, 2017

CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; PR = partial remission; MLFS = morphologic leukemia-free state; SD = stable disease; PD = progressive disease; MR = morphologic relapse after CR/CRi/CRp; NE = not evaluable.
AG-221-AML-005 STUDY: CASE PRESENTATION

• 77-year-old female with atrial fibrillation / atrial flutter and pulmonary emboli at diagnosis
  – WBC 16K, Hgb 8.4 g/dl, platelets 186K, 14% peripheral blasts

• July 2016 BM Biopsy:
  – Hypercellular with MDS-related changes and 27% blasts
  – Cytogenetics with t(7;11)(p15;p15); IDH2-R140Q, NRAS G12D, DNMT3A N797I, and FLT3-ITD 0.016

• Enasidenib 100 mg/ day - Cycle 1 - Day 28 marrow:
  – Hypercellular marrow with 2% blasts
  – Persistent cytogenetics; IDH2, NRAS, DNMT3A and FLT3-ITD abnormalities detected

• Cycle 2 - Day 28 marrow:
  – Normocellular, diploid, only DNMT3A and IDH2 remain. Flow with 2% blasts

• Cycle 4 - Day 28 marrow:
  – IDH2 no longer detected. MRD negative by flow cytometry

• After Cycle 8:
  – AZA dose reduced by 50% for progressive cytopenias

• Cycle 11:
  – Ongoing CR; MRD-negative by cytogenetics, molecular analysis, and flow cytometry
Clot and Smear at Cycle 9

Counts over time

WBC (Trend All)

Platelet (Trend All)
DISCUSSION

• Enasidenib or ivosidenib + AZA combinations were well tolerated in pts with ND-AML
  – 11 pts remained on-study at data cutoff
  – 3 of 6 pts in the enasidenib + AZA arms and 8 of 11 pts in the ivosidenib + AZA arm remained on-study at time of data cutoff

• Most common TEAEs with all regimens: grade 1-2 GI events
  – Indirect bilirubinemia in enasidenib-treated pts likely due to off-target inhibition of UGT1A1 enzyme

• Preliminary efficacy is encouraging:
  – 4 of 6 enasidenib-treated pts had a response (2 CR, 1 PR, 1 MLFS)
  – 8 of 11 ivosidenib-treated pts had a response (4 CR, 1 CRi, 1 PR, 2 MLFS)

• Phase 1b confirms 100 mg enasidenib + AZA and 500 mg ivosidenib + AZA for further study

• Ongoing studies of mIDH inhibitors + AZA:
  – Randomized phase 2 portion of the current study of enasidenib + AZA (enrollment complete in the ivosidenib + AZA arm)
  – Phase 3 placebo-controlled AGILE study of ivosidenib + AZA (NCT03173248) in ND-AML not suitable for intensive therapy