Pharmacokinetic/pharmacodynamic evaluation of ivosidenib or enasidenib combined with intensive induction and consolidation chemotherapy in patients with newly diagnosed IDH1/2-mutant AML

Yue Chen¹, Feng Yin¹, Lei Hua¹, Caroline Almon¹, Salah Nabhan¹, Michael Cooper¹, Mohammad Hossain¹, Hua Yang¹, Bin Fan¹

Agios Pharmaceuticals, Inc., Cambridge, MA, USA

Email: medinfo@agios.com

Presented at the Virtual Edition of the 25th Hematology Association (EHA) Annual Congress, June 11–14, 2020

BACKGROUND

- Isocitrate dehydrogenase 1 and 2 (IDH1/2) are critical metabolic enzymes.
- Mutant IDH1/2 proteins possess novel enzymatic activity, catalyzing the reduction of α-ketoglutarate to produce the oncometabolite 2-hydroxyglutarate (2-HG), which drives multiple oncogenic processes, including impaired cellular differentiation.¹
- Oncogenically activated IDH1/2 mutations occur in multiple solid and hematologic malignancies, including ~20% of cases of acute myeloid leukemia (AML).₂

OBJECTIVES

- To characterize the plasma PK profiles of IVO and ENA given in combination with intensive induction and consolidation chemotherapy in patients with newly diagnosed AML.
- To evaluate the PK/PD relationships of IVO and ENA given in combination with intensive induction and consolidation chemotherapy for the treatment of patients with newly diagnosed AML.
- To explore the relationship between plasma IVO/ENA PK parameters and inhibition of plasma 2-HG.

METHODS

- METHODS (CONTINUED)

  - This was a multicenter, open-label, phase 1 study enrolling patients ≥ 18 years of age with newly diagnosed AML or mIDH1/2 AML (ClinicalTrials.gov NCT02322078).

  - Screening was performed using a validated liquid chromatography-tandem mass spectrometry method.

  - Patients were randomized to receive either IVO 100 mg QD, ENA 100 mg QD, or ENA 300 mg QD in combination with induction and consolidation chemotherapy.

  - The primary endpoint was to determine the maximum tolerated dose (MTD) of IVO or ENA in combination with chemotherapy.

RESULTS

- IVO and ENA were rapidly absorbed, with median peak plasma concentrations at 4 h for single and multiple doses (Table 1).

- Plasma and bone marrow concentrations of 2-HG were reduced throughout the range of 95%–100% inhibition, and 2-HG inhibition was maintained within the range of 95%–100%.

- Plasma IVO/ENA concentrations in combination with chemotherapy were comparable to those observed in healthy volunteers.

CONCLUSIONS

- When combined with intensive induction and consolidation chemotherapy in patients with newly diagnosed AML, IVO and ENA demonstrated PK profiles similar to those observed in healthy volunteers relative to those needed for target inhibition.

  - Pharmacokinetic profiles of IVO and ENA were also similar to those estimated in previous studies, suggesting that IVO and ENA may be suitable for combination with chemotherapy.

  - Plasma concentrations of 2-HG were reduced to within the range of 95%–100% inhibition, and 2-HG inhibition was maintained within the range of 95%–100%.

  - Exploratory analyses of biomarker changes following the completion of induction therapy, as well as trough plasma 2-HG concentrations remained within the range observed in healthy volunteers.

References


Financial disclosure: This study was funded by Agios Pharmaceuticals, Inc. in collaboration with Bristol-Myers Squibb. YC, FY, CA, SN, MC, MH, PK, and TP are employees and stockholders in Agios Pharmaceuticals. CA, PK, and TP are employees and stockholders in Bristol-Myers Squibb. YC, FY, CA, SN, MC, MH, PK, and TP have received research funding and honoraria from Agios Pharmaceuticals and Bristol-Myers Squibb.

Email: medinfo@agios.com

Preparation of Table 1. PK/PD parameters after multiple doses of IVO or ENA in combination with induction chemotherapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVO</th>
<th>ENA</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_{max} (h)</td>
<td>4.18 (0, 23.75)</td>
<td>4.18 (0, 23.75)</td>
</tr>
<tr>
<td>C_{max} (µg/mL)</td>
<td>8200 (40.4)</td>
<td>7650 (40.4)</td>
</tr>
<tr>
<td>AUC_{0–24} (µg•h/mL)</td>
<td>161,000 (40.4)</td>
<td>137,000 (40.4)</td>
</tr>
<tr>
<td>Racc_C{max}</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Racc_AUC_{0–24}</td>
<td>8.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Exploratory analyses of the relationship between plasma IVO/ENA PK parameters and inhibition of plasma 2-HG at induction C1D14 are shown in Figure 4.

For standard ENA schedule at induction C1D14, plasma 2-HG concentration decreased to within the range of 95%–100% inhibition. For standard ENA schedule at induction C1D14, plasma 2-HG concentration decreased to within the range of 95%–100% inhibition. The relationship between plasma 2-HG and Cmax and AUC_{0–24} is shown in Figure 5.

Figure 1. Study design and sampling schedule

Figure 2. Plasma concentrations over time of IVO or ENA in combination with chemotherapy

Figure 3. Plasma 2-HG inhibition over time pre dose and after multiple doses of IVO or ENA in combination with chemotherapy

Figure 4. Comparisons of 2-HG inhibition vs Cmax for IVO or ENA in combination with chemotherapy

Figure 5. Comparisons of 2-HG concentrations in bone marrow and peripheral blood of IVO or ENA in combination with chemotherapy

Acknowledgments

The authors thank the patients participating in the study, Dr. Frank Müller and Dr. Wei Le for their contributions to this work. This study was funded by Agios Pharmaceuticals, Inc. in collaboration with Bristol-Myers Squibb, YC, FY, CA, SN, MC, MH, and YC. All authors declare no financial relationships. This study was conducted at University of California Los Angeles Medical Center, Los Angeles, CA. YC, FY, CA, SN, MC, MH, and YC: employees and stockholders in Agios Pharmaceuticals. CA, PK, and TP: employees and stockholders in Bristol-Myers Squibb. YC, FY, CA, SN, MC, MH, PK, and TP: have received research funding and honoraria from Agios Pharmaceuticals and Bristol-Myers Squibb.