AG-120 (ivosidenib), a first-in-class mutant IDH1 inhibitor, promotes morphologic changes and upregulates liver-specific genes in IDH1 mutant cholangiocarcinoma

Yuko Ishii1, Carlie Sigel2, Maeve A Lowery2,3, Lipika Goyal4, Camelia Gliser1, Liewen Jiang1, Susan Pandya1, Bin Wu1, Sung Choe1, Vikram Deshpande4

1Agios Pharmaceuticals, Inc., Cambridge, MA, USA;  
2Memorial Sloan Kettering Cancer Center, New York, NY, USA [at time of work];  
3Trinity College, Dublin, Ireland [current];  
4Massachusetts General Hospital, Boston, MA, USA

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 26–30, 2017, Philadelphia, PA, USA
Disclosure information

- This study was funded by Agios Pharmaceuticals.
- Editorial assistance was provided by Susanne Vidot, PhD, CMPP, Excel Scientific Solutions, Horsham, UK, and supported by Agios.

I will discuss the following off label use and/or investigational use in my presentation:
ClinicalTrials.gov NCT02073994: Study of Orally Administered AG-120 in Subjects With Advanced Solid Tumors, Including Glioma, With an IDH1 Mutation
IDH1 mutations in cholangiocarcinoma

- Mutations in the isocitrate dehydrogenase 1 (IDH1) gene are detected in 13–15% of cholangiocarcinoma (CC).\(^1\)\(^-\)\(^3\)
  - ~25% of intrahepatic CC

- The mutant IDH1 (mIDH1) enzyme produces the oncometabolite D-2-hydroxyglutarate (2-HG),\(^4\)\(^,\)\(^5\) which leads to epigenetic dysregulation and a block in cellular differentiation.\(^6\)\(^-\)\(^9\)

- AG-120 (ivosidenib) is a first-in-class, oral, potent, reversible, selective inhibitor of the mIDH1 enzyme.\(^10\)\(^-\)\(^12\)

---

AG-120 in mIDH1 cholangiocarcinoma

- AG120-C-002 (ClinicalTrials.gov NCT02073994), a first-in-human phase 1 study, assessed AG-120 in patients with mIDH1 advanced solid tumors.
  - 73 patients with mIDH1 CC (median 2 prior lines of therapy).

- AG-120 was well tolerated and associated with a favorable safety profile.
  - no dose-limiting toxicities or treatment-related deaths\textsuperscript{13,14}

- AG-120 demonstrated encouraging clinical activity in this heavily pre-treated mIDH1 CC population.\textsuperscript{13,14}

- The exploratory objectives included the assessment of morphological and molecular changes in serial tumor biopsy samples.

Histological characteristics of mIDH1 CC

- A cholangiolar pattern was defined as being composed of glands with an antler-horn configuration and angulated shapes, and lined with low cuboidal epithelium.\(^{15-17}\)

- Cholangiolar histology is associated with better clinical outcomes and survival rates in patients with ICC.\(^{15,19}\)

- Untreated mIDH1 ICCs often show heterogeneous histoarchitecture.
  - 61% of tumors lack a dominant pattern\(^{18}\)
  - Cholangiolar histology is commonly present in mIDH1 CC, but often to a limited extent (median 10% cholangiolar histology).\(^{15,18}\)

- Tumor phenotype and morphologic differentiation in CC patients treated with AG-120 have not previously been examined.
Sample Collection
(n = number of patients with samples at baseline and ≥ 1 on-treatment time point)

Procedure
(n = number of patients with data available at baseline and ≥ 1 on-treatment time point)

Sample and data summary

Morphology

Hematoxylin and eosin (H&E) stained slides from FFPE tissue
(n = 27)

Blinded evaluation of architectural, cytologic, and stromal patterns by two gastrointestinal pathologists
(n = 17\textsuperscript{a})

Gene Expression

Fresh frozen biopsies
(n = 38)

Tumor content and assay quality control

Personalis® ACE Transcriptome™ RNAseq platform
(n = 26\textsuperscript{b})

10 patients have both morphology and gene expression data available.

\textsuperscript{a}Includes 16 patients dosed at 500 mg QD and one patient dosed at 100 mg BID

\textsuperscript{b}Includes 22 patients dosed at 500 mg QD, two patients dosed at 1200 mg QD, and two patients dosed at 300 mg QD
The percentage of tumor with a cholangiolar pattern was recorded. A baseline to postdose increase was defined as a ≥20% increase in cholangiolar histology.

The volume of cytoplasm in tumor cells was semi-quantitatively assessed.

These morphologic changes were not associated with AG-120 dose level. All patients had plasma 2-HG reduction upon AG-120 treatment, regardless of post-dose morphology.20

<table>
<thead>
<tr>
<th>Morphology data available</th>
<th>Increase in cholangiolar histology</th>
<th>Cytoplasmic reduction</th>
<th>Cholangiolar and cytoplasmic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>5</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>By treatment responsea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>


aTreatment response measured according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (PR = partial response; SD = stable disease; PD = progressive disease). The clinical data were based on a cutoff date of May 12, 2017.
Example 1: Increased cholangiolar histology and decreased cytoplasm upon AG-120 treatment

Baseline

Cycle 3, Day 1 (SD)
Example 2: Increased cholangiolar histology and decreased cytoplasm upon AG-120 treatment
Increased cholangiolar pattern seems to be associated with increased PFS

Two patients with a 100% cholangiolar pattern at screening and post dose were excluded from this analysis, as they are expected to have better clinical outcomes and survival (Liau JY et al. *Mod Pathol* 2014;27:1163-73; V. Despande, unpublished data, 2017). *Defined as a ≥20% increase from screening to C3D1.*
mIDH1 CCs with cholangiolar increase show upregulation of a broad set of adult liver-specific genes

- Preclinical studies have shown IDH1 mutations to block hepatocyte differentiation and promote biliary cancers.\(^6\),\(^7\)

- Gene expression data were available for two patients with observed cholangiolar pattern increase (≥ 20%).

- Both showed increased expression of liver specific genes (N = 485), derived from two sources:
  - Farshidfar et al. (2017)\(^{21}\)
  - Hsiao et al. (2001)\(^{22}\)
Patients with cytoplasmic decrease show increased expression of immune-response related genes

- Gene expression data were available for five patients with observed cytoplasmic decrease.

- These five patients showed upregulation of multiple immune response-related genes, including CXCL10, CD3G, and CTLA4.

- In preclinical studies, IDH1m glioma showed lower expression of the chemokine CXCL10, and combined IDH1m inhibitor / vaccine treatment resulted in increased CXCL10 expression and CD8 T cell infiltration.23
This is the first demonstration that AG-120 treatment may induce morphologic and molecular changes in a subset of mIDH1 CCs.

Increased cholangiolar histology seems to be associated with increased PFS.

Tumors with increased cholangiolar histology showed upregulation of genes associated with mature liver cells.

The increased expression of immune response related genes in some tumors suggests a potential rationale for AG-120 in combination with immunotherapies.

Given the limited sample size of this dataset, additional studies are warranted to explore the biological and clinical significance of these observations.

AG-120 is under further evaluation in an ongoing, global, phase 3, randomized, placebo-controlled study in previously treated mIDH1 CC (ClarIDHy; ClinicalTrials.gov NCT02989857).
Eligible patients with mIDH1 CC (1 or 2 prior therapies)  

2:1 double-blind randomization (n=186)  

AG-120  
500 mg QD orally  
Continuous 28-day cycles (n=124)  

Crossover from placebo to AG-120 permitted when progressive disease documented  

Matched placebo  
(n=62)  

Assessments  

Primary  
• Progression free survival (PFS), assessed by independent radiology center review  

Secondary  
• Safety and tolerability  
• Overall response rate (ORR)  
• Overall survival (OS)  
• Duration of response (DOR)  
• Time to response (TTR)  
• Pharmacokinetic and pharmacodynamic analyses on plasma  
• Quality of life as assessed by:  
  • EORTC QLQ-C30  
  • EORTC QLQ-BIL21  
  • EQ-5D-5L  

Exploratory:  
• TBC
We would like to thank the patients taking part in this study.

Dr. Nabeel Bardeesy at MGH/Broad Institute provided consultations on gene sets.