AG-120, A First-in-Class Mutant IDH1 Inhibitor in Patients with Recurrent or Progressive IDH1 Mutant Glioma: Updated Results from the Phase 1 Non-Enhancing Glioma Population

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Presented at the Society for Neuro-Oncology Annual Scientific Meeting, November 16-19, 2017; San Francisco, CA, USA
Mutations in the metabolic enzymes IDH1 and IDH2 occur in several human malignancies, including leukemia (AML), cholangiocarcinoma, chondrosarcoma, and glioma.

IDH mutations change the function of the enzyme
→ neomorphic production of the oncometabolite D-2HG
→ epigenetic dysregulation and impaired cellular differentiation
→ oncogenesis

Recent regulatory approval for IDHIFA® (enasidenib), an IDH2 inhibitor, in relapsed/refractory AML.
IDH Mutations and AG-120 in Glioma

- IDH mutations occur in >70% of low-grade gliomas (LGG) and ~ 5% of GBMs\(^1\)

- **AG-120 (ivosidenib)** is a first-in-class, oral, potent, reversible, targeted inhibitor of mutant IDH1 enzyme

- AG-120 is under clinical evaluation in an ongoing phase 1 dose escalation and expansion study of patients with IDH1-mutant advanced solid tumors (n=168), including glioma (n=66)\(^a\)
  - adults with previously treated WHO grade II, WHO grade III, WHO grade IV
  - contrast-enhancing (n=31) or non-enhancing (n=35) on brain MRI
  - preliminary safety and efficacy data presented previously\(^2\)

- Here we report updated safety and efficacy data, and an exploratory volumetric growth rate analysis for the **non-enhancing** glioma patient population

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Dose escalation (n=60) including 20 gliomas

- IDH1-mutant (local testing) advanced solid tumors, including glioma
- Recurred, progressed or not responded to standard therapy
- 9/20 enhancing glioma
- 11/20 non-enhancing glioma

Dose expansion non-enhancing gliomas (n=24)

Other dose expansion cohorts (n=84)

- Cholangiocarcinoma, chondrosarcoma, solid tumors not eligible for other cohorts
- Includes 22 enhancing gliomas

Primary study objectives:
- Evaluate safety and tolerability
- Determine MTD and/or RP2D

Secondary study objectives:
- Pharmacokinetics and pharmacodynamics
- Preliminary clinical activity (ORR, PFS)

Exploratory:
- Change in tumor volumetric growth rate in non-enhancing glioma expansion cohort
- PD evaluation of tissue and plasma

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ClinicalTrials.gov NCT02073994; RT = radiation therapy; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose
Study Status: Non-Enhancing Glioma

- Glioma enrollment complete as of 16Jan2016 (n=66)
- 500 mg QD selected as expansion dose
- 35 pts with non-enhancing gliomas (escalation, n=11; expansion, n=24)
- Study remains ongoing as of data cutoff of 12May2017; median treatment duration for the non-enhancing glioma population is 16 months

<table>
<thead>
<tr>
<th>Disposition, n (%)</th>
<th>100 mg (n=0)</th>
<th>300 mg (n=2)</th>
<th>500 mg (n=28)</th>
<th>600 mg (n=1)</th>
<th>900 mg (n=4)</th>
<th>Total (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On treatment</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>3</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td>0</td>
<td>2</td>
<td>13</td>
<td>1</td>
<td>1</td>
<td>17 (49)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>0</td>
<td>2</td>
<td>13</td>
<td>1</td>
<td>1</td>
<td>17 (49)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Total treated (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>38 (21, 71)</td>
</tr>
<tr>
<td><strong>Gender (M/F), n</strong></td>
<td>23/12</td>
</tr>
<tr>
<td><strong>ECOG status at baseline, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (48.6)</td>
</tr>
<tr>
<td>1</td>
<td>18 (51.4)</td>
</tr>
<tr>
<td><strong>IDH1-R132H mutation</strong></td>
<td>28 (80.0)</td>
</tr>
<tr>
<td><strong>WHO tumor grade</strong></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>24 (68.6)</td>
</tr>
<tr>
<td>Grade III</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td><strong>1p19q co-deleted, n (% of those tested)</strong></td>
<td>10 (34.5)</td>
</tr>
</tbody>
</table>

*aAll patients had IDH1 mutation; other 20% included R132C, R132S and others*

*bMissing for 6 patients (17% of total)*

Data cutoff: 12May2017
## Prior Therapies

<table>
<thead>
<tr>
<th>Prior radiation therapy, n (%)</th>
<th>20 (57.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior systemic therapies, n (%)</td>
<td>24 (68.6)</td>
</tr>
<tr>
<td>Median number of prior systemic therapies, n (range)</td>
<td>2 (1, 5)</td>
</tr>
<tr>
<td>1 prior systemic therapy, n (%)</td>
<td>12 (34.3)</td>
</tr>
<tr>
<td>≥ 2 prior systemic therapies, n (%)</td>
<td>12 (31.4)</td>
</tr>
<tr>
<td>Type of prior systemic therapy</td>
<td></td>
</tr>
<tr>
<td>Temozolomide, n (%)</td>
<td>22 (62.9)</td>
</tr>
<tr>
<td>Bevacizumab, n (%)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Procarbazine/CCNU/vincristine, n (%)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Median time since last systemic therapy, months (range)</td>
<td>7.38 (1, 139.5)</td>
</tr>
<tr>
<td>Median duration of last systemic therapy, months (range)</td>
<td>9.59 (0, 36.0)</td>
</tr>
<tr>
<td>Anticonvulsants at baseline, n (%)</td>
<td>26 (74.3)</td>
</tr>
<tr>
<td>Steroid use at baseline, n (%)</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

* a minimum of 0 indicates missing dates for one patient and actual duration of last therapy could not be calculated

** Data cutoff: 12May2017  b Based on available clinical data and site confirmation; baseline use for one patient not confirmed due to missing data.
Safety Summary

- No DLTs observed, MTD not reached
- No on-treatment deaths
- 32/35 (91%) patients experienced at least 1 AE; 7 (20%) experienced a Grade 3 or higher AE
  - Most common (>15%, all grades) AEs included headache (34%), diarrhea (26%), nausea and vomiting (each 20%), anemia, fatigue, hyperglycemia, neutrophil count decreased, seizure and upper respiratory infection (each 17%)
  - 2 patients experienced Grade 3 hypophosphatemia, no other Grade 3 or higher events were reported in more than 1 patient
- 5/35 (14%) patients experienced at least 1 SAE and all were deemed unrelated to study treatment
  - Seizure was reported in 2 patients; no other SAEs were reported in more than 1 patient

Data cutoff: 12May2017
Pharmacodynamic Analysis of AG-120

**Tumor 2-HG suppression by AG-120**

![Graph showing tumor 2-HG suppression by AG-120 at different doses and IDH mutational status.]

**Baseline plasma 2-HG levels not elevated in glioma**

![Graph showing mean plasma 2-HG levels across different time points and treatment cycles.]

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1 Dang et al. Nature 2009 462(7274): 739; *Choi et al., Nat Med 2012 18(4) 624-629*
### Best Overall Response by Investigator

<table>
<thead>
<tr>
<th>Best Overall Response&lt;sup&gt;a&lt;/sup&gt;</th>
<th>N=35 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor response</td>
<td>2 (5.7)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stable disease</td>
<td>29 (82.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>2 (5.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup>LGG patients in escalation phase assessed by RANO<sup>1</sup>; LGG patients in expansion phase assessed by RANO LGG<sup>2</sup>

<sup>b</sup>Minor responses (>25% but <50% decrease relative to baseline) not centrally confirmed

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Median PFS for ALL non-enhancing patients = 13 mos (not reached for WHO grade II subset)

- Median treatment duration: **16 mos**
- 63% of patients treated for ≥ 1 year

Data cutoff: 12 May 2017
Non-enhancing gliomas display slow but continuous growth,\(^1\) the rate of which may correlate with transformation and survival\(^2,3\).

**Study Inclusion Criteria**

- IDH1-mutant; progression over ≤12 months
- \(\geq 3\) prior full sets of scans (not including screening), each separated by ≥2 months with ≤5 mm slice thickness and up to 1 mm interslice gap on either 2D T2 weighted image, 3D T2 weighted image, or FLAIR
- No tumor resection or RT <6 months prior to enrollment

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239 MRI scans from 24 patients:
- 63 historical MRIs (prior to screening)
- 176 MRIs (screening and on AG-120)

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Case Study #1

- Anapl. Oligo, 1p19q CD
- Tumor Resection 2009
- Radiation 2010
- TMZ 2010-2012
- **AG-120 Start 12/2015**
  - H1 MRI: 7/2014
  - H2 MRI: 5/2015
- **Remains on AG-120**
  - (17 mos @ cutoff)
- Best RANO response: SD

H1-H2 = historical pre-treatment scan; Screen = screening
Case Study #2

- Diffuse Astrocytoma
- Tumor Resection 2009
- No Radiation
- No other therapy
- **AG-120 Start 11/2015**
  - H1 MRI: 7/2013
- **Remains on AG-120**
  - *(18 mos @ cutoff)*
- Best RANO response: SD

H1 = historical pre-treatment scans; Screen = screening
Case Study #2 Co-registered MRIs

Pre-treatment changes

Historical 1
Historical 2
Screening

Screening
AG120_early cycle
AG120_later cycle

On-treatment changes
Case Study #2 Complete MRIs

Pre-treatment changes
- Historical 1
- Historical 2
- Screening

On-treatment changes
- Screening
- AG-120 early cycle
- AG-120 late cycle
Case Study #3

- Oligodendroglioma 1p19q co-del
- Biopsy 2007
- TMZ 2007-2008
- No Radiation
- **AG-120 Start 10/2015**
  - H1 MRI: 10/2014
- **Remains on treatment (18 mos @ cutoff)**
- Best RANO response: SD

H1 = historical pre-treatment scans; Screen = screening
Case Study #3 Co-registered MRIs

Pre-treatment changes
- Historical 1
- Historical 2
- Screening

On-treatment changes
- Screening
- AG-120_early cycle
- AG-120_late cycle
Case Study #4

- Oligodendroglioma (1p19q codel)
- Tumor Resection 2011
- No further treatment
- AG-120 Start 12/2015
  H1 MRI: 6/2013
- Remains on AG120 (17 mos @ cutoff)
  Best RANO response: SD

H1 = historical pre-treatment scans; Screen = screening
Non-enhancing gliomas display slow but continuous growth,\(^1\) the rate of which may correlate with transformation and survival\(^2,^3\)

Study Inclusion Criteria

- IDH1-mutant; progression over \(\leq 12\) months
- \(\geq 3\) prior full sets of scans (not including screening), each separated by \(\geq 2\) months with \(\leq 5\) mm slice thickness and up to \(1\) mm interslice gap on either 2D T2 weighted image, 3D T2 weighted image, or FLAIR
- No tumor resection or RT \(< 6\) months prior to enrollment

Method

- Pre-segmentation of T2/FLAIR
- Quantification of T2/FLAIR hyperintense volume
- Automatic calculation of bidimensional product
- Application of LGG RANO criteria and volumetric assessments
- Tumor growth rate estimates produced using mixed effect model

239 MRI scans analyzed across 24 patients
- 63 historical scans prior to Screening
- 176 during treatment with AG-120

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## Volumetric Growth Rates Pre- and Post-AG120 Treatment

### Volumetric growth rate all patients

<table>
<thead>
<tr>
<th></th>
<th>Natural History Study Pre-treatment&lt;sup&gt;a&lt;/sup&gt; (N=239&lt;sup&gt;c&lt;/sup&gt;)</th>
<th>Pre-AG120 (n=24)</th>
<th>Post-AG120 (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percent change (95% CI) for every 6 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28% (24%, 32%)</td>
<td>24% (12%, 37%)</td>
<td>11% (1%, 23%)</td>
</tr>
</tbody>
</table>

### Volumetric growth rate 1p19q intact subset

<table>
<thead>
<tr>
<th></th>
<th>Natural History Study Pre-treatment&lt;sup&gt;a&lt;/sup&gt; (N=73&lt;sup&gt;c&lt;/sup&gt;)</th>
<th>Pre-AG120 (n=15)</th>
<th>Post-AG120 (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percent change (95% CI) for every 6 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>34% (25%, 44%)</td>
<td>38% (19%, 60%)</td>
<td>14% (-1%, 31%)</td>
</tr>
</tbody>
</table>

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<sup>a</sup>Retrospective centralized multi-center study of 239 patients with progressive non-enhancing IDH mutant LGG  
Pre-treatment growth rate calculated using 3 MRI scans spanning minimum of 6 months prior to treatment using semi-automatic volumetric segmentation and mixed effect model (Presented by Huang et al. Abstract # 4809)  
<sup>b</sup>Percent change is derived based on the slope estimate from the mixed effect model  
<sup>c</sup>Number of subjects is indicated. Some subjects may have had more than one qualifying set of pre-treatment scans included in analysis
Confounding Effect of Prior Radiation

- Oligodendroglioma (WHO II) (1p19q intact)
- Resection: 2013
- **RT: Jun-July 2015**
- MRIs:
  - H1: 4/2015
  - H2: 8/2015
  - H3: 11/2015
  - Screen: 12/2015
- **Started AG-120 01/2016**

H1 = historical pre-treatment scan; Screen = screening
Lessons From Image Analysis

- Retrieval of historical (i.e., pre-screening) MRIs critical to establish kinetics of T2/FLAIR changes
- Review of prior treatment history (in particular, RT and surgery) critical to interpret clinical significance of T2/FLAIR changes
- Further development necessary in order to broadly implement methods for quantification and analyses of 3D tumor volumes and growth rates
- Specific imaging guidelines, methods, and study inclusion criteria are necessary for implementation of a standardized volumetric analysis approach
AG-120 is well tolerated in patients with non-enhancing glioma
AG-120 results in prolonged stable disease in this pretreated glioma population with a median treatment duration of 16 months and warrants further clinical evaluation
- 51% of patients still on treatment
- Preliminary results suggest a reduction in tumor growth rates
Further refinement of volumetric growth rate methodology is needed
Preliminary data suggest that AG-120 suppresses 2-HG in tumors; this will be further evaluated in a planned perioperative study
Acknowledgments

- We would like to thank the principal investigators, their institutions and most importantly the patients who took part in this study.

- This clinical study was funded by Agios Pharmaceuticals.