AG-120, a first-in-class mutant IDH1 inhibitor in patients with recurrent or progressive IDH1 mutant glioma: results from the phase 1 glioma expansion cohorts

Ingo K Mellinghoff¹, Mehdi Touat², Elizabeth Maher³, Macarena de la Fuente⁴, Timothy F Cloughesy⁵, Matthias Holdhoff⁶, Gregory Cote⁷, Howard Burris⁸, Filip Janku⁹, Raymond Huang⁷, Robert Young¹, Benjamin Ellingsson⁵, Julia Auer¹⁰, Liewen Jiang¹⁰, Yuko Ishii¹⁰, Sung Choe¹⁰, Bin Fan¹⁰, Katharine Yen¹⁰, Sam Agresta¹⁰, Eyal Attar¹⁰, Susan Pandya¹⁰, Patrick Y Wen⁷

¹Memorial Sloan Kettering Cancer Center, New York, NY; ²Institut Gustave Roussy, Paris, France; ³University of Texas Southwestern Medical Center, Dallas, TX; ⁴University of Miami, Miami, FL; ⁵University of California, Los Angeles, CA; ⁶Johns Hopkins University, Baltimore, MD; ⁷Dana-Farber/Harvard Cancer Centre, Boston, MA; ⁸Sarah Cannon Research Institute, Nashville, TN; ⁹MD Anderson Cancer Centre, Houston, TX; ¹⁰Agios Pharmaceuticals, Cambridge, MA

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IDH and cancer

- IDH mutations (IDH1 or IDH2) occur in many human cancers
- IDH mutations change the function of the enzyme → neomorphic production of the oncometabolite 2-HG
- Inhibiting the function of the mutant enzyme in patients with IDH1-mutant advanced hematologic malignancies results in objective responses in 36% of patients


IDH mutations in glioma

- 5% GBMs; ~80% of WHO grade II/III gliomas, mostly IDH1*1,2

**2016 WHO classification**

AG-120: oral, selective, first-in-class, potent inhibitor of mutant IDH1; reduces intracellular 2-HG in primary human IDH1-mutant hematological cancer cells


NOS = not otherwise specified
Study design

- Single-arm, open-label, multicenter, dose escalation and expansion study

### Non-enhancing glioma expansion*
- n=24
- IDH1-mutant; progression over ≤12 months
- ≥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

### ‘Basket’ expansion*
- Glioma n=22
- IDH1-mutant progressive tumors not meeting other cohort criteria (includes enhancing glioma)

*Other expansions: cholangiocarcinoma and chondrosarcoma, to be reported elsewhere

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1Burris H et al. Presented at ACR-NCI-EORTC 2015
ClinicalTrials.gov NCT02073994; RT = radiation therapy
Key objectives

- Safety and tolerability
  - Escalation dosing: 100 mg BID, 300, 400, 500, 600, 800, 900, 1200 mg QD
- Identify the maximum tolerated dose and/or recommended phase 2 dose
- Characterize pharmacokinetic/pharmacodynamic relationship
- Characterize preliminary clinical activity
  - Escalation phase, and for enhancing glioma in expansion phase:
    - RANO criteria (local investigators)
  - Non-enhancing glioma in expansion phase:
    - RANO LGG criteria (local investigators and central review)

ClinicalTrials.gov NCT02073994.

BID = twice daily; QD = once daily; RANO = response assessment in neuro-oncology; LGG = low grade glioma
Glioma enrollment complete as of 13 Jan 2016, N=66
- Escalation, n=20
- Expansion, n=46
Expansion dosing: 500 mg QD selected
Study ongoing as of 1 Aug 2016; 28 of 66 (42%) subjects remain on treatment

<table>
<thead>
<tr>
<th>Reasons for discontinuation, n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
</tr>
<tr>
<td>Physician decision</td>
</tr>
<tr>
<td>Adverse event</td>
</tr>
</tbody>
</table>

*aEvidence of clinical progression

Percentages derived from total treated subjects. Data cut-off date 1 Aug 2016
### Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>Total treated glioma N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>41 (21–71)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>41/25</td>
</tr>
<tr>
<td>ECOG status at baseline, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29 (44)</td>
</tr>
<tr>
<td>1</td>
<td>37 (56)</td>
</tr>
<tr>
<td>Tumor type and grade at screening, n (%)</td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma(^a)</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Grade II</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Grade III</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Astrocytoma(^a)</td>
<td>19 (29)</td>
</tr>
<tr>
<td>Grade II</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Grade III</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Grade II</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Grade III</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>12 (18)</td>
</tr>
<tr>
<td>1p19q co-deletion, n (% of those tested)(^b)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>ATRX mutation, n (% of those tested)(^c)</td>
<td>24 (92)</td>
</tr>
</tbody>
</table>

\(^a\) Grade missing for one patient

\(^b\) 11 (17% of total) unknown

\(^c\) 40 (61% of total) unknown

ECOG = Eastern cooperative oncology group
Prior and concomitant therapy

<table>
<thead>
<tr>
<th>Prior therapies</th>
<th>Total treated glioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of prior systemic therapies (range)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>Temozolomide, n (%)</td>
<td>47 (71)</td>
</tr>
<tr>
<td>PCV, n (%)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Bevacizumab, n (%)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Radiotherapy, n (%)</td>
<td>49 (74)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline anticonvulsant use, n (%)</td>
<td>54 (82)</td>
</tr>
<tr>
<td>Baseline steroid use, n (%)</td>
<td>7 (11)</td>
</tr>
</tbody>
</table>

PCV includes Procarbazine, CCNU (lomustine), and Vincristine given as a single regimen
Safety summary

- No DLTs observed; no on-treatment deaths
- MTD not reached
- Patients experiencing at least one serious treatment-emergent AE: 11 of 66 (17%)
  - All deemed unrelated to treatment

<table>
<thead>
<tr>
<th>AEs in glioma patients (regardless of relationship), N=66</th>
<th>All grades, n (%)</th>
<th>Grade ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients experiencing ≥1 AE</td>
<td>62 (94)</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Most frequent AEs (in ≥10% of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17 (26)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (21)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (14)</td>
<td>-</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>8 (12)</td>
<td>-</td>
</tr>
<tr>
<td>Aphasia</td>
<td>7 (11)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (11)</td>
<td>-</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>7 (11)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Assessed with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
DLT = dose-limiting toxicity; MTD = maximum tolerated dose
Pharmacokinetic profile

Plasma AG-120 after single dose (mean + SD)

- Plasma AG-120 steady state achieved in Cycle 1; exposure at 500 mg above efficacious level predicted by a subcutaneous xenograft mouse model
- Increases in plasma exposure above 500 mg QD are not proportional
- Mean terminal half-life: 33.6–71.5 hr
- 500 mg QD selected for expansion based on the observed clinical activity, safety, and PK/PD data

SD = standard deviation; PK/PD = pharmacokinetics/pharmacodynamics
Baseline plasma 2-HG levels in glioma are not elevated beyond the healthy volunteer range

500 mg QD AG-120

![Chart showing mean plasma 2-HG levels and statistically significant reductions compared to baseline.]

- Average 2-HG in healthy volunteers
- Pre-dosing baseline
- Day -3 single dose
- Cycle 1 Day 15
- Cycle 2 Day 1

Mean (+SD)

* P<0.01 vs baseline
** P<0.001 vs baseline

Best % change in sum of the product of diameters

By investigator; patients with ≥1 post-baseline tumor assessment shown, n=60
One additional subject not shown here had best change in SPD of 839% due to merged lesions

25% change is the RANO threshold for progressive disease and –50% change the RANO threshold for partial response
Graph shows best response at any single time point

SPD = sum of the product of diameters
# Best overall response by RANO/RANO LGG criteria (by investigator; efficacy evaluable subjects$^a$)

<table>
<thead>
<tr>
<th>Best response, n (%)</th>
<th>RANO Enhancing n=31</th>
<th>RANO Non-enhancing escalation n=11</th>
<th>RANO Non-enhancing expansion n=23</th>
<th>Overall Total glioma N=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor response</td>
<td>-</td>
<td>-</td>
<td>2 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>14 (45)</td>
<td>8 (73)</td>
<td>19 (83)</td>
<td>41 (63)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15 (48)</td>
<td>3 (27)</td>
<td>2 (9)</td>
<td>20 (31)</td>
</tr>
<tr>
<td>Unknown/not assessed</td>
<td>2 (6)</td>
<td>-</td>
<td>-</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Overall response rate$^b$, n (%) [95% CI]</td>
<td>-</td>
<td>-</td>
<td>2 (9) [1.1–28.0]</td>
<td>2 (3) [0.4–10.7]</td>
</tr>
</tbody>
</table>

RANO and RANO LGG evaluated by local investigators

$^a$Includes subjects who had baseline and post-baseline response assessments or discontinued prematurely

$^b$Defined as complete or minor or partial response
Duration on treatment and best overall response

By investigator; efficacy evaluable patients as of data cut-off 1 Aug 2016

Non-enhancing median duration of treatment, months:
8.1 (range 1.4–17.8)

Enhancing median duration of treatment, months:
1.9 (range 0.4–10.4)

A = astrocytoma
OD = oligodendroglioma
OA = oligoastrocytoma
GBM = glioblastoma
Exploratory imaging: glioma growth rates

- Gliomas display slow but continuous growth,\(^1\) the rate of which may correlate with transformation and survival\(^2;3\)
- Exploratory goal: measurement of effects on tumor growth rates

Non-enhancing glioma expansion
\(n=24\)

- 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

174 MRI scans (\(n=63\) historical scans, \(n=111\) protocol MRIs)

Methods

- Pre-segmentation of T2/FLAIR
- Editing and sign-off by 3 neuroradiologists
- Quantification of T2/FLAIR hyperintense volume
- Automatic calculation of bidimensional product
- Application of LGG RANO criteria and volumetric assessments

Example: volumetric analysis

Case example
H1 Screen C9D1

Figures provided by Jonathan Goldin, MedQIA
Tumor imaging summary

- Non-enhancing expansion subgroup with centralized, computer-assisted analysis (n=24*)
- Patients with stable or decreasing tumor slope on AG-120 compared to historic scans:
  - 14 of 22 (64%) by volumetric
  - 12 of 22 (55%) by bi-dimensional

*Two patients did not have historical scans
Study summary

- AG-120 is well tolerated in patients with IDH1-mutated glioma (as of 1 Aug 2016)
- 42% of patients remain on AG-120 (as of 1 Aug 2016)
- In non-enhancing expansion cohort (efficacy evaluable, n=23), 9% (n=2) with minor response and 83% (n=19) with stable disease
- Volumetric analysis demonstrated decrease in tumor growth rate compared to pre-treatment rate in 64% (n=14 of 22) of non-enhancing expansion patients receiving AG-120 and requires further development as a response evaluation tool
- 2-HG MRS could not be adequately assessed in this study and future efforts will incorporate a standardized methodology
- Further evaluation of mutant IDH inhibitors in glioma is warranted; AG-881, a brain-penetrant pan-IDH inhibitor, is under phase 1 evaluation in patients with IDH1- and/or IDH2-mutated gliomas or other solid tumors (ClinicalTrials.gov NCT02481154)

MRS, magnetic resonance spectroscopy
Acknowledgments

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

- This clinical study was funded by Agios Pharmaceuticals