AG-270 Data at 2019 AACR-NCI-EORTC International Conference 2019

October 27, 2019
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Today’s Agenda

• Opening Remarks – **Jackie Fouse, Ph.D.**, Chief Executive Officer

• Preclinical AG-270 Data – **Kevin Marks, Ph.D.**, Vice President, Head of Biology

• AG-270 Phase 1 Results – **Chris Bowden, M.D.**, Chief Medical Officer

• Q&A – **Keith T. Flaherty, M.D.**, Director of Clinical Research MGH Cancer Center
2019 Key Milestones & Data Presentations Position Agios for Long-term Value Creation

Key 2019 Milestones

- FDA approval and commercialization of monotherapy TIBSOVO® in untreated AML
- Initiate AG-636 Phase 1 dose-escalation trial in lymphoma in 1H 2019
- Complete AG-270 Phase 1 dose-escalation and select go forward dose
- Initiate expansion arms in the AG-270 Phase 1 study in Q3 2019
  - Achieve proof-of-concept for mitapivat in thalassemia in 2H 2019
  - Submit sNDA for TIBSOVO® in second line or later cholangiocarcinoma by YE
- Complete enrollment in PK deficiency pivotal trials ACTIVATE-T and ACTIVATE by YE

Key Upcoming Data Presentations

- Updated data from the perioperative study of ivosidenib and vorasidenib accepted for presentation at the SNO Annual Meeting
- Data from IDH and PKR programs have been accepted for presentation at ASH, including:
  - New data from the extension phase of the Phase 2 DRIVE PK study of mitapivat in adults with PK deficiency
  - Important translational data from the Phase 1 study of TIBSOVO® and azacitidine in frontline AML
Targeting MAT2A in *CDKN2A/MTAP*-deleted Cancers

Kevin Marks, Vice President and Head of Biology
A Key Insight: Deletion of MTAP Makes Cancers Vulnerable to Targeting of MAT2A

1. **MTAP deletion**

2. **Substrate MTA accumulates**

3. **Partial inhibition of PRMT5**

4. **Sensitivity to a ‘second hit’: targeting MAT2A starves PRMT5 of its substrate**

Sources: Marjon et al Cell Reports. 2016 Apr 19;15(3):574-587 and MTAP deletion frequency from Agios analysis of data from The Cancer Genome Atlas
MTAP Deletions Occur in ~15% of All Cancers

MTAP deletion frequencies are from Agios analysis of data from The Cancer Genome Atlas

Source: Adapted from Beroukhim et al Nature 2010
Agios MAT2A Inhibitors Selectively Impact Proliferation of \( MTAP \)-null Cancers

Growth Inhibition in Cancer Cells

\( MTAP \) WT HCT116 +/- \( MTAP \)

\( MTAP \) null

0 25 50 75 100 125
\% Growth
(cell titer glo assay)

Log Conc. (M)

0 \( \times \) 10^{-9} 10^{-8} 10^{-7} 10^{-6} 10^{-5} 10^{-4}

MAT2Ai Tumor volume (mm³)

0 200 400 600 800 1000 1200 1400

Days post implant

Vehicle \( +/- \) S.E.M

MAT2Ai

MTAP-deleted HCT116 Colon Carcinoma Xenograft Model

MTAP-WT HCT116 Colon Carcinoma Xenograft Model

0 200 400 600 800 1000 1200 1400

Days post implant

Vehicle \( +/- \) S.E.M

MAT2Ai

Cell Lines (n=330)

High Sensitivity Low
MAT2A Inhibitor AG-270 Possesses Broad Activity in ‘Mouse Clinical Trial’ Using Patient Derived Xenograft Models

Anti-tumor activity observed in a variety of models, with examples of regressions / tumor stasis

N=3 per model; established tumors treated at 200 mpk AG-270 QD
Mechanistic Understanding of the Pathway Downstream of MAT2A

1. RNA splicing concurrent with transcription

2. Splicing complex requires PRMT5

3. MAT2A inhibition blocks splicing

4. Defects in gene expression, DNA replication, genome integrity

5. DNA repair and cell cycle defects, leading to actionable combination partners including taxanes
AG-270 Treatment Induces Substantial Mitotic Defects in HCT116 MTAP-/- cells

- Single Agent AG-270 treatment leads to DNA damage (γH2AX) and micronuclei formation
- Effects are selectively observed in MTAP-/- cells and not in MTAP-wt cells
AG-270 Enhanced Docetaxel Treatment in an NSCLC (SCC) MTAP-null Mouse Model

4 of 8 animals were tumor free at last dose and remained tumor free until the arm was terminated on Day 141.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Days to ~1000 mm³</th>
<th>Tumor growth inhibition, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>21</td>
<td>–</td>
</tr>
<tr>
<td>AG-270</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>AG-270 + docetaxel</td>
<td>–</td>
<td>91</td>
</tr>
</tbody>
</table>
MAT2A Inhibition Leads to DNA Damage and Cell Cycle Defects, Leading to Strong Synergy with Anti-mitotic Taxanes
A phase 1 trial of AG-270 in patients with advanced solid tumors or lymphoma with homozygous MTAP deletion

Rebecca S Heist, Mrinal M Gounder, Sophie Postel-Vinay, Frederick Wilson, Elena Garralda, Khanh Do, Geoffrey I Shapiro, Patricia Martin-Romano, Gerburg Wulf, Michael Cooper, Caroline Almon, Salah Nabhan, Varsha Iyer, Yanwei Zhang, Kevin M Marks, Elia Aguado-Fraile, Frank Basile, Keith Flaherty, Howard A Burris

1Massachusetts General Hospital, Boston, MA, USA; 2Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; 3Institut Gustave Roussy, Villejuif, France; 4Yale Cancer Center, New Haven, CT, USA; 5Vall d’Hebron Institute of Oncology, Barcelona, Spain; 6Dana-Farber Cancer Center, Boston, MA, USA; 7Beth Israel Deaconess Medical Center, Boston, MA, USA; 8Agios Pharmaceuticals, Inc., Cambridge, MA, USA; 9Sarah Cannon Research Institute, Nashville, TN, USA
Study design

Phase 1, open label, multicenter study (ClinicalTrials.gov NCT03435250)

Adult patients with:
- Advanced solid tumors or lymphoma without effective standard treatment options
- Homozygous CDKN2A or MTAP deletion (Figure 3)

Arm 1, n=39: Continuous oral AG-270 QD or BID in 28-day cycles, until disease progression or unacceptable toxicity

Dose escalation guided by a Bayesian logistic regression model

Primary objective:
MTD of AG-270

Secondary objectives:
- Safety and tolerability
- PK and profiling of potential metabolites
- PD (changes in circulating SAM and methionine concentrations)
- Antitumor activity

Exploratory objective:
- PD in tumor tissue (changes in SDMA methyl marks).

Assessments
PK/PD:
- Plasma SAM and methionine concentrations
- Tumor biopsies for SDMA assessment by IHC before the start of treatment and at C2D1

Efficacy:
- Disease status every 2 cycles

BID = twice daily; C = cycle; D = day; IHC = immunohistochemistry; MTD = maximum tolerated dose; PK/PD = pharmacokinetics/pharmacodynamics; QD = once daily
MTAP and CDKN2A deletion for patient selection

Analysis of Cancer Genome Atlas data

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>CDKN2A deletion, %</th>
<th>MTAP deletion, %</th>
<th>Tumors with CDKN2A/MTAP co-deletion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>28</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>DLBCL</td>
<td>31</td>
<td>23</td>
<td>73</td>
</tr>
<tr>
<td>Esophageal and gastric</td>
<td>25</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>Lung (all)</td>
<td>23</td>
<td>19</td>
<td>82</td>
</tr>
</tbody>
</table>

MTAP and CDKN2A within 100 kbp of each other on chromosome 9p21

- Chr9p21 deleted in ~15% of cancers
- MTAP loss commonly coincides with CDKN2A loss

Required for patient enrollment: evidence of homozygous CDKN2A deletion by local testing (e.g. next-generation sequencing) or of homozygous MTAP deletion by a central IHC assay

IHC assay optimized for MTAP protein expression in FFPE tumor tissue, with <20% MTAP-positive cells as the cutoff value for MTAP deletion

NSCLC (SCC)
MTAP-positive tumor cells = 100%

NSCLC (adenocarcinoma)
MTAP-positive tumor cells = 0%

Pancreatic (adenocarcinoma)
MTAP-positive tumor cells = 100%

Pancreatic (adenocarcinoma)
MTAP-positive tumor cells = 0%

DLBCL = diffuse large B-cell lymphoma; FFPE = formalin-fixed paraffin-embedded; NSCLC = non–small-cell lung cancer; SCC = squamous cell carcinoma
## Patient Characteristics

<table>
<thead>
<tr>
<th>Dose</th>
<th>50 mg QD</th>
<th>100 mg QD</th>
<th>150 mg QD</th>
<th>200 mg QD</th>
<th>400 mg QD</th>
<th>200 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>11</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

### Baseline characteristic (N=39)

<table>
<thead>
<tr>
<th>Age, median (range), years</th>
<th>65 (32–87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60, n (%)</td>
<td>17 (44)</td>
</tr>
<tr>
<td>≥60, n (%)</td>
<td>22 (56)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>21 (54)</td>
</tr>
</tbody>
</table>

**Enrollment on the basis of:**

- **CDKN2A deletion, n (%)**: 34 (87)
- **MTAP deletion, n (%)**: 5 (13)

**Patients with both CDKN2A deletion and tumor tissue evaluable for MTAP deletion by IHC, n (%)**: 22 (56)

**Patients with both CDKN2A deletion and MTAP deletion by IHC, n (%)**: 15 (68)

<table>
<thead>
<tr>
<th>Primary tumor type, n (%)</th>
<th>7 (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile duct cancer</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>4 (10)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Other cancer type</td>
<td>17 (44)</td>
</tr>
</tbody>
</table>

**Number of lines of prior therapy, n (%)**

- **One**: 12 (31)
- **Two**: 9 (23)
- **Three or more**: 18 (46)

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*aCDKN2A status based on local testing, MTAP status by IHC performed centrally*
Pharmacokinetics

- Mean exposure increased in an approximately dose-proportional manner between 50 mg QD and 200 mg QD.
- Mean exposure was lower at 400 mg QD than 200 mg QD, possibly secondary to a reduction in oral bioavailability.
- Due to this observation, a dose of 200 mg BID was evaluated, which increased steady-state area under the plasma concentration-time curve (AUC) by 1.9-fold relative to a dose of 200 mg QD.
Reductions in plasma SAM concentration at steady state (C1D15)

- Plasma SAM concentration at C1D15 decreased by 65–74% across doses of 50–200 mg QD and 200 mg BID
  - The lower reduction in plasma SAM concentration (~54%) observed at 400 mg QD is consistent with the lower AG-270 exposure observed at this dose
- Average reductions in plasma SAM concentration are within the range associated with maximum tumor growth inhibition in preclinical models (60–80%)

Box denotes 25th to 75th percentiles, horizontal bar the median, and + the mean, with whiskers extending to the minimum and maximum values
Analysis of nine paired tumor biopsies by IHC showed decreases in levels of SDMA residues, consistent with MAT2A inhibition.

The average (min, max) H-score reduction compared with baseline was 36.5% (–98.8%, +21.4%).
## Summary of AEs and dose-limiting toxicities by dose cohort

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>50 mg (QD, n=3)</th>
<th>100 mg (QD, n=7)</th>
<th>150 mg (QD, n=6)</th>
<th>200 mg (QD, n=11)</th>
<th>400 mg (QD, n=6)</th>
<th>200 mg (BID, n=6)</th>
<th>Total N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with any AG-270–related AE, n (%)</strong></td>
<td>3 (100)</td>
<td>4 (57)</td>
<td>4 (67)</td>
<td>6 (55)</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>26 (67)</td>
</tr>
<tr>
<td><strong>Most common (&gt;10%) AG-270–related AE, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>0</td>
<td>1 (14)</td>
<td>2 (33)</td>
<td>4 (36)</td>
<td>0</td>
<td>3 (50)</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (67)</td>
<td>3 (43)</td>
<td>1 (17)</td>
<td>1 (9)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (17)</td>
<td>1 (9)</td>
<td>0</td>
<td>1 (17)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (67)</td>
<td>0</td>
<td>2 (33)</td>
<td>1 (9)</td>
<td>0</td>
<td>1 (17)</td>
<td>6 (15)</td>
</tr>
<tr>
<td><strong>Patients with grade 3 or higher</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG-270–related AE, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>2 (18)</td>
<td>0</td>
<td>4 (67)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (9)</td>
<td>0</td>
<td>2 (33)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (9)</td>
<td>0</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Decreased white blood cell count</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Liver injury</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>2 (5)</td>
</tr>
<tr>
<td><strong>Dose-limiting toxicities, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td>Decreased neutrophil count</td>
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<td>0</td>
<td>1 (9)</td>
<td>0</td>
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<td>1 (3)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (17)</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>3 (8)</td>
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<tr>
<td>Acute liver injury</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>
Summary of AEs and dose-limiting toxicities

- Generalized erythematous rash in three patients, treated at 100 mg QD, 150 mg QD and 200 mg BID:
  - Onset during second week of treatment, resolved <1 week after AG-270 interruption
  - Successful rechallenge at a lower dose in two patients.

**QD cohorts**

- Increases in unconjugated bilirubin, starting at 100 mg QD:
  - Consistent with UGT1A1 inhibition, exposure-dependent, reversible.

- Mild myelosuppression, starting at 200 mg QD:
  - Most consistently manifested as reversible thrombocytopenia (with or without leukopenia/anemia).

**200 mg BID cohort**

- Reversible acute liver injury in two of six patients:
  - Asymptomatic grade 3 and 4 increases in alanine aminotransferase, aspartate aminotransferase, and total bilirubin
  - Outpatient treatment with oral steroids, leading to complete resolution
  - Not clearly related to higher AG-270 systemic exposure.

- Grade 3 and 4 thrombocytopenia in two of six patients.

- **MTD was determined to be 200 mg QD.**
Duration of treatment and best overall response in patients receiving AG-270

- A 53-year-old man with a refractory, progressive sex cord stromal tumor continues to have stable disease after 12.8 months of treatment (100 mg QD)
- A 62-year-old woman with bile duct cancer continues to have stable disease after 6.5 months of treatment (150 mg QD)
- A 54-year-old man with a high-grade neuroendocrine carcinoma of the lung achieved a partial response that is ongoing; he remains on treatment (200 mg QD)
Duration of treatment and best overall response in patients receiving AG-270

**Response by dose**

- **50 mg QD**
- **100 mg QD**
- **150 mg QD**
- **200 mg QD**
- **200 mg BID**
- **400 mg QD**

**Response by tumor type**

- **Bile duct**
- **Pancreatic**
- **Mesothelioma**
- **NSCLC**
- **Other**

Legend:
- PR (Partial Response)
- SD (Slight Decrease)
- PD (Progression of Disease)
- NA (Not Applicable)
- UNK (Unknown)
- Ongoing
Conclusions

- AG-270 is the first MAT2A inhibitor to be evaluated in humans.
- The MTD was determined to be 200 mg QD.
  - DLTs included transient diffuse rashes, neutropenia and thrombocytopenia, and reversible acute liver injury.
- AG-270 generates reductions in plasma SAM concentration and in levels of tumor SDMA at well-tolerated doses.
- Average reductions in plasma SAM concentration were similar between 50 and 200 mg QD, and within the range associated with maximum tumor growth inhibition in preclinical models (60–80%).
- Objective tumor response was uncommon in this group of patients with treatment-refractory malignancies.
  - However, a confirmed partial response was observed in a patient with a high-grade neuroendocrine carcinoma of the lung and two patients experienced prolonged stable disease of more than 6 months.
Two arms of the Phase 1 trial combining AG-270 with taxanes currently enrolling patients

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>AG-270 monotherapy</th>
<th>Reported here</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN2A- and/or MTAP-null solid tumors or lymphoma</td>
<td>n=39</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 2</th>
<th>AG-270 with docetaxel</th>
<th>CDKN2A- and/or MTAP-null NSCLC (2nd line)</th>
<th>MTAP-null NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n≈15</td>
<td>n = up to 25</td>
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</table>

<table>
<thead>
<tr>
<th>Arm 3</th>
<th>AG-270 with nab-paclitaxel and gemcitabine</th>
<th>CDKN2A- and/or MTAP-null pancreatic cancer (1st or 2nd line)</th>
<th>MTAP-null pancreatic cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n≈15</td>
<td>n = up to 29</td>
</tr>
</tbody>
</table>

- Dosing with AG-270 in the combination arms will start at 100 mg QD and can be increased to 200 mg QD