A Phase 1 Study of Tazemetostat (EPZ-6438), an Enhancer of Zeste-Homolog 2 (EZH2) Inhibitor: Preliminary Activity in INI1-Negative Tumors

A Italiano, H Keilhack, M Toulmonde, J-M Coindre, J-M Michot, C Massard, L Ottesen, L Reyderman, SJ Blakemore, S Kraljevic, B Thomson, A McDonald, PT Ho, J-C Soria, V Ribrag

Participating Institutions
Insitut Gustave Roussy, Villejuif, France
Institut Bergonie, Bourdeaux, France

Sponsor
Epizyme, Inc
Disclosures

- H. Keilhack, B. Thomson, SJ Blakemore, B Thomson, A McDonald and PT Ho: employees of Epizyme, Inc.

- L Otteson, L Reyderman and S Kraljevic: employees of Eisai, Inc
EZH2 Catalyzed Chromatin Remodeling

- EZH2 is the catalytic subunit of the multi-protein PRC2 (polycomb repressive complex 2)
- PRC2 is the only human protein methyltransferase that can methylate H3K27
  - Catalyzes mono-, di- and tri-methylation of H3K27
  - H3K27me3 is a transcriptionally repressive histone mark
- H3K27 is the only significant substrate for PRC2
- Aberrant trimethylation of H3K27 is oncogenic in a broad spectrum of human cancers

Gene Transcription

Chase 2011
Antagonism of PRC2 and SWI/SNF-Dependent Chromatin Remodeling Regulates Pluripotency

Stem or Progenitor Cells

Highly dependent on EZH2 activity

SWI/SNF

INI1

SMARCA4

PRC2

EZH2

↓ PRC2 target genes

Stem cell programs

↓ Self-renewal and Block in differentiation

Adapted from Wilson 2010
EZH2 Activity Is Down-regulated as Progenitor Cells Become Differentiated

Stem or Progenitor Cells

Highly dependent on EZH2 activity

Differentiated Cells

EZH2 activity down-regulated

SWI/SNF

PRC2

INI1

EZH2

SMARCA4

↓ PRC2 target genes

Stem cell programs

Self-renewal and Block in differentiation

SWI/SNF

PRC2

INI1

EZH2

SMARCA4

↑ PRC2 target genes

Stem cell programs

Quiescence and Differentiation

Adapted from Wilson 2010
INI1 Loss Creates an Oncogenic Dependency on EZH2 in Tumors

Stem or Progenitor Cells

Highly dependent on EZH2 activity

SWI/SNF

PRC2

INI1

EZH2

SMARCA4

↓↓↓ PRC2 target genes

Hyper-repression of PRC2 targets

↑↑ Stem cell programs

Potentiation of stem cell programs

Oncogenic Transformation

INI1-negative tumors, e.g.:
Malignant rhabdoid tumor (MRT)
Epithelioid sarcoma

EZH2 knockout reverses oncogenesis induced by INI1 loss

Adapted from Wilson 2010
• Malignant Rhabdoid Tumors
  – Often pediatric, however adult cases reported
  – Occur in the kidney, CNS and soft tissue
  – Chemo-resistant
  – Dismal prognosis with survival rates <25%

INI1-Negative Rhabdoid Tumors are a Group of Devastating Diseases

MRT in an Infant
Image courtesy of S. Goldman, MD

Tomlinson 2005

Horazdovsky 2013
Tazemetostat (EPZ-6438): Potent and Highly Selective EZH2 Inhibitor

Novel Structure, Potent Target Inhibition

\[ \text{Ki} < 2.5 \text{ nM} \]
Selectivity >20,000-fold (100-fold for EZH1)

Antitumor Activity in Xenograft Model of INI1-negative MRT (G401)
Phase 1 Trial Design
E7438-G000-001 (NCT01897571)

- Population: relapsed or refractory solid tumors or B-cell lymphoma
- Study design: 3+3 dose-escalation completed
  - Expansion cohorts at 800 mg and 1600 mg completed
  - Food effect sub-study at 400 mg completed
- Primary endpoint: determination of RP2D/MTD
- Secondary endpoints: safety, PK, PD and tumor response (every 8 wks)
- Data cut: 31-Aug-2015

<table>
<thead>
<tr>
<th>Dose (mg BID)</th>
<th>Patients (n=51)</th>
<th>Solid tumors (n=30)</th>
<th>B-cell NHL (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100*</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>200</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>400</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>800</td>
<td>14</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>1600</td>
<td>12</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Food Effect</td>
<td>13</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

*NHL data presented by Ribrag, ICML 2015*
## Patient Tumor Types

<table>
<thead>
<tr>
<th>Relapsed or refractory solid tumor</th>
<th>N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>INI1-negative (SMARCB1)*</td>
<td></td>
</tr>
<tr>
<td>Malignant rhabdoid tumor</td>
<td>5</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>SMARCA4-negative*</td>
<td></td>
</tr>
<tr>
<td>Malignant rhabdoid tumor of ovary (SCCOHT)</td>
<td>2</td>
</tr>
<tr>
<td>Thoracic sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>GI malignancy</td>
<td>9</td>
</tr>
<tr>
<td>GU malignancy</td>
<td>2</td>
</tr>
<tr>
<td>GYN malignancy (non-SCCOHT)</td>
<td>2</td>
</tr>
<tr>
<td>CNS tumor/other sarcoma</td>
<td>3</td>
</tr>
<tr>
<td><strong>Relapsed or refractory NHL</strong></td>
<td><strong>N=21</strong></td>
</tr>
</tbody>
</table>

* INI1- or SMARCA4-negative by IHC
### Solid Tumor Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years [range]</td>
<td>53.5 [18-79]</td>
</tr>
<tr>
<td>Sex (M / F)</td>
<td>12/18</td>
</tr>
<tr>
<td># of prior therapeutic systemic regimens</td>
<td></td>
</tr>
<tr>
<td>0*</td>
<td>3 (10)</td>
</tr>
<tr>
<td>1</td>
<td>5 (17)</td>
</tr>
<tr>
<td>2</td>
<td>6 (20)</td>
</tr>
<tr>
<td>3</td>
<td>4 (13)</td>
</tr>
<tr>
<td>4</td>
<td>2 (7)</td>
</tr>
<tr>
<td>≥5</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Prior autologous hematopoietic cell transplant</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>17 (57)</td>
</tr>
</tbody>
</table>

* Malignant rhabdoid tumor pts - definitive surgery and/or adjuvant radiotherapy only
Safety Profile in NHL and Solid Tumor Patients (n=51)

<table>
<thead>
<tr>
<th></th>
<th>All Events*</th>
<th>All Treatment-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade &gt;3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Frequency >10% regardless of attribution
**EZH2 Target Inhibition in Tumor Tissue**

### Pre-Dose

**Rhabdoid Tumor of Kidney**
INI1-negative

- **H3K27me3**
  - Diffuse positive 1+: 100% tumor

**Epithelioid Sarcoma**
INI1-negative

- **H3K27me3**
  - Diffuse positive 1+: 100% tumor

### Post-Dose: Week 4

**H3K27me3**

- **Rhabdoid Tumor of Kidney**
  - Negative: 100% tumor

- **Epithelioid Sarcoma**
  - Negative: 50% tumor
Best Response in Patients with Solid Tumors

- Patients censored at time of progression
- Four additional other solid tumor patients with pending disease evaluation
<table>
<thead>
<tr>
<th>Tumor</th>
<th>Dose (mg BID)</th>
<th>Best Response</th>
<th>Time on study (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INI1-negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant rhabdoid tumor</td>
<td>800</td>
<td>CR week 8*</td>
<td>65+</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>PR week 8</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>SD week 8</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>SD week 8</td>
<td>12+</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>PD week 8</td>
<td>35</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>800</td>
<td>PR week 8</td>
<td>25+</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>SD week 8</td>
<td>24+</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>PD week 8</td>
<td>11</td>
</tr>
<tr>
<td><strong>SMARCA4-negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant rhabdoid tumor of ovary (SCCOHT)</td>
<td>1600</td>
<td>PR week 8*</td>
<td>25+</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>SD week 8</td>
<td>26+</td>
</tr>
<tr>
<td>Thoracic sarcoma</td>
<td>1600</td>
<td>PD week 5</td>
<td>6</td>
</tr>
</tbody>
</table>

* Confirmed response by RECIST 1.1 criteria
+ Patients who remain on study
CR in Patient with INI1-Negative Malignant Rhabdoid Tumor

55 y.o. male
800 mg BID

INI1 IHC

Tazemetostat: ongoing response week 65+

2013 Accomplishments

CR in Patient with INI1-Negative Malignant Rhabdoid Tumor

Baseline

Week 4

Week 8: CR

Week 20

Surgery + XRT

Diagnosis

2013

CR

2014

PD

Week 8: CR

2015

Week 20: pathologic CR
PR in Patient with INI1-Negative Epithelioid Sarcoma

**Baseline**

- 44 y.o. male
- 800 mg BID

**Week 8: PR**

- Tazemetostat: ongoing week 25+

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**Diagnosis**

- XRT
- everolimus
- sunitinib

**2011 - 2013**

- CR
- PD

**2014**

- 2015

**2016**

- Week 8: PR
- Week 16: PD
- Week 24: SD
Malignant Rhabdoid Tumor of Ovary is Characterized by Loss of SMARCA4

- SMARCA4, like INI1, is a subunit of the SWI/SNF complex
- MRT of ovary is also called Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT)
- Accounts for less than 1% of all ovarian cancer diagnoses, with an average age of 24 years at diagnosis
- Aggressive clinical course with 2-year survival <35%

Bailey 2004
PR in Patient with SMARCA4-Negative Malignant Rhabdoid Tumor of Ovary (SCCOHT)

2013 Accomplishments

PR in Patient with SMARCA4-Negative Malignant Rhabdoid Tumor of Ovary (SCCOHT)

2014 2015 2013

27 y.o. female
1600 mg BID

Baseline Week 8 Week 16

Tazemetostat: ongoing week 24+

2013 2014
CR CR PD
2015

Week 8: PR
Week 16: PR
Conclusions

- Tazemetostat has an acceptable safety profile
- Clinical activity (SD ≥6 months, PR or CR) observed in patients with relapsed INI1- and SMARCA4-negative tumors
  - Malignant rhabdoid tumor
  - Malignant rhabdoid tumor of ovary (SCCOHT)
  - Epithelioid sarcoma
- Pharmacodynamic inhibition of H3K27me3 demonstrated in tumor tissue
- Phase 2 study for INI1- and SMARCA4-negative tumors to open in US, Europe and Australia
  - Pediatric phase 1 to open concurrently
- Phase 2 study in EZH2 mutant and wild-type NHL (DLBCL and follicular lymphoma) enrolling in Europe and Australia
Acknowledgements

We thank our co-investigators and their teams and, most importantly, the patients and families who participated in the study.