A Phase 1 Study of Tazemetostat (EPZ-6438), an Inhibitor of EZH2: Preliminary Safety and Activity in Patients with Relapsed or Refractory NHL and Advanced Solid Tumors

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Participating Institutions
Institut Gustave Roussy, Villejuif, France
Institut Bergonie, Bordeaux, France

Sponsor
Epizyme, Inc
2013 Accomplishments

Methylation of H3K27me3 by PRC2 Mediates Transcriptional Repression

- EZH2 is the catalytic subunit of the multi-protein PRC2 (Polycomb Repressive Complex 2)
- PRC2 is the only protein methyltransferase complex that can methylate H3K27
  - Generates mono-, di- and tri-methylation of H3K27
  - H3K27me3 is a transcriptionally repressive histone mark, and is the only significant substrate for PRC2
- Aberrant trimethylation of H3K27 is oncogenic in a broad spectrum of human cancers, such as B-cell NHL
- Mutations in other proteins that affect H3K27 and chromatin accessibility in general are prevalent across almost all cancer types
EZH2 Regulates B-cell Maturation and Cell Fate

EZH2 is the “gatekeeper” for cell fate decisions.
EZH2 Gain of Function Mutations Result in Elevated H3K27me3 Levels

Wild-Type EZH2

Y641 or Y646 Mutant EZH2

Heterozygous WT/Y641 or Y646 Mutant EZH2

H3K27Me3 Production

+++

+/-

++++++

Sneeringer et al, PNAS, 2010
Tazemetostat (EPZ-6438): Potent and Highly Selective EZH2 Inhibitor

**Novel Structure, Potent Target Inhibition**

Ki < 2.5 nM

**Selective for EZH2**

Selectivity > 20,000-fold (100-fold for EZH1)

**Antitumor Activity in EZH2 Mutant and WT Xenograft Models of DLBCL**

**KARPAS-422 (EZH2 Y646N)**

- Vehicle, BID x 28
- 62.5 mg/kg BID x 28
- 125 mg/kg BID x 28
- 250 mg/kg BID x 28

**OCI-LY19 (EZH2 WT)**

- Vehicle, BID x 20
- 125 mg/kg BID x 20
- 500 mg/kg BID x 20

Knutson et al., Mol. Cancer Therapeutics, 2014
Thomenius et al. Molecular Targets Conference, 2015
First-in-Human Phase 1 Trial
E7438-G000-001 (NCT01897571)

- Population: relapsed or refractory B-cell lymphoma or solid tumors
- Study design: 3+3 dose-escalation completed
  - Expansion cohorts (800 mg and 1600 mg BID) completed
  - Food effect sub-study (400 mg BID) completed
  - Drug-drug interaction sub-study (800 mg BID) completed
- Primary endpoint: determination of RP2D/MTD
- Secondary endpoints: safety, PK, PD and tumor response (every 8 wks)
- Data cut: 7-Nov-2015

<table>
<thead>
<tr>
<th>Dose (mg BID)</th>
<th>Patients (n=58)</th>
<th>Solid tumors (n=37)**</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>
<tr>
<td>Drug-Drug</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

* 2 formulations

**Solid tumor data presented by A. Italiano, ESMO/ECC 2015

from Ribrag et al., ASH 2015
## Patient Tumor Types

### Relapsed or refractory NHL

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>GCB</th>
<th>Non GCB</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse Large B cell Lymphoma (DLBCL)</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Follicular lymphoma (FL)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marginal Zone lymphoma (MZL)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### Relapsed or refractory solid tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>INI1-deficient or negative</td>
<td>5</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>3</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>22</td>
</tr>
</tbody>
</table>

2/17 NHL patients tested to date are EZH2 mutant by cobas® test (in development, Roche Molecular Systems, Inc.)

from Ribrag et al., ASH 2015
Clinical Pharmacokinetics

- Rapid absorption ($t_{\text{max}} = 1-2$ h) with a mean terminal $t_{1/2} = 3 - 5$ h
- Dose-proportional $C_{\text{max}}$ and $AUC_{0-12h}$ at steady-state (day 15) through 1600 mg BID
- Decrease in systemic exposure between day 1 and day 15 with no further reduction afterwards
  - 42% decrease in $AUC_{0-12h}$ on day 15 vs. day 1 at 800 mg BID
  - $C_{\text{trough}}$ levels reach steady-state by day 15

from Ribrag et al., ICML 2015
Target inhibition in skin:
- Reduction of H3K27me3 by IHC at week 4 at all doses
- Exposure-dependent reductions in H3K27me3
- Differential effects by epithelial layer
  - Stratum basale - minimal change
  - Stratum spinosum – pronounced change
  - Full epidermis – composite signal of stratum spinosum and basale
- Reduction in H3K27me3 signal equivalent at 800 and 1600 mg BID

from Ribrag et al., ASH 2015
### Safety Profile in All Patients
(n=55: 20 NHL and 35 Solid Tumors)

<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 ≥3</td>
</tr>
<tr>
<td><strong>Asthenia</strong></td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td><strong>Decreased appetite</strong></td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dry skin</strong></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dysgeusia</strong></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Muscle spasms</strong></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hypophosphatemia</strong></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Night sweats</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Peripheral edema</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hepatocellular injury</strong></td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* All AEs with frequency >5% regardless of attribution shown

** All grade ≥3 treatment-related events shown

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*Ribrag et al., ASH 2015*
## NHL Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=21 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years [range]</td>
<td>63 [24-84]</td>
</tr>
<tr>
<td>Sex (M / F)</td>
<td>15/6</td>
</tr>
<tr>
<td># of prior therapeutic systemic regimens</td>
<td>1 (10)</td>
</tr>
<tr>
<td></td>
<td>2 (10)</td>
</tr>
<tr>
<td></td>
<td>1 (5)</td>
</tr>
<tr>
<td></td>
<td>8 (38)</td>
</tr>
<tr>
<td></td>
<td>3 (14)</td>
</tr>
<tr>
<td></td>
<td>7 (33)</td>
</tr>
<tr>
<td>Prior autologous hematopoietic cell transplant</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>17 (57)</td>
</tr>
</tbody>
</table>

from Ribrag et al., ASH 2015
Objective Response in NHL
All Patients (n=21)

Food Effects (FE):
200 mg on day -8 and day -1
400 mg BID from day 1

Data as of 27-May 2015
Response in EZH2-mutated DLBCL

53 year old female (EZH2\textsuperscript{Y646H}) treated at RP2D (800 mg BID)

Baseline SPD: 8282mm\textsuperscript{2}  
Wk 16 SPD: 3864 mm\textsuperscript{2} (PR)  
Wk 40 SPD: 3506 mm\textsuperscript{2} (PR)

Images courtesy of A. Italiano, Institut Bergonie

Data as of 27-May 2016
# Tazemetostat Phase 2 Dose Selection

<table>
<thead>
<tr>
<th>Dose BID</th>
<th>Efficacy</th>
<th>Safety</th>
<th>PK/PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response in NHL (%)</td>
<td>Grade ≥3 TEAE *</td>
<td>H3K27me3 Inhibition Emax **</td>
</tr>
<tr>
<td>&lt;800 mg</td>
<td>2/9 (22%)</td>
<td>7/24 (29%)</td>
<td>-</td>
</tr>
<tr>
<td>800 mg</td>
<td>5/8 (62%)</td>
<td>3/19 (16%)</td>
<td>81%</td>
</tr>
<tr>
<td>1600 mg</td>
<td>2/4 (50%)</td>
<td>4/12 (33%)</td>
<td>91%</td>
</tr>
</tbody>
</table>

* Treatment Emergent Adverse Events in all patients (n=55)

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** H3K27me3 Emax vs. Exposure

From Ribrag et al., ASH 2015
Subunits of SWI/SNF Complexes Are Mutated Across Many Indications

Adapted from Kadoch 2015
Antagonism of PRC2 and SWI/SNF-Dependent Chromatin Remodeling Regulates Pluripotency

Stem or Progenitor Cells

Highly dependent on EZH2 activity

SWI/SNF

PRC2

INI1

SMARCA4

↓ 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
- SWI/SNF
- PRC2
- INI1
- SMARCA4
- PRC2 target genes
- Stem cell programs
- Self-renewal and Block in differentiation

**Differentiated Cells**

- EZH2 activity down-regulated
- SWI/SNF
- PRC2
- INI1
- SMARCA4
- PRC2 target genes
- Stem cell programs
- Quiescence and Differentiation

Adapted from Wilson 2010
INI1 or SMARCA4 Loss Can Creates an Oncogenic Dependency on EZH2 in Tumors

**Stem or Progenitor Cells**

- Highly dependent on EZH2 activity
- SWI/SNF
- PRC2
- \(\downarrow\downarrow\downarrow\) PRC2 target genes
- \(\uparrow\uparrow\) Stem cell programs
- Oncogenic Transformation

**INI1 or SMARCA4-negative tumors**

- Malignant rhabdoid tumor (MRT)
- Malignant rhabdoid tumor of the ovary (MRTO/SCCOHT)
- Epithelioid Sarcoma (ES)
- Renal Medullary Carcinoma (RMC)

**EZH2 knockout reverses oncogenesis induced by INI1 loss**

Adapted from Wilson 2010

\[\text{Graph showing tumor-free survival vs. days}}\]
INI1- and SMARCA4-negative Rhabdoid Tumors are Aggressive in Children and Young Adults

Malignant Rhabdoid Tumors (MRT)
- Often pediatric, however adult cases reported
- Occur in the kidney, CNS and soft tissue
- Chemo-resistant
- Dismal prognosis with survival rates <25%

Malignant Rhabdoid Tumor of the Ovary (MRTO)
- Also known as Small Cell Carcinoma of the Ovary Hypercalemic Type (SCCOHT)
- Average age of diagnosis at 24 years
- Chemo-resistant
- Dismal prognosis with survival rates <35%

MRT in an Infant

MRTO in a 15-Yr Old

Image courtesy of S. Goldman, MD

Bailey et al., 2014
INI1- and SMARCA4-Negative Rhabdoid Tumor Models are Sensitive to Tazemetostat

**In vitro and in vivo cell killing of mutant INI1 MRT cells**

![Graph showing cell killing of mutant INI1 MRT cells](image1)

**In vitro and in vivo cell killing of mutant SMARCA4 MRTO cells**

![Graph showing cell killing of mutant SMARCA4 MRTO cells](image2)

Knutson et al. PNAS, 2013
Penebre et al. EORTC, 2015
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**
Negative: 100% tumor

**H3K27me3**
Negative: 50% tumor
## 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>Malignant rhabdoid tumor</td>
</tr>
<tr>
<td></td>
<td>Epithelioid sarcoma</td>
</tr>
<tr>
<td>SMARCA4-negative*</td>
<td>Malignant rhabdoid tumor of ovary (SCCOHT)</td>
</tr>
<tr>
<td></td>
<td>Thoracic sarcoma</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td></td>
</tr>
<tr>
<td>GI malignancy</td>
<td></td>
</tr>
<tr>
<td>GU malignancy</td>
<td></td>
</tr>
<tr>
<td>GYN malignancy (non-SCCOHT)</td>
<td></td>
</tr>
<tr>
<td>CNS tumor/other sarcoma</td>
<td></td>
</tr>
<tr>
<td><strong>Relapsed or refractory NHL</strong></td>
<td>N=21</td>
</tr>
</tbody>
</table>

* INI1- or SMARCA4-negative by IHC

from Italiano et al., ECC 2015
**Best Response in Patients with Solid Tumors**

* Patients censored at time of progression

** Four additional other solid tumor patients with pending disease evaluation

from Italiano et al., ECC 2015
CR in Patient with INI1-Negative Malignant Rhabdoid Tumor

55 y.o. male
800 mg BID

Diagnosis
Surgery + XRT

Week 4
June 20, 2014

Week 8: CR

Week 20

Tazemetostat: ongoing response week 65+

from Italiano et al., ECC 2015
PR in Patient with SMARCA4-Negative Malignant Rhabdoid Tumor of Ovary

Baseline

Week 8

Week 16

27 y.o. female
1600 mg BID

Tazemostat: ongoing week 24+

2013 2014 CR CR PD 2015 Week 8: PR Week 16: PR

from Italiano et al., ECC 2015
Clinical Pharmacology:
Food Effect and Drug-Drug Interaction

- The effect of food on tazemetostat pharmacokinetics
  - Patients (n=13) received tazemetostat 200 mg after an overnight fast and immediately after a high-fat breakfast in a randomized crossover fashion with 7 days between doses
  - Plasma tazemetostat concentrations were determined over 24 hours after each dose
  - Patients received tazemetostat 400 mg BID after completing the food effect component of the study

- The effect of tazemetostat on CYP3A4/5-mediated metabolism
  - Patients (n=13) received an oral dose of midazolam 2 mg on Day -1 and Day 15
  - Tazemetostat 800 mg BID administration started on Day 1 and continued throughout the study
  - Plasma midazolam concentrations were determined over 24 hours after each dose
Clinical Pharmacology: Food Effect

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fed:Fasted Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>0.72</td>
<td>0.52, 1.00</td>
</tr>
<tr>
<td>(ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{AUC}_{(0-\infty)}$</td>
<td>0.93</td>
<td>0.66, 1.30</td>
</tr>
<tr>
<td>(ng·h/mL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- $\text{AUC}_{(0-\infty)}$ and $C_{\text{max}}$ decreased by 7% and 28%, respectively.
- The 90% CI for both ratios contained 1.

Administration of tazemetostat with a meal resulted in a non-clinically relevant effect on systemic disposition and overall systemic exposure from Suttle et al., AACR 2016.
Pharmacokinetic results after administration of midazolam with and without tazemetostat demonstrate that tazemetostat is a weak inducer of Cyp3A4/5 from Smith et al., AACR 2016

Change relative to administration of midazolam alone
Phase 1 Summary

- Tazemetostat demonstrates clinical activity as monotherapy in patients with both B-cell NHL and solid tumors
- Relapsed or refractory DLBCL (both GCB and non-GCB), FL and MZL
  - Objective responses in B-cell NHL with either wild-type or mutated EZH2
  - Responses are durable – patients ongoing at 10+ to 21+ months
- Relapsed INI1- and SMARCA4-negative tumors
  - Malignant rhabdoid tumor, malignant rhabdoid tumor of ovary (SCCOHT), epithelioid sarcoma
  - Objective responses (CR and PR) and SD ≥6 months
- Pharmacodynamic inhibition of H3K27me3 demonstrated in tumor tissue and in surrogate tissue (skin)
- Safety profile as monotherapy is favorable for both monotherapy and combination development
- Pharmacokinetic results demonstrate that tazemetostat may be taken without regard to meals and is a weak inducer of CYP3A4/5
- RP2D dose of 800 mg BID supported by safety, efficacy, PK/PD
Current Tazemetostat Development

- **Non-Hodgkin Lymphoma**
  - Phase 2 trial for DLBCL and FL – France, Australia, UK, Italy, Canada, US, Germany.
    - Five cohorts – prospectively stratified according to cell-of-origin and EZH2 mutation status
  - Phase 1/2 trial in DLBCL of tazemetostat in combination with R-CHOP in front-line elderly high-risk patients to start in 2016
  - Phase 1b trial in DLBCL of tazemetostat in combination with a checkpoint inhibitor to start in 2016

- **Rhabdoid and non-rhabdoid INI1-negative or SMARCA4-negative Tumors and Synovial Sarcoma**
  - Phase 2 trial in adults – US, Belgium, France, Italy, Australia, Canada, Germany, Taiwan
  - Phase 1 trial in children (oral suspension formulation) – US, Australia, Denmark, France, Canada, UK, Germany.

- **Mesothelioma**
  - Phase 2 trial in mesothelioma with BAP1 loss of function to start in 2016 in US, France and UK
We thank our co-investigators and their teams and, most importantly, the patients and families who participated in the study.