Phase 1 Study of EPZ-6438 (E7438), an Enhancer of Zeste Homolog-2 (EZH2) Inhibitor: Dose Determination and Preliminary Activity in Non-Hodgkin Lymphoma


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

Sponsor
Epizyme, 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
- Hyper-trimethylation of H3K27 is tumorigenic in a broad spectrum of human cancers, including germinal center NHL

Chase A, Cross NC, Clin Cancer Res 2011
EPZ-6438 (tazemetostat): Potent and Highly Selective EZH2 Inhibitor

**EZH2 Mutations are Gain-of-Function**

<table>
<thead>
<tr>
<th>EZH2</th>
<th>H3K27me3 Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-Type</td>
<td>++</td>
</tr>
<tr>
<td>Y646 Mutant</td>
<td>+/-</td>
</tr>
<tr>
<td>Wild-Type and</td>
<td>+++</td>
</tr>
<tr>
<td>Y646 Mutant</td>
<td>+++</td>
</tr>
</tbody>
</table>
| A682G or A692V Mutant | ++++

**Selectivity for EZH2**

EPZ-6438: Knutson 2013, Knutson 2014

**Novel Structure, Potent Target Inhibition**

EPZ-6438:
Ki \(< 2.5\) nM
Selectivity >20,000-fold (100-fold for EZH1)
Rodent oral bioavailability: 15-55%

**In Vivo Efficacy with Oral Dosing**

Mean tumor volume ± SEM (mm³)
First-in-human Phase 1 Trial
E7438-G000-001 (NCT01897571)

- EPZ-6438: oral dosing from 100 mg to 1600 mg BID
- Population: relapsed or refractory B-cell lymphoma or solid tumors
- Study design: 3+3 dose-escalation
  - Expansion cohorts at 800 mg (n=6 planned) and 1600 mg (n=6 planned)
  - Food effect sub-study at 400 mg (n=12 planned)
- Primary endpoint: determination of RP2D/MTD
- Secondary endpoints: safety, PK, PD and tumor response (every 8 wks)
- Data cut-off: 8-Jun-2015

<table>
<thead>
<tr>
<th>Dose (mg BID)</th>
<th>Patients (n=45)</th>
<th>Solid tumors (n=26)</th>
<th>B-cell NHL (n=19)</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>7</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

* 2 formulations
## Patient Tumor Types

<table>
<thead>
<tr>
<th>Relapsed or refractory NHL</th>
<th>n=19 *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
<td></td>
</tr>
<tr>
<td>GCB</td>
<td>4</td>
</tr>
<tr>
<td>non-GCB</td>
<td>6</td>
</tr>
<tr>
<td>undetermined</td>
<td>3</td>
</tr>
<tr>
<td>Follicular lymphoma (FL)</td>
<td>5</td>
</tr>
<tr>
<td>Marginal zone lymphoma (MZL)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relapsed or refractory solid tumor</th>
<th>n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>INI1-deficient tumor</td>
<td>10</td>
</tr>
<tr>
<td>GI malignancy</td>
<td>7</td>
</tr>
<tr>
<td>GU malignancy</td>
<td>5</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>1</td>
</tr>
</tbody>
</table>

* 14 NHL patients tested to date: 13 WT + 1 mutant by cobas® EZH2 Mutation Test (in development, Roche Molecular Systems, Inc.)
# NHL Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=19) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>61 (24 - 84)</td>
</tr>
<tr>
<td>Sex (M / F)</td>
<td>14 (74) / 5 (26)</td>
</tr>
<tr>
<td># of prior therapeutic regimens</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (10)</td>
</tr>
<tr>
<td>2</td>
<td>1 (5)</td>
</tr>
<tr>
<td>3</td>
<td>7 (37)</td>
</tr>
<tr>
<td>4</td>
<td>2 (10)</td>
</tr>
<tr>
<td>≥5</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Refractory to last prior regimen</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Prior autologous hematopoietic cell transplant</td>
<td>5 (26)</td>
</tr>
</tbody>
</table>
Pharmacokinetics

- Rapid absorption ($t_{\text{max}} = 1\text{–}2\ \text{h}$) with a mean terminal $t_{1/2} = 3\text{–}5\ \text{h}$
- Dose-proportional $C_{\text{max}}$ and $AUC_{0\text{–}12\text{h}}$ 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 $AUC_{0\text{–}12\text{h}}$ on day 15 vs. day 1 at 800 mg BID
  - $C_{\text{trough}}$ levels reach steady-state by day 15
PK-PD: EZH2 Inhibition in Surrogate Tissue

Evidence of target inhibition in skin:
- Reduction of H3K27-Me3 IHC signal observed at week 4 at all doses
- Exposure-dependent reductions in H3K27-Me3 IHC signal
- Differential effects by epithelial layer
  - Minimal changes to stratum basale
  - Pronounced changes in stratum spinosum
  - Full epithelium represents composite signal of stratum spinosum and basale
## Adverse Events

### Patients with:
- DLT (thrombocytopenia) = 1
- Dose reduction = 1
- Drug discontinuation = 1
- Dose interruption = 7

### All Events vs. Treatment-Related

<table>
<thead>
<tr>
<th>Event</th>
<th>All Grades</th>
<th>Grade ≥3</th>
<th>All Grades</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any patient with AE</td>
<td>42</td>
<td>13</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>23</td>
<td>1</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Transaminase ↑</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* >10% of patients
† all patients
Overall Best Response: NHL
9/15 Evaluable Patients Have CR+PR

<table>
<thead>
<tr>
<th>Evaluable Patients (n=15)</th>
<th>DLBCL (n=9)</th>
<th>FL (n=5)</th>
<th>MZL (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+PR *</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Legend**
- Complete Response
- Partial Response
- Stable Disease
- Progressive Disease
- No Assessment
- Remains on-study
- G: GCB
- N: non-GCB
- * Cheson criteria
Target Lesion Activity: NHL
Evolution of Response

% change from baseline vs. months

- DLBCL
- FL
- MZL

* truncated
CR in Primary Mediastinal B-Cell Lymphoma

Baseline

23 y.o. male
200 mg BID

Week 40: CR

EPZ-6438: ongoing response week 78

Diagnosis
R-ACVBP
MTX
R-DHAP
R-ICE

2013 PR PD PD PD 2014 Week 16: PR
2015 Week 40: CR
CR in Follicular Lymphoma (EZH2\textsuperscript{wt})

78 y.o. male
800 mg BID

Week 60: CR

Baseline

EPZ-6438: ongoing response week 60
Response in DLBCL (EZH2\(^{Y646H}\))

53 y.o. female
800 mg BID

Mutant by cobas® EZH2 Mutation Test (in development). Confirmed Y646H by NGS.

EPZ-6438: ongoing response week 24
CR in INI1-Negative Malignant Rhabdoid Tumor

55 y.o. male
800 mg BID

Baseline
Week 4

May 09, 2014
June 25, 2014

Week 8: CR

Baseline
Week 8
Week 20

May 21, 2014
July 17, 2014
September 11, 2014

Baseline
Week 8
Week 20

Surgery + XRT

EPZ-6438: ongoing response week 58

Diagnosis

CR
PD
Week 8:
CR

2013
2014
2015
Conclusions

- EPZ-6438 has an acceptable safety profile
- 800 mg BID dose confirmed as Recommended Phase 2 Dose
  - Supported by PK, PK/PD in surrogate tissue, safety, efficacy
- Objective response (CRs, PRs) in relapsed DLBCL (both GCB and non-GCB) and FL
  - PR first observed as early as 2 mos and as late 10 months
  - Evolution of objective response (SD → PR, PR → CR) seen in 7 patients
  - Responses in patients with EZH2 wild-type and mutant tumors
- Phase 2 study for DLBCL (GCB and non-GCB) and FL open in France and Australia. UK to open in July.
  - Five parallel cohorts based on Cell of Origin and EZH2 mutation status
  - First patient enrolled on 10-June-2015
We thank the investigators and their teams and, most importantly, the patients and families who participated in the study.
Back-up Slides
## Grade $\geq 3$ Treatment-Related Adverse Events by Dose Level

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg BID)</th>
<th>Grade $\geq 3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>800</td>
<td>1/14</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>800</td>
<td>1/14</td>
</tr>
<tr>
<td>Transaminase</td>
<td>800</td>
<td>1/14</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1600</td>
<td>1/12</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>1600</td>
<td>1/12</td>
</tr>
</tbody>
</table>

* Protocol-defined DLT
All other AE’s occurred in cycle $\geq 2$ or in extension cohort patients
Response in Follicular Lymphoma (EZH2\textsuperscript{wt})

Baseline

Week 60: ongoing PR

55 y.o. male
800 mg BID

Diagnosis

1999

CHOP + XRT

CR

2005

PD

R-DHAP + SCT

CR

2014

PD

Week 8: SD

2015

Week 40: PR

EPZ-6438: ongoing response week 56