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, Bordeaux, 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**

- **EZH2 Mutations**
  - Wild-Type
  - Y646 Mutant
  - Wild-Type and Y646 Mutant
  - A682G or A692V Mutant

**Novel Structure, Potent Target Inhibition**

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

**Selective for EZH2**

**In Vivo Efficacy with Oral Dosing**

EPZ-6438: Knutson 2013, Knutson 2014
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>
2013 Accomplishments

Pharmacokinetics

- Rapid absorption ($t_{\text{max}} = 1-2 \text{ h}$) with a mean terminal $t_{1/2} = 3 - 5 \text{ h}$
- Dose-proportional $C_{\text{max}}$ and $\text{AUC}_{0-12h}$ 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 $\text{AUC}_{0-12h}$ 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

<table>
<thead>
<tr>
<th>Any patient with AE</th>
<th>n = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Events</td>
</tr>
<tr>
<td></td>
<td>All Grades *</td>
</tr>
<tr>
<td>Asthenia</td>
<td>23</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
</tr>
<tr>
<td>Transaminase ↑</td>
<td>2</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></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>

**Evaluable Patients (n=15)**

* Cheson criteria

**Diagram Notes:**
- **Complete Response** (green)
- **Partial Response** (orange)
- **Stable Disease** (blue)
- **Progressive Disease** (red)
- **No Assessment** (black)
- **Remains on-study** (gray arrow)

**Legend:**
- **G** GCB
- **N** non-GCB
2013 Accomplishments

Target Lesion Activity: NHL

Evolution of Response

% change from baseline

months

-100% -50% 0% 50% 100%

DLBCL
FL
MZL

* truncated
2013 Accomplishments

CR in Primary Mediastinal B-Cell Lymphoma

Baseline

23 y.o. male
200 mg BID

EPZ-6438: ongoing response week 78

Week 40: CR

Week 16: PR

2013

PR

PD

PD

PD

R-ACVBP

MTX

R-DHAP

R-ICE

2014

2015

2013

PR

PD

PD

PD
CR in Follicular Lymphoma (EZH2$^{wt}$)

Baseline

78 y.o. male
800 mg BID

Week 60: CR

EPZ-6438: ongoing response week 60

Week 8: Week 16: Week 32:
SD PR CR 2015
Response in DLBCL (EZH2^{Y646H})

53 y.o. female
800 mg BID

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

Baseline

Week 16: PR

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

55 y.o. male
800 mg BID

Baseline
May 09, 2014

Week 4
June 25, 2014

Week 8
May 21, 2014

Week 20
September 11, 2014

Diagnosis: Surgery + XRT

EPZ-6438: ongoing response week 58

2013 CR

2014 PD

2015 CR
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