EZH2 Inhibitor EPZ-6438 (E7438) in Non-Hodgkin Lymphoma: Pre-Clinical Models and Early Clinical Observations


12 August 2014
I have the following financial relationships to disclose:

- Grant/Research support from: LLS, MMRF, GSK, Eisai & Celgene
- Stockholder in and Employee of: Epizyme, Inc.
- Scientific Advisory Board Member of: Mersana
- Ad hoc Consultant for: New Enterprise Associates

and

- I will not discuss off-label use in my presentation
Key Topics

Pre-Clinical Data

- Mutant EZH2 plays a key role in germinal center (GC) B-cell NHL
- Emerging biology suggests additional roles of wild type (WT) EZH2 in GC NHL
- EZH2 inhibitor single agent activity in pre-clinical models of mutant and WT EZH2 NHL\(^1,2\)
- EPZ-6438 synergy in combination with CHOP components in pre-clinical models of mutant and WT EZH2 NHL\(^3\)

Clinical Data

- EPZ-6438 (E7438) Phase 1 design
- Safety, PK and PD among first three cohorts
- Early anti-lymphoma observations in NHL patients to date (cohorts 1-3)

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1. Knutson et al. 2014 MTC
2. Beguelin et al. 2013 *Cancer Cell*
EZH2 Catalyzed Chromatin Remodeling

- EZH2 is the catalytic subunit of the multiprotein PRC2 (polycomb repressive complex 2) complex
- PRC2 is the only PMT in humans that can methylate H3K27
- H3K27 is the only significant substrate for PRC2
- PRC2 catalyzes mono-, di- and tri-methylation of H3K27
- H3K27me3 is a transcriptionally repressive histone mark
- Hyper-trimethylation of H3K27 is tumorigenic in a broad spectrum of human cancers, including GC NHL
Gene Regulation in B-Cell Maturation and Lymphoma

Incidence: 72,000*
Prevalence: 185,000*

*Source: Clarion Report (2014), incorporating SEER and GLOBOCAN epidemiology, and recent literature from ASH, NCI, NIH, and academic investigators
Gene Regulation in B-Cell Maturation and Lymphoma

Genetic Alterations Affecting H3K27me3

- Point mutations of EZH2
- Overexpression of EZH2
- Overexpression of other PRC2 subunits
- LoF of HATs
- LoF of MLL2

Incidence: 72,000*
Prevalence: 185,000*

Kuppers 2005 Nat Rev Cancer
*Source: Clarion Report (2014), incorporating SEER and GLOBOCAN epidemiology, and recent literature from ASH, NCI, NIH, and academic investigators
Pre-Clinical Characterization of the Clinical Candidate EPZ-6438: Robust Single-Agent Activity

Novel Structure, Potent Target Inhibition

EPZ-6438
Ki = \leq 2.5 \text{nM}
Selectivity > 20,000-fold
Rodent Oral Bioavailability: 15-55%

Potent Tumor Growth Inhibition
*KARPAS422 (Y646N)*

Correlative PK/PD
*KARPAS422 Tumor*

EC$_{50}$ = 13 ng/mL
**EPZ-6438 Synergy with CHOP Components: Driven by GR Agonists and Extends to GC DLBCL with WT EZH2**

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>WSU-DLCL2 (mutant EZH2 GC)</th>
<th>SU-DHL-10 (mutant EZH2 GC)</th>
<th>SU-DHL-6 (mutant EZH2 GC)</th>
<th>DOHH2 (WT EZH2 GC)</th>
<th>SU-DHL-5 (WT EZH2 GC)*</th>
<th>OCI-LY-19 (WT EZH2 GC)*</th>
<th>Toledo (WT EZH2 ABC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Mafosfamide</td>
<td>Additive</td>
<td>Additive</td>
<td>Additive</td>
<td>No effect</td>
<td>--</td>
<td>--</td>
<td>No effect</td>
</tr>
<tr>
<td>H Doxorubicin</td>
<td>Synergy</td>
<td>Additive</td>
<td>Additive</td>
<td>No effect</td>
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<td>--</td>
<td>No effect</td>
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<tr>
<td>O Vincristine</td>
<td>Additive</td>
<td>Additive</td>
<td>Additive</td>
<td>No effect</td>
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<td>--</td>
<td>No effect</td>
</tr>
<tr>
<td>P Prednisolone</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
</tbody>
</table>

→ Synergy also seen with B-cell signaling pathway agents and BCL2 antagonists in mutant and WT cell lines

* Data only available for combinations with GR agonists

Johnston, Knutson et al. 2013 Blood (ASH Annual Meeting Abstracts) and submitted for publication
EPZ-6438 Synergy with CHOP Components: Driven by GR Agonists and Extends to GC DLBCL with WT EZH2

**Synergy: Increased Potency**

*WSU-DLCL2 (EZH2 Y646F)*

- EPZ-6438 IC\(_{50}\) (nM), Day 7
- [Dexamethasone], nM

**Synergy: Extended Activity**

to WT EZH2 GC DLBCL

- >1000
- >1000
- 530
- 20
- 9.6
- 190

in sensitive to single agent EZH2i

Johnston, Knutson et al. 2013 *Blood (ASH Annual Meeting Abstracts)*
Submitted for publication
Ongoing Phase 1 Study (clinicaltrials.gov: NCT01897571)

- Primary Objectives: Define MTD or RP2D
- Secondary Objectives: PK/PD, safety
- Advanced solid tumors & hematologic malignancies
- Modified Fibonacci dosing scheme

3 cohorts completed

- Dose-proportional PK
- 12 evaluable patients
- 4 of these NHL*

- 1600 mg enrolling
- 800 mg enrolling
- 400 mg 3 pts
- 200 mg 3 pts
- 100 mg 6 pts**

*Includes full cell-of-origin and EZH2 sequencing information
** First dosing cohort included three patients on liquid formulation and three patients on tablet formulation being used in study currently
EPZ-6438 (E7438) – Phase 1 Dose Escalation Study

- MTD not reached; no DLTs or AE-related treatment discontinuations
- PD evidence of target inhibition in skin (IHC)
- Single agent anti-lymphoma activity seen among NHL patients

<table>
<thead>
<tr>
<th>Dose (mg BID)</th>
<th>Disease</th>
<th>EZH2 Mutant Status</th>
<th>Best Response to Date</th>
<th>Weeks on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Transformed DLBCL (GC)</td>
<td>WT</td>
<td>PR</td>
<td>23</td>
</tr>
<tr>
<td>200</td>
<td>DLBCL, non-GC</td>
<td>WT</td>
<td>PD</td>
<td>6</td>
</tr>
<tr>
<td>200</td>
<td>PMBCL</td>
<td>WT</td>
<td>PR</td>
<td>34+</td>
</tr>
<tr>
<td>400</td>
<td>Follicular (GC)</td>
<td>Y646S</td>
<td>SD</td>
<td>17</td>
</tr>
</tbody>
</table>

Cell of origin determination by central IHC (Hans)
Mutation status determination by NGS

Skin H3K27me3 IHC

Baseline (Day 1)

Day 29
Patient Case 1, Cohort 1, 100mg: 66% Reduction in Lesion Size, CT

- 58-year-old male with transformed DLBCL, ECOG 0
- WT EZH2
- Clinical history:
  - FL diagnosed in 2006
  - 6 prior lines of therapy, including CHOP (complete response), rituximab/carboplatin, DHAP, BEAM/ ASCT (complete response), investigational Ab, oxaliplatin/ gemcitabine (progressive disease)
- Treatment: EPZ-6438 (E7438) 100mg PO BID, single agent
  - PD H3K27 trimethylation in skin biopsy: 21% reduction from baseline
- Best Response: PR
Patient Case 2, Cohort 2, 200 mg: 73% Reduction in Lesion Size, CT

- 23-year-old male with primary mediastinal B-cell lymphoma (clinical presentation), ECOG 0
- Cell-of-origin (IHC): non-GC
- WT EZH2
- Clinical history:
  - Diagnosed Feb 2013
  - 4 prior lines of therapy, including R-ACVBP, R-DHAP, R-ICE, primary progression through last 3 regimens
- Treatment: EPZ-6438 (E7438) 200mg PO BID, single agent
  - PD H3K27 trimethylation in skin biopsy: 39% reduction from baseline
- Best Response: PR
Patient Case 2, Cohort 2, 200 mg: Reduction in FDG Uptake

27 November 2013
BASELINE

23 May 2014
EPZ-6438 (E7438): Summary and Future Plans

• Summary: Pre-Clinical Data
  – Demonstrated utility of single agent EPZ-6438 in mutant-bearing GC NHL
  – In combination with steroids, potency increased and activity broadened to all GC NHL independent of EZH2 mutant status

• Summary: Clinical Data for Cohorts 1-3 (100mg-400mg)
  – MTD not reached; no DLTs or AE-related treatment discontinuations
  – Dose-proportional PK
  – PD evidence of target inhibition in skin (IHC)
  – Single-agent anti-lymphoma activity seen among NHL patients

• Future Plans
  – More complete Phase 1 dose escalation data from all five dosing cohorts to be presented at a medical conference later in 2014
  – Initiate Phase 2 studies in GC DLBCL, PMBCL and FL, mutant and WT EZH2 as single agent (late 2014) and in combination with steroids
  – Initiate Phase 2 study in INI1-deficient tumors in late 2014
We would like to thank the principal investigators and their institutions, the employees of Epizyme and Eisai, and most importantly, the patients participating in the Phase 1 study