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November 11, 2013

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Epizyme (EPZM - OUTPERFORM): Anticipated Upcoming Data at ASH (Dec 7-10)

Price: $33.88 **12-Month Price Target: $37**

- **EPZM will present preclinical data for EPZ-6438 at the upcoming ASH Annual Meeting (December 7-10) that suggests enhanced anti-tumor activity in combination with other active therapies.** The combination of EPZ-6438 plus chemotherapy caused increased killing in two EZH2 mutant cell lines. EPZ-6438 did not have anti-tumor activity in EZH2 wildtype cells. EPZ-6438 and CHOP combination therapy elicited durable tumor regressions of EZH2 mutant xenograft models (Figure 1), where either treatment alone had little or no activity. In another EZH2 mutant xenograft model, EPZ-6438 plus CHOP combination without doxorubicin had anti-tumor activity.
- **EZP-6438 dose escalation studies continue, with no DLT observed to date. Phase II studies are set to begin in EZH2 mutated DLBCL and Grade 3 FL in 2014.** Epizyme also plans to expand development of EPZ-6438 beyond EZH2 mutated NHL into the INI1-deficient tumor setting, based upon pre-clinical work published in April (here) and at AACR (here). EZH2 has an oncogenic role in MRT and synovial sarcomas. These indications have an incidence of 1,700 patients and are not included in our current estimates.
- **Preclinical studies suggesting synergistic activity for EPZ-5676 (Dot1L) plus standard-of-care or DNA hypomethylating therapies in MLL-rearranged leukemia cells will also be presented.** The combination of EPZ-5676 with other standard AML treatments cytarabine or daunorubicin showed synergy in 2 MLL-rearranged cell lines, but not with an MLL wild-type line. This effect was noted even if EPZ-5676 was removed prior to the addition of the standard of care agents, suggesting that chromatin alteration is persistent and can potentially enhance the effect of chemotherapeutic agents. In other studies, combining EPZ-5676 with other epigenetic drugs such as DNA hypomethylating agents generates a synergistic response. Overall, EPZM's studies suggest that EPZ-5676 could have activity as both a single agent and in combination with other drugs in MLL-rearranged cells.
- **Top-line data from the Phase I dose escalation study of EPZ-5676 in the MLL-r leukemia setting is anticipated in Q4:13. Importantly, EPZM also announced that based on data to date, a pediatric MLL-r study is set to begin in 2014. This suggests to us that EPZ-5676 has an exceptionally strong safety profile.** Early evidence of efficacy could, in this high unmet medical need setting, be potentially sufficient for an accelerated registration application ahead of our current H2:16 estimate.
- **EPZM will be presenting preclinical data of Dot1L inhibitor EPZ004777 suggesting activity in MLL-partial tandem duplication (PTD) positive leukemia cells.**
- **EPZM also plans to initiate a trial for EPZ-5676 in cancers with MLL-PTD, in 2014.** Data presented at AACR (here) shows that MLL-PTD cell lines responded similarly to MLL-r cell lines with respect to DOT1L inhibition. MLL-PTD can be identified by cytogenetic markers and has an estimated annual incidence of 2,300 patients in U.S., EU and Japan. The MLL-PTD opportunity represents upside to our estimates.
- **Reiterate OUTPERFORM rating and $37 price target.** Our price target of $37/share is derived from applying 8x and 15x multiples to our 2019 estimated sales and royalty revenues, respectively, discounted by 35% annually (fully-diluted share count, assumes an increase of 2 million additional shares for future financings). We note that with positive data, a decline in our discount rate from 35% per year to 20% per year yields a potential value in 12 months of $66/share.
- Risks to the achievement of our price target include clinical, regulatory or market failure for EPZ-5676 and/or EPZ-6438.

Other histone methyltransferase oral and poster presentations that will be presented at ASH include studies that show the effects of the methyltransferase inhibitor UNC0638 (Millipore, Sigma-Aldrich) upon gamma globin gene and protein expression being erythroblast differentiation stage specific, the Jumanji histone demethylase KDM2B control of EZH2 expression in myelodysplastic syndromes, the enhancement of TRAIL induced apoptosis in mantle cell lymphoma cells as a result of EZH2 inhibition, the induction of gamma-globin gene re-expression in sickle cell anemia by protein arginine methyltransferase 5 (PRMT5) inhibition, the mechanistic role of DOT1L in MLL-rearranged leukemia, and the cooperation of EZH2 and transcriptional repressor BCL6 to inhibit diffuse large B cell lymphoma proliferation.

Abstract Number	Title
4416	EZH2 Inhibitor EPZ-6438 Synergizes With Anti-Lymphoma Therapies In Preclinical Models
1256	Myeloid Leukemia Cells With *MLL* partial Tandem Duplication Are Sensitive To Pharmacological Inhibition of the H3K79 Methyltransferase DOT1L
3930	DOT1L Inhibitor EPZ-5676 Displays Synergistic Antiproliferative Activity in Combination with Standard of Care Drugs or DNA Hypomethylating Agents in *MLL*-Rearranged Leukemia Cells
3453	The Effects Of The Histone Methyltransferase Inhibitor UNC0638 Upon Gamma Globin Gene and Protein Expression Are Erythroblast Differentiation Stage Specific
4425	Histone 3 Methyltransferase (EZH2) Inhibition Enhances TRAIL-Induced Apoptosis In Mantle Cell Lymphoma Cells By Accelerated cFLIP Degradation
1543	The Jumanjii Histone Demethylase KDM2B controls EZH2 Expression In Myelodysplastic Syndromes (MDS) Via Mir Let-7b (let7b), a Pathway That Is Bypassed By The Histone Methylation Inhibitor DZNep
1	EZH2 and BCL6 Cooperate To Create The Germinal Center B-Cell Phenotype and Induce Lymphomas Through Formation and Repression Of Bivalent Chromatin Domains
1007	Targeting The PRMT5 Enzyme To Induce γ-*Globin* Gene Derepression In Sickle Cell Anemia
598	Genome-Wide RNAi Screen Identifies The Mechanistic Role For DOT1L in *MLL*-Rearranged Leukemia

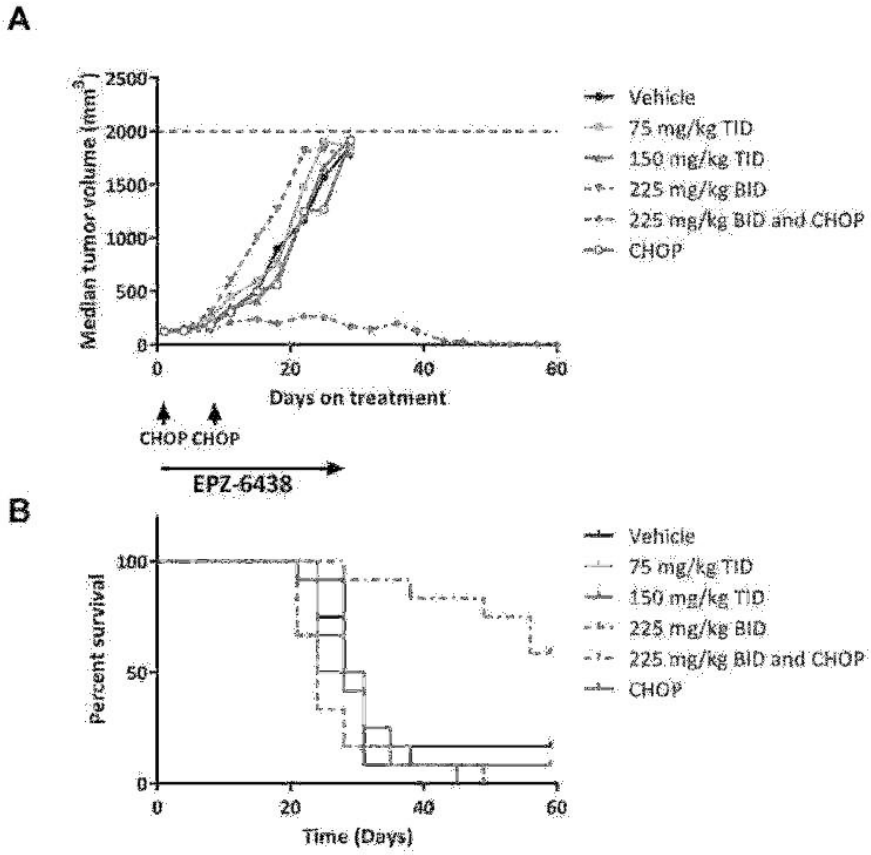
Investment Thesis

Epizyme is focused on developing drugs that are highly specific for individual HMTs and the company seeks to prove that the treatment of a genetically definable patient with a potent and highly selective HMT inhibitor can lead to deep and durable levels of disease control. EPZM's most advanced product candidate, EPZ-5676, is in Phase I in AML/ALL patients, including mixed lineage rearranged leukemia (MLL-r). The company's second most advanced product candidate, EPZ-6438, is in an ongoing Phase I/II trial in a genetically defined subtype of non-Hodgkin's lymphoma (NHL). The company has entered into therapeutic collaborations with Celgene, Eisai, and GlaxoSmithKline (GSK), but maintains 100% of the US rights to EPZ-5676 and rights to opt into 50% of the US economics for EPZ-6438. As a result of the cause and effect link between the oncogenic HMT driver and malignancy, we would expect early evidence of deep and durable efficacy, potentially in even just a few genetically pre-defined patients, to lead to significant appreciation of EPZM's shares as investors price in clinical, regulatory and market success.

Milestones

Q4:13	Begin second stage of the Phase I/II study of EPZ-5676 in AML/ALL patients with MLL-r
Q4:13	Interim data for the Phase I study of EPZ-5676 in the AML/ALL setting
H1:14	Partner Eisai to initiate Phase II study of EPZ-6438 in the NHL (DLBCL and grade 3 FL) setting
H2:14	Begin pivotal Phase II trial for EPZ-5676 in adults with MLL-r
2014	Final data for the Phase I study of EPZ-6438 in the NHL setting
2014	Initiation of Phase II trials for EPZ-6438 in patients with INI1-defficient tumors (synovial sarcoma)
2014	Final data for the Phase I/II study of EPZ-5676 in the MLL-r setting
2014	Initiation of Phase I study of EPZ-5676 in the pediatric MLL-r setting
2014	Initiation of Phase I/II study of EPZ-5676 in the MLL-PTD setting
Q1:15	Begin pivotal Phase II/III trial for EPZ-6438 in EZH2-driven NHL
Q2:15	Begin pivotal Phase II trial for EPZ-5676 in children with MLL-r
H2:15	Data from pivotal Phase II trial for EPZ-5676 in adults with MLL-r
H2:15	Data from pivotal Phase II/III trial for EPZ-6438 in EZH2-driven NHL
H2:16	File NDA for EPZ-5676
H1:17	File NDA for EPZ-6438

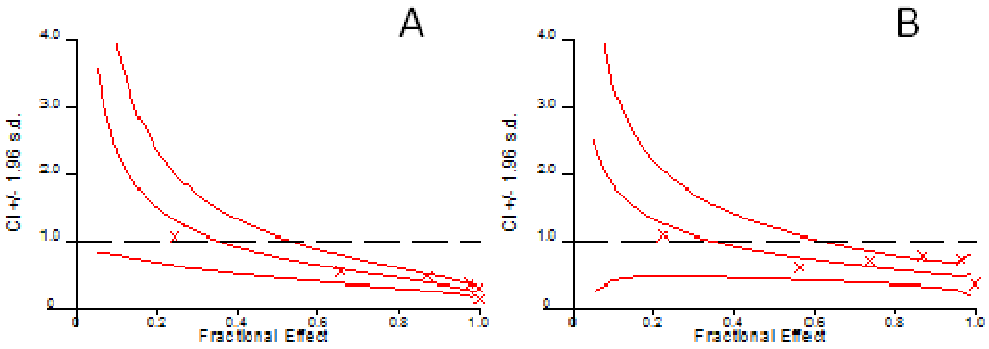
Figure 1: Potent Combination Benefit of EPZ-6438 with CHOP Chemotherapy in the SUDHL6 EZH2 Y646N Mutant Mouse Xenograft Model



*EPZ-6438 was dosed for 28 days by oral gavage as indicated. CHOP cycles were administered on days 1 and 8.

Source: Epizyme

Figure 2: Fa-CI Plots Show that EPZ-5676 and Cytarabine Act Synergistically to Induce an Antiproliferative Effect in the Molm-13 Cell Line in a Pre-Treatment Model



(A) Ten-day continuous dosing of EPZ-5676 with addition of cytarabine at day 7 showed a range of fractional effects with CI values <1 denoting synergy.

(B) EPZ-5676 was removed at day 7 prior to the addition of cytarabine showing durable combination benefit.

Source: Epizyme

Analyst Certification
I, Gregory R. Wade, Ph.D., David M. Nierengarten, Ph.D., Christopher N. Marai, Ph.D., certify that the views expressed in this report accurately reflect my personal opinion and that I have not and will not, directly or indirectly, receive compensation or other payments in connection with my specific recommendations or views contained in this report.

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The Investment Ratings are based on the expected performance of a stock (based on anticipated total return to price target) relative to the other stocks in the analyst's coverage universe (or the analyst's team coverage).*

Rating Distribution (as of September 30, 2013)	**Investment Banking Relationships (as of September 30, 2013)**
Outperform:55% Neutral: 41% Underperform: 4%	Outperform:14% Neutral: 2% Underperform: 0%

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Wedbush Equity Research Disclosures as of November 11, 2013

Company	Disclosure
Epizyme	1,3,5,7

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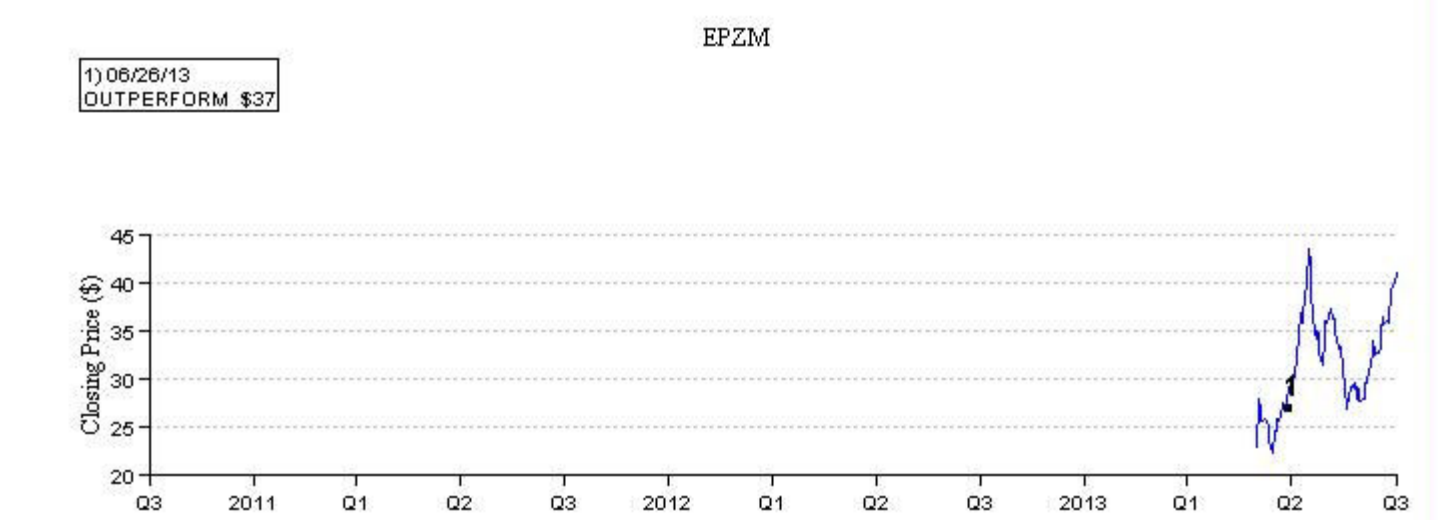

* WS changed its rating system from (Strong Buy/Buy/Hold/Sell) to (Outperform/ Neutral/Underperform) on July 14, 2009.
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