Epizyme, Inc. (EPZM)

Initiating Coverage at Market Outperform; Showing the World How It's Done in Epigenetics-Based Cancer Drugs

MARKET DATA

Price	$27.55
52-Week Range:	$18.60 - $30.86
Shares Out. (M):	28.4
Market Cap ($M):	$782.4
Average Daily Vol. (000):	127.0
Cash (M):	$160
Cash/Share:	$5.80
Enterprise Value (M):	$725
Float (M):	28.0
LT Debt (M):	$0

Cash (M): Reflects cash, equivalents, and short-term investments
Source: Thomson Reuters and JMP Securities LLC

FY DEC		2012A	2013E	2014E
Revenue ($M)	1Q	$5.7	$8.9A	$29.9
	2Q	--	$19.8	$4.9
	3Q	--	$7.8	$4.9
	4Q	--	$7.5	$38.7
	FY	**$45.2**	**$44.1**	**$78.5**
EPS	1Q	($3.38)	($4.24)A	$0.30
	2Q	--	($0.08)	($0.41)
	3Q	--	($0.44)	($0.41)
	4Q	--	($0.50)	$0.58
	FY	**($0.72)**	**($2.03)**	**$0.25**

Source: Company reports and JMP Securities LLC

STOCK PRICE PERFORMANCE

MARKET OUTPERFORM | Price: $27.55 | Target Price: $40.00

INVESTMENT HIGHLIGHTS

Initiating coverage of Epizyme with a Market Outperform rating and a 12-month $40 price target, based on the synthesis of our sum-of-the-parts NPV and standardized CAGR methodologies. We view Epizyme as the rare opportunity to invest in a best-of-breed, pure play, epigenetics-focused biotech company with clinical stage assets and a robust drug discovery product platform capable of consistently delivering multiple new therapeutic candidates. We believe the company's clinical assets, EPZ-5676, targeting DOT1L (for mixed lineage leukemia) and EPZ-6438, targeting EZH2 (currently being evaluated for non-Hodgkins lymphoma), represent particularly compelling biology given that they are directed against clonally initiating mutations. This biologic focus, in combination with the selection of a genetically defined patient population, as providing capability for each asset to rapidly accelerate through the clinic and into registration-directed trials within 18 months. We believe this development strategy, coupled with the use of companion diagnostics, will also lead to significant commercial success. While the company's shares have performed strongly since its recent IPO (in which the offering was upsized and shares ultimately priced at $15), we expect shares to rise another 45% to $40 over the next 12 months on the back of clinical data from the ongoing Phase I trials.

Clinical stage assets addressing genetically defined patient populations that offer rapid path to market. Epizyme is targeting patient populations with mutations that have significant unmet need and can be identified through companion diagnostics. This allows efficient and accelerated clinical development by focusing efforts and resources strictly on those patients with a biological rationale to respond to treatment. We expect this to allow earlier demonstrations of efficacy, justifying initiation of pivotal trials relatively faster than traditional drug development, leading to potentially quicker timelines to approval and commercial launch.

Collaborations with deep pocketed partners accompanied by retention of attractive economics Though the company has established partnerships with Celgene (CELG, MO, $148), Eisai, and GSK (Not Covered), it retains commercial rights to both EPZ-5676 (U.S.) and the right to opt-in to the U.S. commercial development of EPZ-6438. Nevertheless, the upfront payments from these partnership agreements and the downstream milestones will continue to provide a non-dilutive source of funds.

Industry-leading technology platform. Beyond the two defined assets (EPZ-5676 and EPZ-6438), Epizyme's platform technology allows the company to target the entire 96-member HMT class, potentially offering a deep pipeline of product candidates against a wide range of oncologic diseases. The company has disclosed that it has prioritized 20 target HMTs (DOT1L and EZH2 the first two). We expect additional details over the next 18 months on the company's efforts to further develop a next set of IND candidates.

Michael G. King, Jr.
mking@jmpsecurities.com
(212) 906-3520

Carter L. Gould
cgould@jmpsecurities.com
(212) 906-3522

INVESTMENT THESIS

The future 800-pound gorilla in the epigenetics white space

We are initiating coverage of Epizyme with a Market Outperform rating and a $40 price target. We view Epizyme as one of the future leaders in the epigenetics landscape. Epizyme enjoys a significant first-mover advantage, having chosen a highly valuable area within the topology of epigenetics, namely, histone methyltransferases (HMTs) a large yet tractable set of drug targets. In our view, the study and exploitation of the biology of epigenetics, a term which describes how genes are turned on and off in the context of disease by mechanisms not directly related to gene sequence, could potentially equal or exceed that of the study of kinases (an area of research that has produced billions in product sales and market capitalization).

Epizyme has created an enviable assemblage of biologically validated targets, a management team with the requisite drive and skills, to enable development and commercialization partnerships with deep financial resources capable of catalyzing substantial market capitalization. Investors will no doubt learn about such epigenetic targets as EZH2, DOT1L, bromodomains (BRD4), and SET domains, much in the same way they have learned about and profited from VEGF, Bcr-abl, EGF, ELM4-ALK, BTK, and BRAF in the kinase inhibitor space. In our opinion, an investment in Epizyme today holds as much long-term potential as the shares of Ariad (ARIA, MO, $32) and Pharmacyclics (PCYC, MO, $116) held a few years ago.

A differentiating aspect of interdiction against driver epigenetic mutations is the possibility of complete eradication of the initiating clone, a prospect that makes this field a potential game-changer. While it is still early in the game, we cannot help but be excited about the consistent shape of the pre-clinical kill curves seen in Epizyme's preclinical studies (and recapitulated in an MLL patient treated with 5676). That is, in contrast to conventional cytotoxic agents and even the best of the targeted kinase inhibitors (with some exceptions of course), targeted epigenetic therapies are demonstrating complete tumor eradication as compared to right-shifted growth curves. As mentioned, these pre-clinical results have yet to fully play out in well-controlled studies, but we remain optimistic about the outlook for these agents. We will discuss the science and potential of epigenetics later in this report, as well as in our Epigenetics Primer, published as an appendix to this report.

FIGURE 1. Upcoming Milestones

Timing	Drug	Milestones
2H13	EPZ-5676	Initiate expansion cohort of Phase I study with DOT1L
Dec 2013	EPZ-5676	Read-out of interim results from the Phase I at ASH
1Q14	EPZ-5676	Initiate enrollment of MLL-r patients at ex-U.S. sites for Phase I study
2H14	EPZ-5676	Initiate Phase II global pivotal trials
2014	EPZ-6438	Read-out of interim results from Phase I study
2014	-	Identify next IND candidate

Source: Epizyme press releases, presentations, and SEC filings

VALUATION

We arrive at our 12-month price target of $40 based on the synthesis of our NPV sum-of-the-parts, and standardized CAGR methodologies (Figure 2). This approach is built upon our forecast of revenues and expenses for EPZ-5676 and EPZ-6438 and expenses towards product platform and new IND development. For the sake of all valuation methodologies, we assume Epizyme will exercise its option to co-promote EPZ-6438 in the U.S. We elaborate on our methodology below.

FIGURE 2. Price Target Derivation

Methodology	Valuation
Sum-of-the-Parts NPV	$38.31
Standardized CAGR	$42.12
Price Target	$40.00

Source: JMP Securities LLC

Sum-of-the-Parts Methodology

We forecast cash flows to the company through 2031, combining modeling specific revenues (sales, milestones, and collaboration revenue (further details on the partnerships can be found on pages 19-20 and 26) and expenses through 2025. We then forecast 6% growth in free cash flow (in line with estimated growth rates at the end of the 2025 timeframe) through 2031. For our sum-of-the-parts model, we assigned discount rates of 25% to EPZ-5676 and EPZ-6438. We then calculated the NPV in the U.S. and ex-U.S. regions of each product separately through 2031, assigned what we believe to be a conservative platform value of $150MM, and added estimated cash on hand at the end of 2Q14 (~$110MM) to arrive at an equity valuation of $38.31 per share. Our sum-of-the-parts analysis is summarized below in Figure 3.

FIGURE 3. Sum-of-the-Parts Valuation

Sum of Parts Epizyme NPV		
Assets	**Value ($ MM)**	**Per Share**
EPZ-5676 - MLL	**$432.0**	**$12.92**
US Sales	$267.3	$7.99
Ex-US Royalty	$164.7	$4.92
EPZ-6438 - FL and DLBCL	**$589.7**	**$17.63**
US Profit Share	$488.9	$14.62
Ex-US Royalty	$100.8	$3.01
Platform	**$150.0**	**$4.49**
Cash and Equivs on Hand	**$109.5**	**$3.27**
Total NPV	**$1,281.1**	**$38.31**

Source: JMP Securities LLC

Standardized CAGR Methodology

We also arrived at a valuation based on our standardized CAGR methodology. We begin by calculating the profitable biotech PEG ratio (0.96), based on the mean 2013 P/E (30x) and a mean forward CAGR of 31%. Based on projected EPS in 2018 and a discount rate of 25%, we arrived at a valuation of $42.12 per share. Our assumptions are detailed in Figure 4.

FIGURE 4. Standardized CAGR Valuation

CAGR Valuation		
Comparables		
Biotech Group P/E (2013)		30.0x
Biotech Group Forward CAGR		31.0%
Valued Company		
Year used for discounting		2018
Price Target Year		2014
3-year EPS CAGR (18-23)		89.1%
Second Profitable Year EPS	$	1.19
Blended Discounted Rate		25.0%
# Years for Discounting		4
Target Price		**$42.12**

Sensitivity Analysis					
	Discount Rate				
CAGR	20.0%	22.5%	25.0%	27.5%	30.0%
83.1%	$46.24	$42.58	$39.28	$36.29	$33.57
85.1%	$47.36	$43.61	$40.22	$37.16	$34.38
87.1%	$48.47	$44.63	$41.17	$38.03	$35.19
89.1%	$49.59	$45.66	**$42.12**	$38.91	$36.00
91.1%	$50.70	$46.69	$43.06	$39.78	$36.81
93.1%	$51.81	$47.71	$44.01	$40.66	$37.62
95.1%	$52.93	$48.74	$44.95	$41.53	$38.43

Source: JMP Securities LLC

Share count

For the purpose of our valuation models, we utilize a fully diluted share count (~33.4 million) comprising both estimated issued shares (~28.4 million shares) and estimated stock options outstanding (~5 million) at the end of 2Q14.

INVESTMENT RISKS

Clinical. Drug development is an inherently risky business. As clinical trials always carry a risk of failure, Epizyme's assets (EPZ-5676, EPZ-6438, or future products), may fail to demonstrate clinically meaningful levels of efficacy in ongoing or future trials. Further, it is unclear whether resistance pathways may develop to the epigenetic mechanisms being targeted.

Regulatory. The ability of Epizyme or its partners to market its drugs is dependent upon those drugs obtaining approval from the U.S. FDA and foreign regulatory authorities. Failure to achieve approval or delays in the timeline to approval could lead to a substantial decrease in the company's share price.

Competitive. Epigenetics is an increasingly competitive field and Epizyme will face competition both from companies focused in the space, as well as players targeting related mechanisms. As such, there is no assurance that Epizyme's product will be competitive or differentiated from other drugs.

Commercialization. Epizyme has stated its plans to retain U.S. commercial rights to its products and develop a commercial infrastructure to market those products. The company has limited commercial experience and infrastructure in place. As such, the company will face significant expenses developing or acquiring these resources.

Reimbursement. There is no guarantee that Epizyme, or its partners, will garner adequate reimbursement for its products. Failure to obtain adequate levels of reimbursement could negatively impact the company's share price.

Partners. Epizyme has formed development and commercial partnerships with Celgene, Eisai, and GSK. Epizyme is highly dependent upon these partnerships to provide non-dilutive sources of capital. Celgene and Eisai are critical to the development and commercialization of Epizyme's clinical stage assets. Changes to, or terminations of, these partnerships could affect Epizyme's shares negatively.

Financial. Post-IPO, we estimate that the company will end 2Q13 with approximately $160MM in cash and cash equivalents. While the company has guided that even excluding any milestone payments from Celgene, Eisai, or GSK (which we expect) it has adequate resources to fund the company into 2015, we wholly expect the company to revisit the capital markets to further fund clinical development of its assets, develop a commercial infrastructure in the U.S., and to identify other assets using its platform technology and expertise. We currently forecast that the company will conduct secondary offerings in 2014 and 2015 before reaching profitability in 2017. While we view this as common for similar stage biotechnology companies, the risk of dilution may create an overhang at times.

COMPANY OVERVIEW

Epizyme (EPZM) is a biopharmaceutical company, based in Cambridge, Massachusetts, focused on the discovery, development, and commercialization of personalized therapeutics for epigenetically-defined cancers. The company's technology is focused on the development of small molecule drugs specifically targeted against the individual members of the 96-member histone methyltransferase (HMT) class of enzymes. To date, the company has entered into strategic collaborations with Celgene, Eisai, and GSK regarding specific products, as well as the underlying technology platform. .

The company's lead product EPZ-5676, is partnered with Celgene and is currently in Phase I studies. EPZ-5676 targets DOT1L and is being developed for mixed-lineage leukemia (MLL-r), an aggressive sub-type of acute leukemia (AML and ALL). The company's second asset, EPZ-6438 targets EZH2 and is partnered with Eisai. A phase I/II trial of EPZ-6438 in genetically defined sub-types of non-Hodgkins lymphoma was initiated in 2Q13.

FIGURE 5. Epizyme Portfolio

Program	Status	Indication
EPZ-5676[1]	Phase I	Adult mixed-lineage leukemia (in AML and ALL)
EPZ-6438[2]	Phase I	Non-Hodgkins lymphoma

[1]*Partnered with Celgene ex-U.S.*

[2]*Eisai has WW rights, subject to Epizyme option on 50% of U.S. rights*

Source: Epizyme presentations and SEC filings

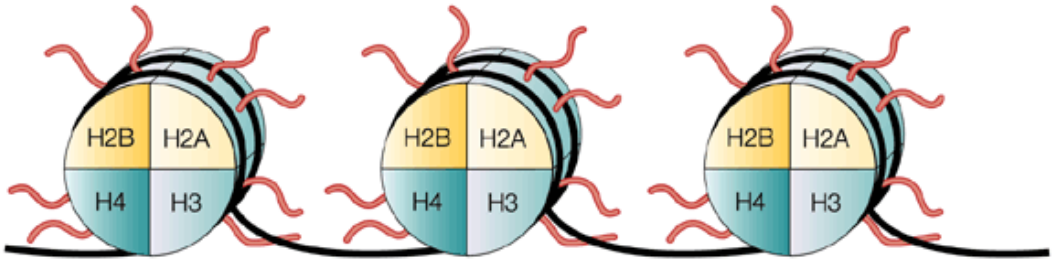
EPIGENETICS – MASTER PUPPETEER OF THE GENOME

Epigenetics is the study of changes in gene expression based on mechanisms not encoded in the underlying DNA of the genome

Epigenetics is the study of changes in gene expression patterns due to mechanisms not encoded in the underlying DNA of the genome. The advancement of the field has challenged the long-held view in biology that DNA base pair sequences are the prime determinant of the cell's phenotype (normal or transformed). The corollary to that view was that regulatory genes alone governed expression of structural genes. While that has been confirmed in limited cases, epigenetic control, driven by changes in the chromatin structure, appears to be a more significant regulatory system. Analysis of epigenetics and the therapeutic approaches leveraging this biology requires consideration of DNA in the context of chromatin.

In eukaryotic cells (those with an organized nucleus, such as higher order animals and yeast), DNA is primarily found tightly wound around proteins known as histones into a hierarchy of structures referred to individually as nucleasomes, and collectively as chromatin. The nucleasome comprises 147 base pairs of DNA wrapped around an octamer of four core histones (H2A, H2B, H3, and H4) (Figure 6). The organization of DNA in this manner serves as an elegant packaging strategy for physically manipulating DNA into the nucleus. It also serves as a complex mechanism for limiting the accessibility of promoter regions to transcription factors for specific genes, in essence "silencing" portions of a DNA sequence. Epigenetic remodeling of chromatin has been demonstrated to govern this access and the transcription patterns of associated genes. Chromatin remodeling is believed to be mediated by two predominant epigenetic mechanisms: DNA methylation and histone post-translational modifications (hPTMs). These mechanisms trigger remodeling by changing the electrostatic landscape and/or altering the affinity of chromatin-binding proteins.

FIGURE 6. Nucleasome Structure (DNA shown wound in black)



Source: Marks, P. et al., Nat. Rev. Cancer 1 (2001) 194-202

It is therefore not surprising that the collection of biochemical systems behind chromatin remodeling must be tightly controlled in order to ensure optimal cell growth and differentiation. Indeed, there is a growing body of evidence to suggest that dysregulated epigenetic enzymatic activity can contribute to uncontrolled cell proliferation, enhanced cell migration, or invasion in malignancies. Not surprisingly, epigenetic dysfunction has been implicated in metabolic, inflammatory, neurodegenerative, and cardiovascular disease. Therefore, selectively modulating the aberrant action of epigenetic enzymes may hold promise for the treatment of a range of diseases. However, because of the relatively early nature of our understanding of the biology of epigenetics and the representative drug targets, cancer provides the logical first disease category in which this knowledge will be exploited, given the greater tolerance for drug- or target-related toxicity.

Mechanisms of Epigenetic Modification

As noted above, the two best understood mechanisms of epigenetic remodeling of chromatin are histone post-translational modifications (hPTMs) and DNA methylation. For this review, we focus our discussion on hPTMs given the relevance to Epizyme's platform and clinical assets. However, for the sake of completeness we briefly review the role of DNA methylation in shaping the epigenome.

Post-Translation Histone Modifications – Readers, Writers, and Erasers

There are five major families of histones, comprising two subsets: core histones (H2A, H2B, H3, H4) and linker histones (H1). The core histones are characterized by two distinct domains: the globular core, around which DNA is wrapped, and protruding N-terminal tails protruding from the nucleasome. These tails represent the most accessible targets and can be modified through a series of covalent reactions, including methylation, acetylation, phosphorylation, and ubiquitination. The best characterized modifications and the focus of this review will be on methylation and acetylation. These post-translational modifications are driven by distinct families of enzymes including: protein methyltransferases (PMTs), lysine methylases (LDMTs), and histone deacetylases (HDACs), whose role is to add or remove functional groups at a variety of residues on histone tails. The resulting "marks" are then recognized by the "reader" proteins that interpret the information and assemble it into complexes that facilitate chromatin remodeling. The reader proteins are able to recruit the factors that initiate mRNA transcription and drive mRNA elongation.

Histone PTMs affect chromatin structure and dynamics can generally be divided into two categories. Histone PTMs can directly influence histone-DNA and histone-histone interactions, or they can be targeted by protein effectors (also referred to as histone-binding domains or readers of PTMs). Our review will focus on the following modifications to histones: acetylation and methylation.

Acetylation of lysines is a prevalent post-translational modification, and has a large role in altering the electrostatic landscape of chromatin. The addition of an acetyl moiety to the side-chain nitrogen of lysine leads to neutralization of charge, which can significantly influence protein conformation and protein–protein interactions. This has been shown to significantly alter enzyme activities and protein assembly. Specifically, acetylation of lysine residues is associated with weakened attraction between histone and DNA, serving to de-condense chromatin and facilitate transcription. Histone deacetylases carry out the opposite process. There have been two HDAC inhibitors approved by the FDA (Figure 7).

FIGURE 7. Approved Histone Deacetylation Inhibitors

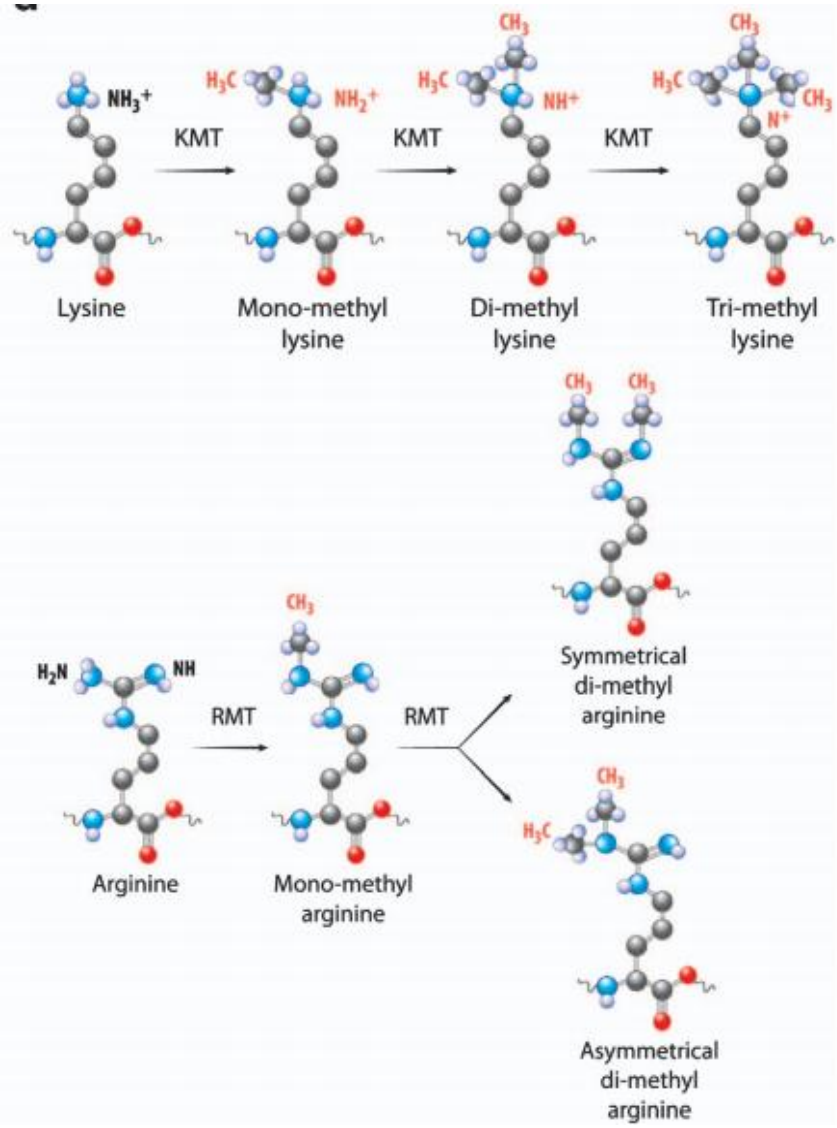
Drug	Company	Indication
Zolinza (vorinostat)	GSK	PTCL[1]
Istodax (romidepsin)	Celgene	PTCL[1]

1 Peripheral T-cell lymphoma

Source: Biomedtracker

In contrast, histone methylation can be either repressive or activating. Human protein methyltransferases fall into two major families: protein lysine methyltransferases (PKMTs) and protein arginine methyltransferases (PRMTs) (Figure 8). These 96 PMTs (51 PKMTs and 46 PRMTs) constitute the 96-member family upon which Epizyme is focused. Epizyme has thus far prioritized two of the 20 HMTs (Figure 9). Given that Epizyme's focus is on histone methyltransferases, this initiation report purposefully excludes commentary on bromodomains and recent discoveries surrounding BRD4. Instead, we refer readers to our epigenetics primer, published as Appendix B to this report.

FIGURE 8. PKMT and PRMT Mechanisms



KMT = Lysine Methyltransferase; RMT = Arginine Methyltransferase

Source: Copeland RA et al., Oncogene (2012), 1–8

FIGURE 9. Select Genetic Alterations Affecting Enzymatic Function of PMTs

Enzyme	Class	Alteration	Cancer
DOT1L	PKMT	Recruited to ectopic sites by MLL translocation	Mixed lineage leukemia
EHMT2	PKMT	Increased expression	Lung, prostate, liver
EZH2	PKMT	Somatic mutations; amplification	NHL, breast, prostate, others
MLL	PKMT	Translocation	Leukemia
MLL4	PKMT	Amplification	Pancreatic, glioblastoma
NSD1	PKMT	Translocation	Acute myeloid leukemia
PRDM14	PKMT	Amplification; highly expressed	Breast
SMYD3	PKMT	Increased expression	Breast, liver, colon, gastric
SUV39H1	PKMT	Increased expression	Colon
WHSC1	PKMT	Translocation; highly expressed	Myeloma
WHSC1L1	PKMT	Amplified	Lung, breast
PRMT5	PRMT	Increased expression	Lymphoma
CARM1	PRMT	Increased expression	Breast, prostate, colorectal
UTX	Other	Loss of function; increased H3K27me3	Myeloma

Epizyme clinical targets are shaded

PKMT = Protein Lysine Methyltransferase; PRMT = Protein Arginine Methyltransferase

Source: Adapted from Copeland, R.A., Drug Discovery Today (2011)

DNA Methylation

A series of enzymes called methyltransferases methylate DNA, specifically cytosines at the 5' position of C-phosphate-G dinucleotides (i.e., "CpG islands"), which are common at gene promoter sequences. Methylated CpG promoter regions suppress gene expression by attracting by binding proteins, which result in the formation of transcriptionally repressive conformation. Aberrant DNA methylation has been detected in several cancer types and groups of genes that are epigenetically silenced by this process are known to include tumor suppressors and cell-cycle regulatory genes (e.g., *Rb, VHL, APC, CDH1, CDKN2A,* and *CDKN2B*) that would normally function to attenuate hyperproliferative cell signaling.

DNA methylation is the best understood of the epigenetic regulatory mechanisms. There are currently two drugs approved (Figure 10) by the FDA for cancer treatment that are based on the concept of blocking the methylation reaction.

FIGURE 10. Approved Hypomethylating Agents

Drug	Company	Indication	2012 Sales ($ MM)
Vidaza (azacitidine)	Celgene	MDS and AML	$823MM
Dacogen (decitabine)	Eisai (US) JNJ (EU)	US: MDS EU: MDS and AML	~$230MM

1 Assumes minimal EU sales in 2012. Dacogen was approved in the EU in 2H12.

Source: Celgene SEC filings, Biomedtracker

EPIZYME PLATFORM – MAKING SURE CANCER DOESN'T COME BACK

As highlighted above, the Epizyme platform is centered on the defined 96-member "HMTome" comprising protein lysine and protein arginine methyltransferases. The technology underlying this platform was in-licensed by the company from the laboratory of Dr. Yi Zhang, then at University of North Carolina.

The underlying technology, in combination with the company's expertise in rational drug design, is focused on developing small molecule inhibitors, in conjunction with companion diagnostics, to target true oncogenes within this class. Out of the 96 enzymes defining the HMTome, Epizyme has prioritized development of 20 HMT as attractive targets for personalized therapeutics, including DOT1L and EZH2.

EPZ-5676 (DOT1L INHIBITOR)

Overview of EPZ-5676

EPZ-5676 is a small molecule inhibitor of DOT1L

EPZ-5676 is a small molecule of inhibitor of DOT1L histone methyltransferase (HMT) being developed for the treatment of genetically defined mixed lineage leukemia, comprising a subset of leukemias spanning acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). Mixed lineage leuekmia is a prototypical example of a cancer driven by mutations involving an epigenetics regulator. In the case of MLL-r the regulator of note is DOT1L. EPZ-5676 is a highly selective and potent inhibitor of DOT1L. Upon binding to DOT1L by EPZ-5676, a conformational change in DOT1L protein is induced. This inhibits H3K79 methylation and MLL-fusion target expression, and in turn accumulation of cells in the G_1/G_0 phase, resulting in cell death (apoptosis). Given that MLL-fusions are clonal initiating mutations, we believe that targeting DOT1L represents compelling biology, potentially leading to significant and prolonged responses to therapy.

EPZ-5676 is currently being evaluated in a Phase I study enrolling patients with hematologic malignancies, including a cohort of patients with MLL-r leukemia. The trial, which is expected to enroll approximately 40 patients, will evaluate the drug's safety, pharmacokinetics, and pharmacodynamics of escalating doses of EPZ-5676, as well as providing a preliminary assessment.

In April 2012, Epizyme entered into a collaboration agreement with Celgene to discover, develop, and commercialize small molecule inhibitors targeting DOT1L. Under the terms of the agreement, Celgene received ex-U.S. rights to commercialize these inhibitors. In exchange, Epizyme received $90MM, and $160MM in development and regulatory milestones.

We believe EPZ-5676 offers a potential transformative option for adult and pediatric patients with mixed lineage leukemia. We find it reasonable to expect a potential pivotal study for the drug in a genetically defined population of MLL patients to initiate in 2H14, leading to potential read-out in 2016, and approval by or near the end of 2016, leading to a commercial launch shortly thereafter in 2017. We currently estimate that EPZ-5676 could reach peak sales of ~$775MM (U.S.: $415MM, EU: $360MM) in 2025.

Biology of DOT1L and its role in Mixed Lineage Leukemia

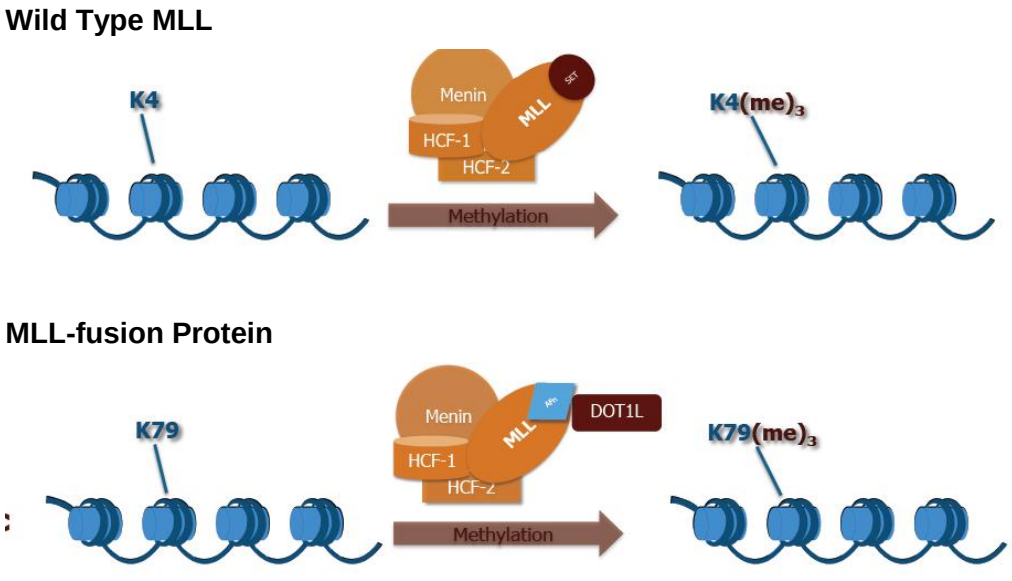
The wild-type phenotype of mixed lineage leukemia (MLL) protein is a histone methyltransferase with specific enzymatic activity for lysine 4 of histone 3 (H3K4). Methylation of H3K4 generally correlates with transcriptional activation, and is believed to be a key step in the regulation of hematopoesis. This role in transcription is mediated by a highly-conserved carboxyl-terminal SET domain on the wild type MLL protein. However, in subsets of acute leukemia, 11q23 chromosomal translocations of the MLL protein result in loss of the catalytic activity seen in the wild-type phenotypes. Instead, those regions are replaced with sequences from partner proteins (Figure 11). This, in turn, leads to dimerization of the MLL fusion protein, which is mediated by DOT1L. Fusions of MLL have been identified in 50-60 different partner genes.

FIGURE 11. Incidence of MLL-Fusion Proteins

Partner Proteins	% Incidence	Age predominance	Disease
AF4	30%	Infants and children	B-ALL
AF9	25%	None	ALL
ENL	5%	Infants	ALL
ELL	5%	Adults	ALL
AF6	5%	Children / Teens	ALL
Other	30%	Mixed	Mixed

Source: Adapted from Tamai et al., J Clin Exp Hematolopathol 50,2 (Nov 2010)

FIGURE 12. Methylation Patterns with Wild Type MLL and MLL-fusion Proteins



Source: Adapted from Epizyme presentations

These fusion proteins disrupt the role of wildtype MLL in regulating hematopoesis, namely the expression of HOX genes (regulators of hematopoietic differentiation), and result in upregulation of HOXA9, HOXA7, and cofactor MEIS1, which lead to acute leukemias through upregulated proliferation and blocked differentiation.

DOT1L is the only known methyltransferase for lysine 79 in histone 3 (H3K79me1/2/3), making it a highly attractive drug target (Figure 12). Its role in leukemia was discovered when abnormally high dimethylation of H3K79 was found to be with genes bound to one of the more common MLL fusion proteins (MLL-AF4) in samples from murine and human leukemia. Further genome wide studies revealed unique transcriptional and H3K79 methylation profiles distinguishing MLL-r leukemias from MLL-germline leukemias. Thus, it is possible that the institution of abnormal histone methylation patterns at key loci is a crucial step in MLL-fusion mediated transformation.

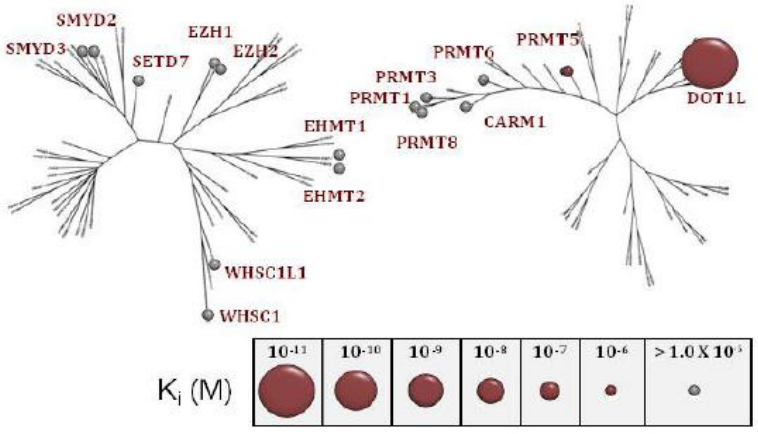
Consequently, Epizyme pursued the development of DOT1L inhibitors. This approach is further supported by genetic and inactivation studies of the protein which led to a collapse of MLL-driven transcription program upregulated from MLL-fusion bindings.

EPZ-5676 Pre-Clinical Data

EPZ-5676 was developed based on structure-guided design and previous findings that aminonucleoside compounds were potent and selective inhibitors of DOT1L. Using its HMTome platform, Epizyme demonstrated that EPZ-5676 is highly selective (37,000 fold) for DOT1L against all other protein methyltransferases (Figure 13).

Epizyme has shown, through a series of *in vitro* and in vivo experiments, EPZ-5676 to be a potent and selective inhibitor of DOT1L, specifically inhibiting dimethylation of H3K79 in various cell lines with a nanomolar IC_{50}.

FIGURE 13. Selectivity Profile of EPZ-5676 for DOT1L

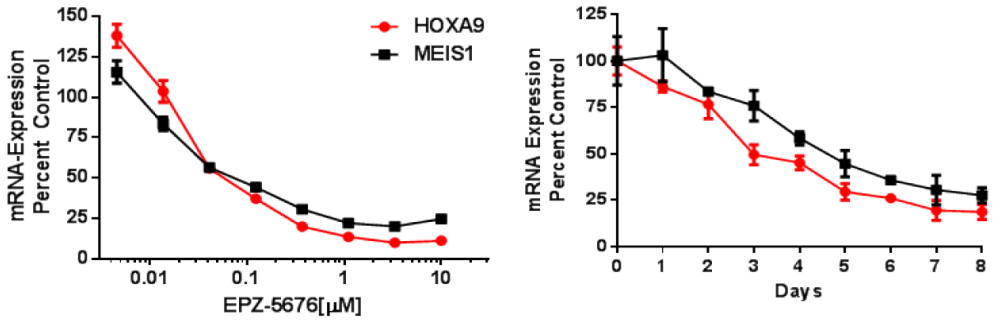


Source: Pollock et al., ASH 2012

In these *in vitro* experiments, EPZ-5676 acted in a highly selective manner, inhibiting only the targeted DOT1L-associated methylation and no other histone methyl marks.

Further, additional experiments demonstrated that the inhibition of dimethylation was reversible, but was also correlated to inhibition of key downstream genes (HOXA9 and MEIS1) believed to play crucial roles in leukemogenesis. Data also showed that cell killing was spared cells expressing wild-type MLL.

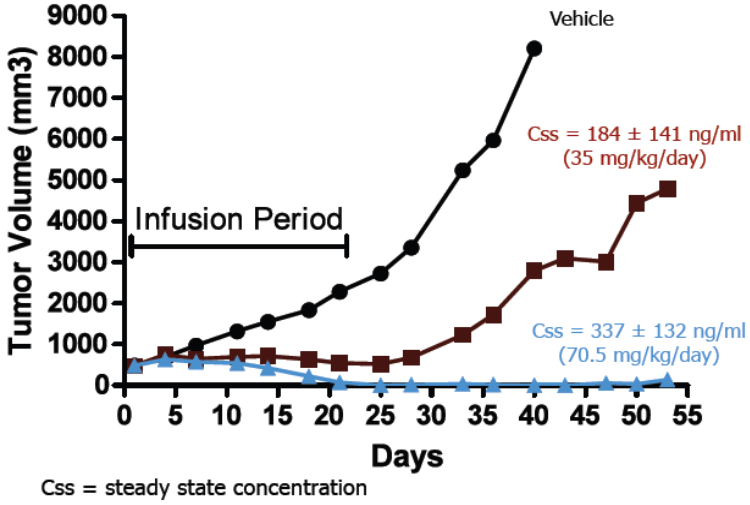
FIGURE 14. Dose-dependent inhibition of HOXA9 and MEIS1 mRNA in Vitro



Source: Pollock et al., ASH 2012

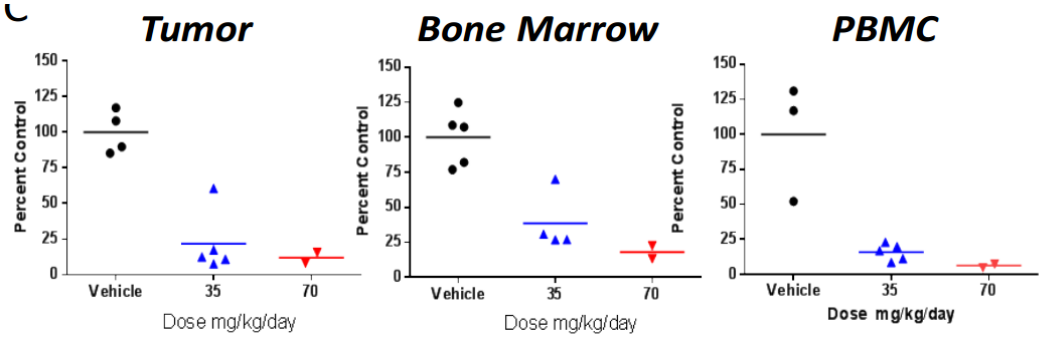
However, the most compelling data generated thus far in support of EPZ-5676 has been data that generated in nude rat xenografts. EPZ-5676 was administered to rats in which human MLL-r cells were implanted subcutaneously and allowed to establish tumors. EPZ-567 was administered at three dose levels (35mg/kg per day, 70mg/kg per day, 67 mg/kg for eight hours per day) for 21 days by continuous intravenous infusion versus a vehicle alone arm. At the highest dose of 70mg/kg per day, tumors in nine of ten mice were reduced to undetectable levels by the end of the 21 day treatment period. No regrowth of tumors was observed in eight of nine rats through the end of the study – 32 days after the end of the 21 day treatment period (Figure 15). Additionally, tumor, bone marrow, samples from these animals demonstrated dose dependent reductions in H3K79 dimethylation (Figure 16) and the mRNA in oncogenes HOXA9 and MEIS1 implicated in patients with MLL (Figure 17).

FIGURE 15. EPZ-5676 Efficacy in Nude Rat Model of MLL-Fusion Leukemia



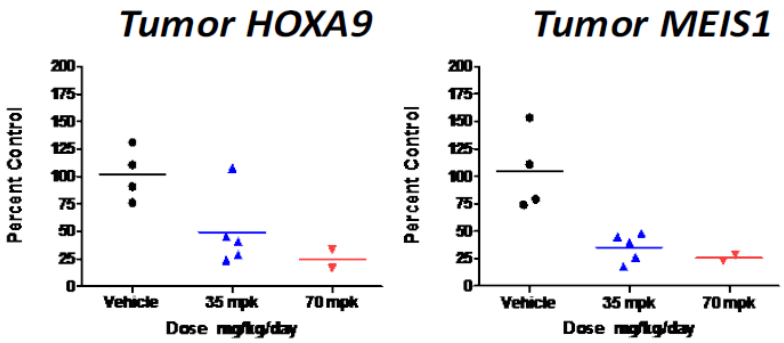
Source: Pollock et al., ASH 2012, Poster 2379

FIGURE 16. Reduction in H3K70me2 Levels in Tumor, Bone Marrow, and PBMCs with EPZ-5676 in Nude Rat Xenografts



Source: Pollock et al., ASH 2012, Poster 2379

FIGURE 17. Reduction in HOXA9 and MEIS1 mRNA with EPZ-5676 in Nude Rate Xenografts



Source: Pollock et al., ASH 2012, Poster 2379

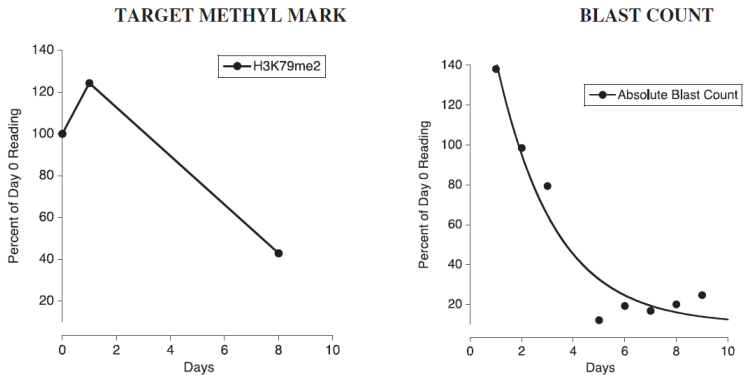
Clinical Data and Development Plans

Based on the above data, Epizyme and Celgene elected to initiate the first clinical study of EPZ-5676, a Phase I, open-label, dose escalation study, in September 2012. The study consists of two phases: a dose escalation phase enrolling patients with AML, ALL, MDS, CML or other myeloproliferative disorders, including some patients with MLL-r, for the purpose of determining the maximum tolerated dose (MTD), and second phase in which the MTD will be evaluated in patients with MLL-r. leukemia. The company has opened four sites to the study (Memorial Sloan Kettering Cancer Center, Sarah Cannon Research Institute, MD Anderson Cancer Center, and Duke University), and anticipates adding up to 12 sites for the expansion phase.

The primary goal of the study is evaluate the safety and tolerability and to determine the MTD of the 21-day intravenous infusion of EPZ-5676. As of late May 2013, four patients had completed dosing in the dose escalation phase (one patient was enrolled to 12 mg/m2/day and three to 24 mg/m2/day). As of that point in time, no dose-limiting toxicities had been reported greater than Grade 2, and no adverse events had warranted a modification of dose or dosing scheduled. The only Grade 2 AE noted had been a single case of transient hypertension. Patients continue to be enrolled to the 24mg/m2/day cohort.

A single patient enrolled to the 24mg/m2/day cohort was diagnosed with ALL and had the MLL-r genetic alteration. In this patient, the drug demonstrated the desired DOT1L target inhibition, with the patient experiencing a 90% reduction in circulating leukemic blast count by the fifth day of therapy. Additionally, the patient experienced resolution of fever, a typical manifestation of leukemia. Unfortunately, EPZ-5676 therapy was terminated on day 10 due to CNS disease progression.

FIGURE 18. Methyl Mark Inhibition and Blast Count Reduction in MLL-r Patient



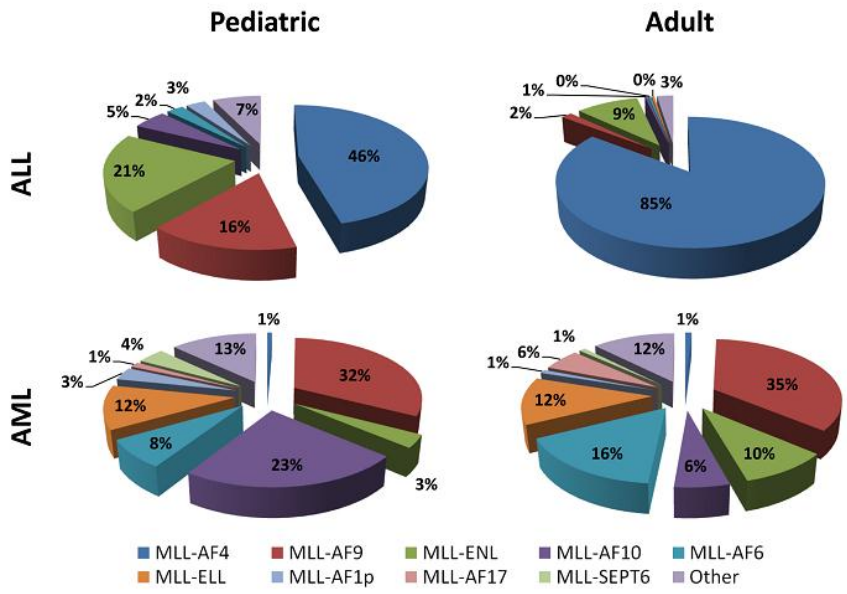
Source: Epizyme S-1 filing

Current Treatment Paradigm for Mixed Lineage Leukemia

MLL rearrangement is observed in approximately 5-10% of acute myeloid leukemia (AML) cases in adults and in over 70% of pediatric acute lymphoblastic leukemia (ALL). MLL rearrangements among adults arise de novo but frequently occur as a consequence of exposure to prior treatment with chemotherapy (etoposide, anthracyclins) in response to a primary malignancy. Current treatment options for adults with MLL rearranged AML, however, are not dissimilar from other high-risk protocols, typically consisting of induction chemotherapy with cytarabine and an anthracycline (either idarubicin or daunorubicin) followed by a period of consolidation. Survival analysis from a retrospective study of 45 patients with confirmed MLL-r leukemia treated at single institution in Europe published in 2012 observed a median overall survival duration of 22 months in adults (over 18 yrs of age), most of whom had AML (Figure 19). The five-year survival rate among adults was approximately 27%, in-line with survival rates reported from larger meta-analyses of AML patients with intermediate- or adverse-risk karyotypes (Figure 20).

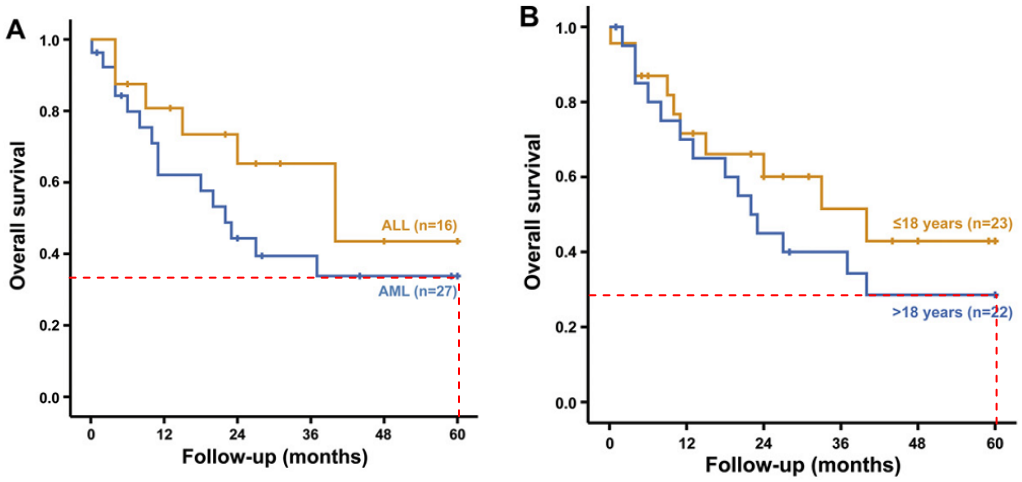
Similarly, MLL rearrangement predicts for poorer prognosis in pediatric acute leukemia and optimal treatment options remain elusive. Little advancement has been made beyond the optimization of chemotherapeutic regimens developed in the 1970s which typical follow a progression of induction, consolidation, and continuation therapy with a combination of glucocorticoid, vincristine and an anthracycline. Allogeneic stem-cell transplant had formally been recommended for higher-risk ALL, particularly for children diagnosed during infancy. Success rates with ASCT, however have been low (<30%) and the small numbers evaluated patients reported in the literature suggests low levels of utilization. A retrospective analysis of MLL rearranged pediatric ALL found no benefit to ASCT versus chemotherapy among children with t(4;11) translocation in which median disease-free survival ranged from ~1.8 – 2.5 year (Figure 21). A second meta-analysis of survival outcomes in pediatric ALL treated at St. Jude Children's research hospital between 1991 and 1999 found that, whereas, overall five-year event free survival rates were high at around ~80%, outcome were far worse among children MLL chromosome rearrangements. Median survival MLL rearranged leukemia was approximately 1.3 years, with a five-year survival rate 27% (Figure 22).

FIGURE 19. MLL Translocations Observed in Adult and Pediatric Acute Leukemia



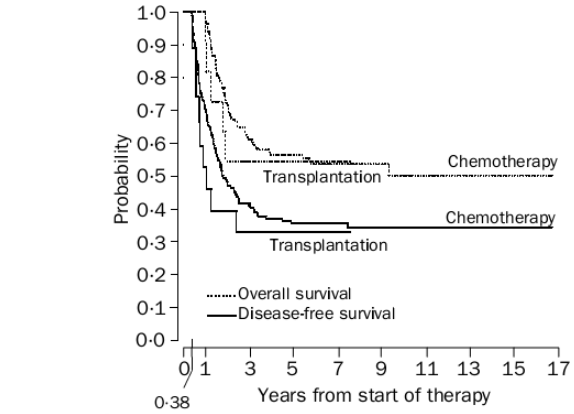
Source: Muntean and Hess, Annu Rev Pathol, 7:283-301, 2012.

FIGURE 20. Five-year overall survival among ALL and AML patients with confirmed MLL Rearrangement



Source: Modified from: Cerveira et al, Molecular Oncology 6:553-564, 2012

FIGURE 21. DFS and OS in retrospective analysis of pediatric ALL

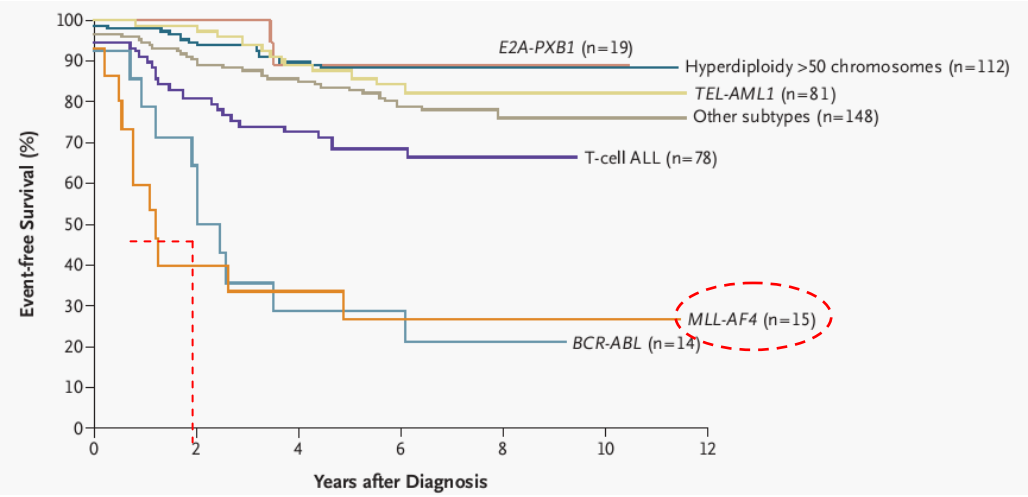


Patients at risk

Overall survival							
Chemotherapy	134	80	70	44	18	11	
Transplantation	11	6	3	2	0	0	
Disease-free survival							
Chemotherapy	183	109	63	50	35	15	10
Transplantation	14	8	5	2	2	0	0

Source: Modified from Pui et al, Lancet, 359: 1909-1915, 2002.

FIGURE 22. Event-free survival by leukemic sub-type among children with ALL enrolled into treatment protocols at St. Jude Children's Research Hospital, 1991-1999.



Source: Modified from: Pui et al, NEJM, 350:1535-48,2004.

Collaboration with Celgene

The partnership with CELG is structured as such that CELG has the exclusive option to license ex-U.S. rights for HMT inhibitor programs, including EPZ-5676, targeting DOT1L during an initial three-year period through July 2015. Celgene has the right to extend this period for selecting additional targets through July 2016 for an additional payment to Epizyme. Epizyme retains all U.S. rights and received a $90MM upfront payment, which included an equity investment. For each HMT inhibitor licensed, Epizyme is eligible to earn more than $160MM in milestone payments and up to double-digit royalties on ex-U.S. sales. For the purposes of our estimates, we forecast that Celgene will extend the period to 2016, and select two additional targets (one in 2015 and one in 2016)

Commercial Opportunity

In modeling the commercial opportunity available for mixed lineage leukemia we segmented the market into underlying disease (AML, ALL), geographies (U.S., EU, and Japan), line of therapy (first line or relapsed) and age (adult, childhood, and infant) to account for different rates of incidence, relapse, and potential duration of response to therapy (our surrogate for duration of therapy). We detail our methodology for the U.S., and complete similar analyses for EU and Japan.

We developed an incidence driven model with an annual addressable populations for DOT1L defined MLL in AML and ALL in the U.S. For AML, we forecast an annual newly addressable patient population of ~1,700 patients in the U.S. (with ~40% in the relapsed setting) at the time of projected launch in 2017. Similar analysis for AML, identified an addressable population of 930, leading to a total addressable population of ~2,600 patients in the U.S. alone. We modeled in peak market share penetration of 90% in the relapsed setting (for patients not previously exposed to EPZ-5676) and ~55% in the front-line setting. We modeled in a steady state duration of therapy of 18 months in the front-line setting and 12 months in the relapsed setting, but readily acknowledge that these are rough estimates based on the limited clinical data generated to date. That said, we believe there is a meaningful possibility of prolonged duration of therapy given that the drug is targeting the initiating underlying mutation driving the disease.

We forecast a list price of $15,000 per month at launch, growing 3.5% annually, and a 15% gross-to-net adjustment. Based on these assumptions, as well as launches in 2018 for Japan and Europe, we forecast worldwide sales of $510MM in 2020 ($265MM in the U.S.) and $770MM in 2025 ($415MM in the U.S.). We summarize our revenue forecast by geography and line of therapy in Figure 23, and delineate our U.S. market model in Figure 24.

FIGURE 23. Summary of EPZ-5676 Sales by Geography and Disease and Revenues to EPZM

EPZ-5676 (DOT1L) Revenue Summary	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
EPZ-5676 WW Sales	**$ 18.6**	**$ 138.7**	**$ 326.8**	**$ 509.2**	**$ 630.1**	**$ 686.9**	**$ 717.7**	**$ 747.2**	**$ 771.9**
US Sales	15.9	87.8	180.8	266.3	328.2	354.7	374.2	396.5	415.5
Ex-US Sales	2.7	50.9	146.0	242.8	301.9	332.2	343.5	350.7	356.4
Effective royalty on ex-US Sales	6.0%	6.0%	6.0%	6.4%	6.7%	6.8%	6.8%	6.9%	6.9%
Royalty revenue	0.2	3.1	8.8	15.4	20.2	22.6	23.5	24.1	24.5
Total Revenues to EPZM for EPZ-5676	**$ 16.0**	**$ 90.8**	**$ 189.6**	**$ 281.8**	**$ 348.3**	**$ 377.3**	**$ 397.7**	**$ 420.5**	**$ 440.0**
Sales milestones	**$ 25.0**			**$ 15.0**					
Breakdown by Geography									
US Sales	**$ 15.9**	**$ 87.8**	**$ 180.8**	**$ 266.3**	**$ 328.2**	**$ 354.7**	**$ 374.2**	**$ 396.5**	**$ 415.5**
ALL	5.6	30.9	63.7	94.2	117.0	128.0	136.3	144.7	152.7
AML	10.3	56.9	117.1	172.1	211.2	226.7	237.9	251.8	262.8
EU Sales	**$ 2.7**	**$ 38.7**	**$ 120.0**	**$ 200.0**	**$ 249.9**	**$ 274.2**	**$ 283.7**	**$ 288.9**	**$ 294.8**
ALL	2.7	33.0	64.2	92.8	110.6	116.2	118.7	120.9	122.4
AML	0.0	5.7	55.8	107.2	139.3	158.1	165.0	167.9	172.4
JPN Sales	**$ -**	**$ 12.1**	**$ 26.0**	**$ 42.9**	**$ 52.0**	**$ 57.9**	**$ 59.9**	**$ 61.8**	**$ 61.6**
ALL	0.0	1.1	4.6	12.7	19.0	22.8	24.2	25.2	25.1
AML	0.0	11.0	21.4	30.1	33.1	35.1	35.6	36.6	36.5
Total WW Sales	**$ 18.6**	**$ 138.7**	**$ 326.8**	**$ 509.2**	**$ 630.1**	**$ 686.9**	**$ 717.7**	**$ 747.2**	**$ 771.9**

Source: JMP Securities LLC, Company reports

FIGURE 24. EPZ-5676 Revenue Model (MLL-r in AML and ALL)

EPZ-5676 MLL-r Revenue Model US, Incidence Driven	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E
Acute Lymphoblastic Leukemia									
Incidence of Leukemia, US	47,986	48,418	48,854	49,294	49,737	50,185	50,637	51,092	51,552
% y/y growth	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%
Incidence of ALL, US (as % of all leukemias)	13%	13%	13%	13%	13%	13%	13%	13%	13%
Incidence of ALL, US	6,238	6,294	6,351	6,408	6,466	6,524	6,583	6,642	6,702
ALL-MLL-r, 1L Setting									
ALL-MLL-r, 1L addressable population	557	562	567	572	577	582	587	593	598
EPZ-5676 Market Share	5%	15%	30%	45%	50%	52%	53%	54%	55%
Total 1L ALL-MLL-r Patients Starting Therapy	28	84	170	257	288	303	311	320	329
ALL-MLL-r, Relapsed Setting									
Total Relapsed Addressable Patients Population	363	355	346	331	316	308	300	301	303
EPZ-5676 Market Share	20%	65%	80%	88%	90%	90%	90%	90%	90%
1L ALL-MLL-r Relapsed Patients Starting Therapy	73	230	277	289	285	277	270	271	272
Total New Patients Starting Therapy	100	315	447	547	573	579	581	591	601
Total Months on Therapy	438	2,341	4,666	6,667	7,996	8,454	8,695	8,920	9,095
Price of Therapy, per month	$ 15,000	$ 15,525	$ 16,068	$ 16,631	$ 17,213	$ 17,815	$ 18,439	$ 19,084	$ 19,752
y/y % price increases		3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%
Gross-to-net discount	15%	15%	15%	15%	15%	15%	15%	15%	15%
Effective Price	$ 12,750	$ 13,196	$ 13,658	$ 14,136	$ 14,631	$ 15,143	$ 15,673	$ 16,222	$ 16,789
US Sales, ALL	$ 5.6	$ 30.9	$ 63.7	$ 94.2	$ 117.0	$ 128.0	$ 136.3	$ 144.7	$ 152.7
Acute Myelogenous Leukemia									
Incidence of Leukemia, US	47,986	48,418	48,854	49,294	49,737	50,185	50,637	51,092	51,552
% y/y growth	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%
Incidence of AML, US (as % of all leukemias)	29%	29%	29%	29%	29%	29%	29%	29%	29%
Incidence of AML, US	13,916	14,041	14,168	14,295	14,424	14,554	14,685	14,817	14,950
AML-MLL-r, 1L Setting									
AML-MLL-r, 1L addressable population	1,010	1,019	1,028	1,038	1,047	1,056	1,066	1,075	1,085
EPZ-5676 Market Share	5%	15%	30%	45%	48%	49%	50%	50%	50%
Total 1L AML-MLL-r Patients Starting Therapy	51	153	309	467	503	518	533	538	543
AML-MLL-r, Relapsed Setting									
Total Relapsed Addressable Patients Population	672	657	643	608	582	566	541	545	550
EPZ-5676 Market Share	20%	65%	80%	88%	90%	90%	90%	90%	90%
1L AML-MLL-r Relapsed Patients Starting Therapy	134	427	514	532	524	510	487	491	495
Total New Patients Starting Therapy	185	580	823	999	1,027	1,027	1,020	1,029	1,037
Total Months on Therapy	806	4,312	8,574	12,174	14,435	14,969	15,181	15,520	15,652
Price of Therapy, per month	$ 15,000	$ 15,525	$ 16,068	$ 16,631	$ 17,213	$ 17,815	$ 18,439	$ 19,084	$ 19,752
y/y % price increases		3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%
Gross-to-net discount	15%	15%	15%	15%	15%	15%	15%	15%	15%
Effective Price	$ 12,750	$ 13,196	$ 13,658	$ 14,136	$ 14,631	$ 15,143	$ 15,673	$ 16,222	$ 16,789
US Sales, AML	$ 10.3	$ 56.9	$ 117.1	$ 172.1	$ 211.2	$ 226.7	$ 237.9	$ 251.8	$ 262.8

Source: JMP Securities LLC, SEER

EPZ-6438 (EZH2 INHIBITOR)

Overview of EPZ-6438

EPZ-6438 is an orally available inhibitor of EZH2. The drug has demonstrated an ability to selectivity inhibit H3K27 methylation leading to specific killing of EZH2 SET domain mutants in lymphoma cell lines and xenograft models. In addition, a number of other studies have been published over the past year detailing a role for mutant EZH2 in a range of other tumors (e.g., rhabdosarcoma, breast, prostate, CLL, T-cell lymphomas), as well as the role of overexpressed wild-type EZH2 in the pathogenesis of NHL. While we do not include these in our models, we believe critical to understand that the overall opportunity for EPZ-6438 extends far beyond the initial area of focus (i.e., NHL).

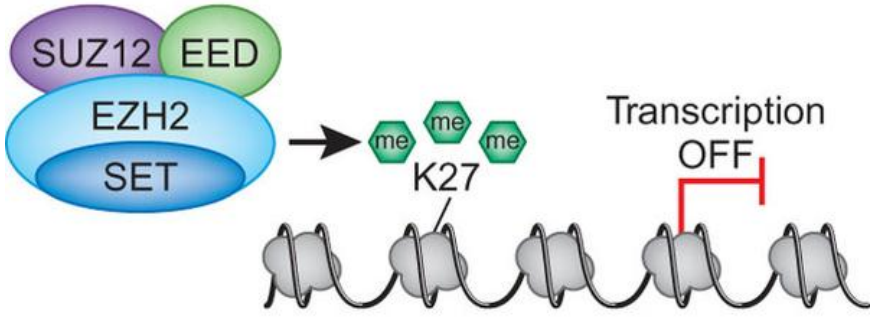
A Phase I/II trial of EPZ-6438 in NHL patients with oncogenic point mutations in EZH2 recently enrolled its first patient. The trial comprises two parts. The first part will be an open label dose escalation study including an undetermined number of patients with an EZH2 point mutation. The second part of the study will exclusively enroll patients with confirmed relapsed or refractory DLBCL or follicular lymphoma (FL) along with an EZH2 point mutation.

In April 2011, Epizyme entered into a worldwide partnership to discover, develop, and commercialize therapeutics targeting EZH2, with Epizyme retaining an opt-in right to co-develop, co-commercialize, and share profit with Eisai on licensed products in the U.S. As a result of the recent trial initiation, Epizyme earned a $6MM milestone from Eisai. Epizyme and Eisai are also working Roche (RHBBY, Not Covered) to develop a companion diagnostic for EZH2.

Biology of EZH2

EZH2 is the catalytic subunit of the polycomb repressive complex (PRC2), which acts as a protein methyltransferase, catalyzing mono- through trimethylation of lysine 27 on histone 3 (H3K27). Trimethylation of H3K27 is believed to act as an epigenetic mechanism for suppressing specific proximal genes to the site of histone modification. Though silenced in somatic cells, EZH2 is typically expressed in undifferentiated stem and progenitor cell types.

FIGURE 25. Role of PRC2 in Transcription



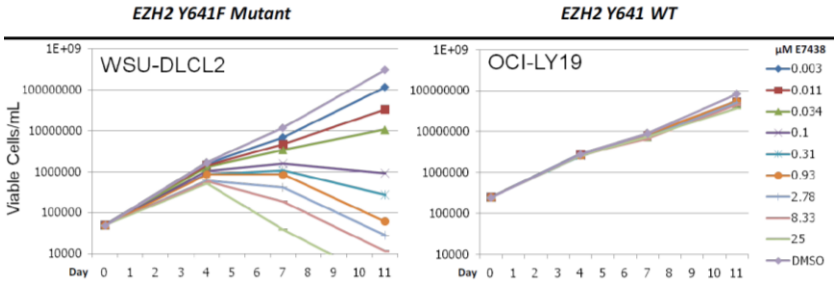
Source: Martines-Garcia et al., Nature Genetics 42: 100-101 (2010)

A number of somatic mutations of tyrosine residue 641 (Y641) for EZH2 have been identified and found to be associated with FL and germinal-center B-cell like (GCB) subype of DLBCL. Curiously, in each case the mutant EZH2 gene was found to be heterozygous, expressing both wild type and mutant alleles. It was later shown that the malignant phenotype observed required (1) wild-type EZH2 to monomethylate H3K27 and (2) mutant EZH2 to convert H3K27 to its tri-methylated form. As such, targeting of EZH2 has been identified as an experimental strategy for development of specific drugs for those patients with EZH2-mutant forms of FL and GCB-type DLBCL.

Pre-Clinical Data on EZH2 in NHL

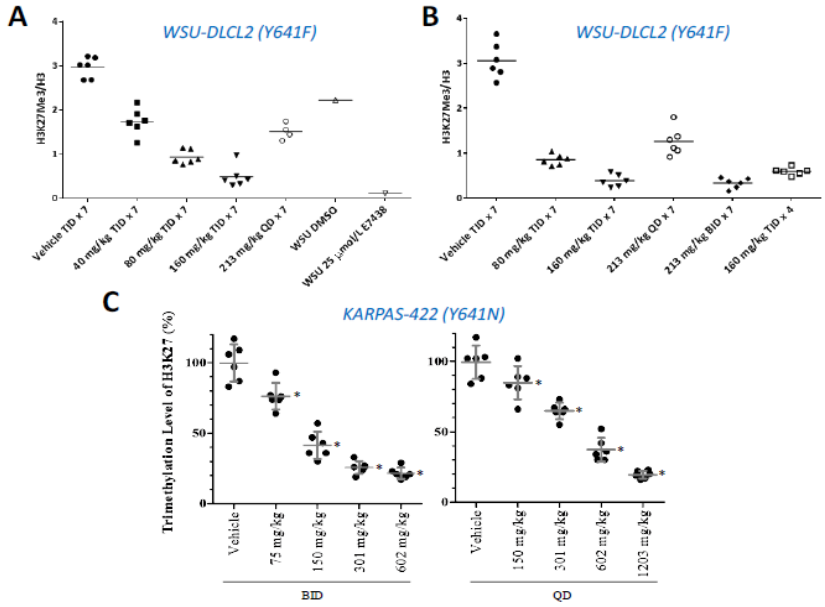
EPZ-6438 was evaluated pre-clinically in a variety in vitro and in vivo models. The drug showed potent selectivity for EZH2 relevant to other members of the 96-member HMTome. Further, the drug demonstrated an ability to selectively kill mutant EZH2 in cell lines (Figure 26). This was later supported by mouse xenograft study showing potent and selective killing of various mutant forms of EZH2 in tumors relative to those expressing wild-type EZH2. These data demonstrated potent knockdown of methylation as well prolonged responses at dose just north of 300mg/kg.

FIGURE 26. Selective Killing of EZH2 Y641 Mutant Lymphoma Cells (vs. WT EZH2)



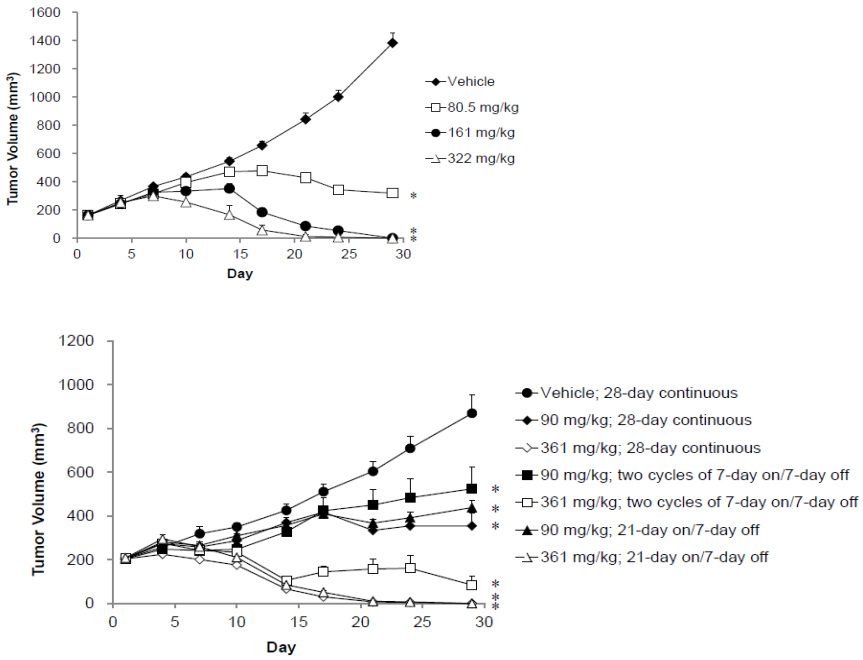
Source: Keilhack, ASH 2012, #3712

FIGURE 27. Inhibition of H3K27 Methylation with EPZ-6438 in Y641 Mutant Lymphoma Xenografts



Source: Keilhack, ASH 2012, #3712

FIGURE 28. EPZ-6438 Anti-tumor Activity in Mice Xenografts with Y641N Mutation – Twice a Day Dosing Schedule



Source: Keilhack, ASH 2012, #3712

Pre-Clinical Data on EZH2 in NHL – EZH2 Activation Mediates Solid Tumorigenesis

The SWI/SNF complex is a multi-subunit protein complex capable of remodeling chromosomes by repositioning nucleosomes through ATP dependent processes (Figure 30). A growing body of evidence now shows that SWI/SNF complex proteins are tumor suppressive and that defects to component proteins are linked to several solid tumor and hematologic malignancies. Biallelic inactivating mutations of *SNF5* are identified in nearly all malignant rhabdoid tumors (MRTs) – a rare, aggressive cancer occurring in young children that can affect the brain, kidney, and other soft tissues. Mutations to a second SWI/SNF subunit gene, PBRM1 (which encodes the BAF180 protein subunit) have been observed in ~40% of renal cell carcinomas as well as in a minority of breast cancers. As further examples, subunit ARIDA1A is mutated in nearly half of ovarian and endometriod carcinomas, while subunit BRG1 is mutated in about a third of non-small cell lung cancers.

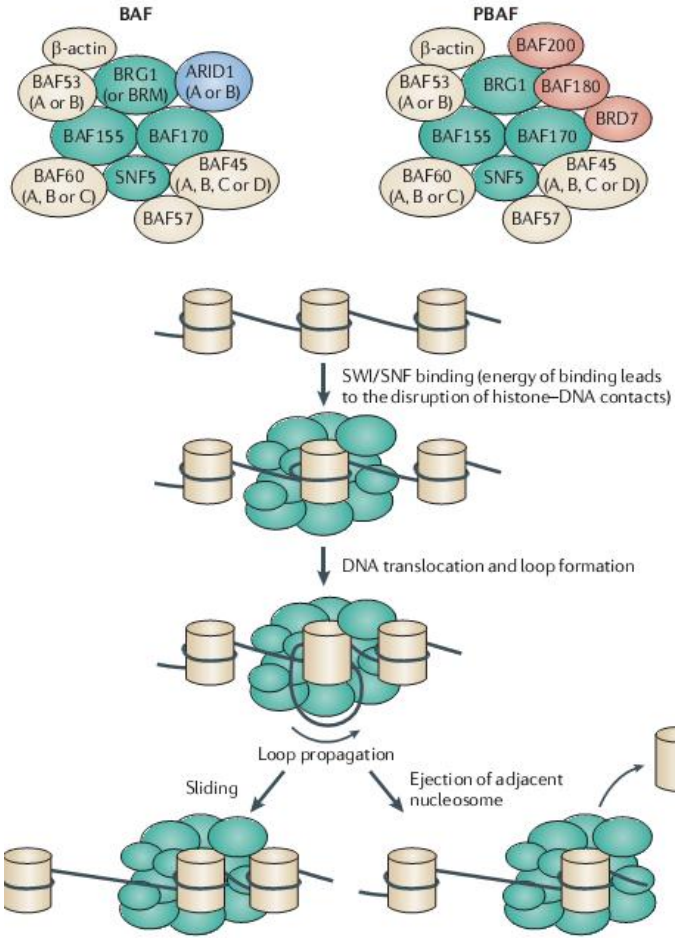
The link between SWI/SNF deregulation and tumor formation has been attributed, at least in part, to changes epigenetic control over cell-cycle regulating tumor suppressors, specifically via EZH2 activity. Work published in Cancer Cell in 2010 by Wilson et al., showed that SNF5-containing SWI/SNF complexes were antagonistic to EZH2 PRC2 complexes, and effectively maintained expression of CDK inhibitory proteins such as $p16^{Ink4a}$ (Figure 31). MRT models with SNF5 loss exhibit elevated EZH2 expression relative to normal neuronal tissue, higher levels of H3K27 tri-methylation at PRC2 target promoters and lower levels of $p16^{Ink4A}$ expression as a result. Knocking down EZH2 by shRNA in this context recovers p16 expression and dramatically reduces tumor proliferation.

Epizyme investigators have shown that treatment of malignant rhabdoid tumor models with EPZ-6438, both in vitro and in vivo (Figure 32), similarly provokes tumor growth inhibition at 125mg/kg and tumor regression at concentrations ≥250mg/kg. As the preclinical evaluation of EZP-6438 in solid tumors continues, we anticipate the company will initiate a Phase I solid tumor clinical study in 2014.

Collaboration with Eisai

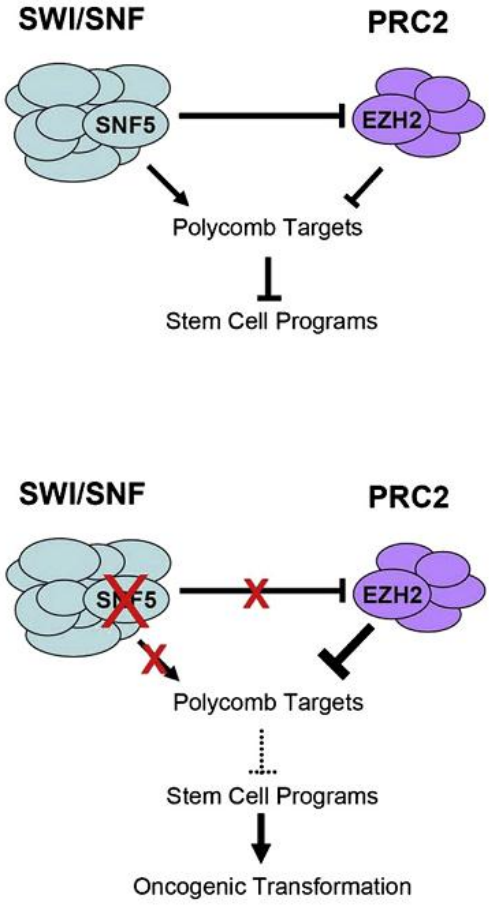
The collaboration with Eisai is for the exclusive worldwide license to the Epizyme EZH2 program, including EPZ-6438. Epizyme retains the right to exercise its option to co-develop, co-commercialize, and share profits with Eisai to U.S. rights of said products, including EPZ-6438. Epizyme is eligible to receive $80MM additional research, development, and regulatory milestones, and sales based milestones totaling $115MM. Should Epizyme exercise its right to the U.S., the milestones will reduced by approximately half and the company will required to share ongoing U.S. development costs. We expect Epizyme to exercise its opt-in, and our model reflects this.

FIGURE 29. SWI/SNF chromatin remodeling complexes and function



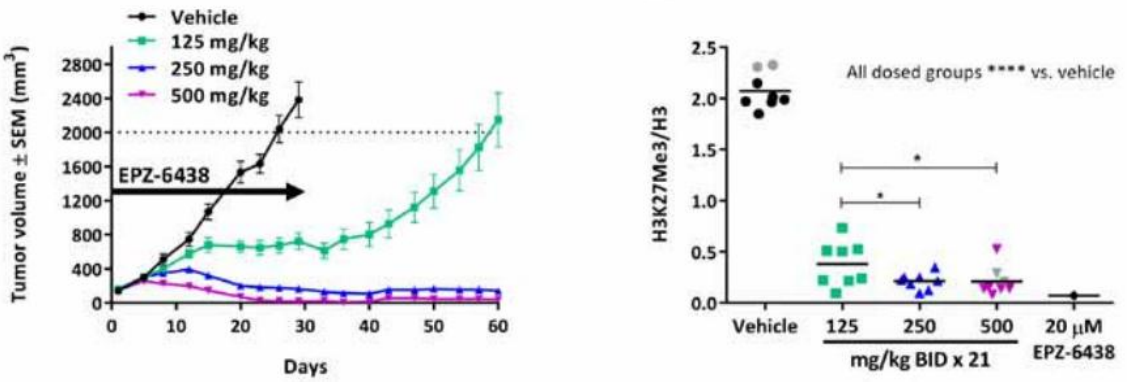
Source: Wilson and Roberts, Nat Rev Cancer, 2011.

FIGURE 30. Model of EZH2 antagonism by SNF5 (SWI/SNF complex) during tumorigenesis



Source: Wilson and Roberts, Nat Rev Cancer, 2011.

FIGURE 31. Pharmacologic Inhibition EZH2 by EPZ-6438 Inhibits MRT Tumor Growth



Source: Epizyme company presentation

Commercial Opportunity

For EPZ-6438 we limited our evaluation of the commercial opportunity just to EZH2 mutants in FL and GCB-DLBCL. We defined addressable populations for the first-line and relapsed patient populations in both settings, as well as for the U.S., EU, and Japan. For the time being, we exclude any front-line sales in either segment from our projections given the predominance of Rituxan chemoimmunotherapy regimens. We defined addressable populations in the relapsed setting of GCB-DLBCL at ~850 patients in the US, and ~3,500 in the FL setting. Given that the population will be genetically defined, we forecast a significant market penetration (~90%) after six years, and duration of therapy of eight months in the relapsed setting.

Based on these estimates and a price at launch of ~$12,000 per month, we forecast U.S. sales of $710MM in 2020 growing to $1.0 bn by 2025. We forecast additional sales outside the U.S. will bring worldwide totals to ~$1bn in 2020 and $1.5 by 2025. The interesting question to ponder is whether the inhibition of EZH2 could potentially play a role in all GCB-type NHL. A recent publication by Melnick, et al., in Cancer Cell, May 13, 2013, describes the essential role of EZH2 in the maturation process of B cells in the germinal center. EZH2 plays a gatekeeper function whereby B cells are pushed into maturity and migrate out of lymph node or undergo apoptosis. Given that the majority of B cell lymphomas arise from germinal center B cells, the inhibition of EZH2 could potentially play a major role in this important sub-category of NHL. Given the early days of our understanding, we have not included any upside in our numbers from the broader use of EPZ-6438.

FIGURE 32. Summary of EPZ-6438 Revenue Model

EPZ-6438 (EZH2) Revenue Summary	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
EPZ-6438 WW Sales	**$ 84.5**	**$ 414.3**	**$ 852.0**	**$ 1,210.9**	**$ 1,533.2**	**$ 1,774.1**	**$ 1,958.7**	**$ 2,076.1**	**$ 2,166.4**
US Sales	45.4	224.5	489.7	716.0	906.6	1,049.6	1,153.8	1,212.1	1,265.8
Ex-US Sales	39.1	189.8	362.3	494.9	626.6	724.5	804.9	864.0	900.7
Portion of sales <$200MM	39.1	189.8	200.0	200.0	200.0	200.0	200.0	200.0	200.0
Portion of sales btw $200 - 400MM	0.0	0.0	162.3	200.0	200.0	200.0	200.0	200.0	200.0
Portion of sales >$600MM	0.0	0.0	0.0	94.9	226.6	324.5	404.9	464.0	500.7
Effective royalty	6.0%	6.0%	6.9%	7.6%	8.1%	8.3%	8.5%	8.6%	8.7%
Royalties on Ex-US Sales	2.3	11.4	25.0	37.5	50.7	60.5	68.5	74.4	78.1
Total Revenues to EPZM for EPZ-6438	**$ 47.7**	**$ 235.9**	**$ 514.7**	**$ 753.5**	**$ 957.3**	**$ 1,110.1**	**$ 1,222.3**	**$ 1,286.5**	**$ 1,343.8**
Sales milestones	**$ 12.5**	**$ 25.0**	**$ 32.5**						
Breakdown by Geography									
US Sales	**$ 45.4**	**$ 224.5**	**$ 489.7**	**$ 716.0**	**$ 906.6**	**$ 1,049.6**	**$ 1,153.8**	**$ 1,212.1**	**$ 1,265.8**
DLBCL	14.3	67.4	114.7	173.8	220.3	248.7	271.0	283.0	295.5
FL	31.0	157.1	375.0	542.2	686.3	800.9	882.8	929.1	970.2
EU Sales	**$ 32.6**	**$ 159.7**	**$ 317.6**	**$ 435.7**	**$ 551.5**	**$ 638.9**	**$ 711.2**	**$ 764.0**	**$ 797.2**
DLBCL	11.7	54.4	81.1	112.1	152.2	181.1	203.0	219.8	227.9
FL	20.9	105.3	236.6	323.6	399.3	457.9	508.2	544.2	569.3
JPN Sales	**$ 6.5**	**$ 30.1**	**$ 44.7**	**$ 59.2**	**$ 75.1**	**$ 85.6**	**$ 93.7**	**$ 100.0**	**$ 103.4**
DLBCL	2.8	13.2	19.5	26.9	36.5	43.3	48.4	52.3	54.0
FL	3.6	16.9	25.1	32.3	38.6	42.3	45.3	47.8	49.4
Total WW Sales	**$ 84.5**	**$ 414.3**	**$ 852.0**	**$ 1,210.9**	**$ 1,533.2**	**$ 1,774.1**	**$ 1,958.7**	**$ 2,076.1**	**$ 2,166.4**

Source: JMP Securities LLC, Epizyme SEC filings

FIGURE 33. EPZ-6438 Revenue Model (GCB-DLBCL and FL)

EPZ-6438 Revenue Model US, Incidence Driven	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E
GCB-type DLBCL									
NHL Incidence US	71,679	72,324	72,975	73,632	74,295	74,963	75,638	76,319	77,006
% y/y growth	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%
Incidence of DLBCL, US (as % of all leukemias)	35%	35%	35%	35%	35%	35%	35%	35%	35%
Incidence of DLBCL, US	25,088	25,314	25,541	25,771	26,003	26,237	26,473	26,712	26,952
GCB-DLBCL, 1L Setting									
1L GCB-DLBCL addressable population	2,622	2,645	2,669	2,693	2,717	2,742	2,766	2,791	2,816
EPZ-6438 Market Share	0%	0%	5%	10%	13%	15%	15%	15%	15%
Total 1L GCB-DLBCL Patients Starting Therapy	-	-	133	269	340	411	415	419	422
GCB-DLBCL, Relapsed Setting									
% relapsing	33%	33%	33%	33%	33%	33%	33%	33%	33%
Total Relapsed Addressable Patients Population	865	873	881	889	897	905	913	921	929
EPZ-6438 Market Share	20%	65%	80%	88%	90%	90%	90%	90%	90%
Total Relapsed GCB-DLBCL Patients Starting Therapy	173	567	705	778	807	814	822	829	836
Total Months on Therapy	1,125	5,107	8,400	12,297	15,060	16,423	17,290	17,446	17,603
Price of Therapy, per month	$ 15,000	$ 15,525	$ 16,068	$ 16,631	$ 17,213	$ 17,815	$ 18,439	$ 19,084	$ 19,752
y/y % price increases		3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%
Gross-to-net discount	15%	15%	15%	15%	15%	15%	15%	15%	15%
Effective Price	$ 12,750	$ 13,196	$ 13,658	$ 14,136	$ 14,631	$ 15,143	$ 15,673	$ 16,222	$ 16,789
US Sales, GCB-DLBCL	$ 14.3	$ 67.4	$ 114.7	$ 173.8	$ 220.3	$ 248.7	$ 271.0	$ 283.0	$ 295.5
Follicular Lymphoma									
NHL Incidence US	71,679	72,324	72,975	73,632	74,295	74,963	75,638	76,319	77,006
% y/y growth	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%	0.9%
Incidence of FL, US (as % of all leukemias)	25%	25%	25%	25%	25%	25%	25%	25%	25%
Incidence of FL, US	17,920	18,081	18,244	18,408	18,574	18,741	18,910	19,080	19,251
FL, 1L Setting									
1L FL addressable population	3,745	3,779	3,813	3,847	3,882	3,917	3,952	3,988	4,024
EPZ-6438 Market Share	0%	0%	5%	10%	18%	20%	20%	20%	20%
Total 1L FL, Patients Starting Therapy	-	-	191	385	679	783	790	798	805
FL, Relapsed Setting									
Total Relapsed Addressable Patients Population	3,745	3,779	3,813	3,847	3,882	3,917	3,952	3,988	4,024
EPZ-6438 Market Share	10%	35%	65%	75%	78%	79%	80%	80%	80%
Total Relapsed FL Patients Starting Therapy	375	1,323	2,478	2,885	3,028	3,094	3,162	3,190	3,219
Total Months on Therapy	2,434	11,904	27,453	38,356	46,904	52,890	56,326	57,273	57,789
Price of Therapy, per month	$ 15,000	$ 15,525	$ 16,068	$ 16,631	$ 17,213	$ 17,815	$ 18,439	$ 19,084	$ 19,752
Effective Price	$ 12,750	$ 13,196	$ 13,658	$ 14,136	$ 14,631	$ 15,143	$ 15,673	$ 16,222	$ 16,789
US Sales, FL	$ 31.0	$ 157.1	$ 375.0	$ 542.2	$ 686.3	$ 800.9	$ 882.8	$ 929.1	$ 970.2

Source: JMP Securities LLC, Epizyme SEC filings

COLLABORATION WITH GSK

In January 2011, Epizyme and GSK entered into a collaboration and license agreement to discover, develop, and commercialize novel small molecular HMT inhibitors directed against targets available in the company's platform. As per the agreement, GSK has the option to obtain an exclusive worldwide license rights to HMT inhibitors directed to up to three targets. GSK has since selected and licensed the three targets. In return, Epizyme received an upfront payment of $20MM, in addition to research funding and development milestone payments. Epizyme is entitled to receive up to $120MM in pre-clinical and clinical research and development milestones, $240MM in regulatory milestones, and $270MM in sales-based milestones, on top of royalties ranging from mid-single digits to low-double digits.

We view any future revenues coming from the collaboration with GSK as upside to our estimates, and currently model in zero incremental revenues beyond reimbursement of research and development expenses associated with the partnership in 2013.

SUMMARY AND CONCLUSION

As previously stated, we believe Epizyme has all the elements under one roof to enable enormous success in oncology drug discovery. The company has a dominant (though not exclusive) position in the biology of HMTs, superb chemistry that allows the company to produce potent and selective inhibitors of SET domains with predictable regularity, and a committed management team that understands both clinical development and commercial strategy.

Investors have enjoyed significant gains in the shares of a number of companies in the oncology space when their lead programs show preliminary signs of efficacy in genetically targeted tumors. Amongst these we would include Ariad Pharmaceuticals (ARIA, MO, $32), Pharmacyclics (PCYC, MO, $112), Puma Biotechnology (PBYI, Not Covered), Stemline (STML, NC), Clovis Oncology (CLVS, NC), and Tesaro (TSRO, NC).

Our excitement over EPZM is the fact that the company is developing two targeted therapies in close succession, and will likely have additional clinical development candidates to announce over the next 12-24 months. Should the EPZM story unfold in a similar manner as the other companies we mentioned, investors could enjoy significant returns on their investment. We are therefore initiating coverage of EPZM with a Market Outperform rating and 12-month price target of $40.

FIGURE 34. Income Statement

Epizyme Income Statement ($MM)	2012A	2013E	1Q14E	2Q14E	3Q14E	4Q14E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
REVENUES													
Product Sales and Royalties													
EPZ-5676 (DOT1L) US Sales								0.0	0.0	15.9	87.8	180.8	266.3
EPZ-6438 (EZH2) US Profit Share								0.0	0.0	7.9	53.9	134.7	232.7
EPZ-5676 (DOT1L) Ex-US Royalties								0.0	0.0	0.2	3.1	8.8	15.4
EPZ-6438 (EZH2) Ex-US Royalties								0.0	0.0	2.3	11.4	25.0	37.5
Total Product Sales and Royalties								0.0	0.0	26.3	156.1	349.2	552.0
Collaboration Revenue & Milestones													
Celgene	23.9	14.2	26.5	1.5	1.5	36.5	66.1	38.0	35.8	90.0	15.0	10.0	15.0
Eisai	11.6	17.9	0.4	0.4	0.4	0.4	1.6	0.0	10.0	12.5	25.0	32.5	0.0
GSK	9.7	12.0	3.0	3.0	3.0	1.8	10.8	0.0	0.0	0.0	0.0	0.0	0.0
Total Collaboration Revenue	45.2	44.1	29.9	4.9	4.9	38.7	78.5	38.0	45.8	102.5	40.0	42.5	15.0
TOTAL REVENUE	45.2	44.1	29.9	4.9	4.9	38.7	78.5	38.0	45.8	128.8	196.1	391.7	567.0
COGS		0.0					0.0	0.0	0.0	1.4	13.8	29.2	44.9
Gross Profit	45.2	44.1	29.9	4.9	4.9	38.7	78.5	38.0	45.8	127.4	182.3	362.5	522.1
Operating Expenses													
R&D	38.5	64.1	16.0	12.0	11.5	12.5	52.0	55.0	65.0	73.1	80.4	86.5	92.5
SG&A	7.5	15.2	4.2	4.5	5.0	5.5	19.2	24.0	32.0	50.0	57.5	63.3	68.0
Total Operating Expenses (R&D, SG&A)	46.0	79.3	20.2	16.5	16.5	18.0	71.2	79.0	97.0	123.1	137.9	149.7	160.5
Operating Income (Loss)	(0.8)	(35.2)	9.7	(11.6)	(11.6)	20.7	7.3	(41.0)	(51.2)	5.7	44.4	212.8	361.5
Non-operating income (expense)	0.1								0.6	0.5	0.5	0.6	1.2
Earnings before Taxes	(0.7)	(35.2)	9.7	(11.6)	(11.6)	20.7	7.3	(41.0)	(50.7)	6.1	44.9	213.5	362.7
Provision for income taxes (benefit)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	21.3	72.5
Tax Rate(%)		0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	10%	20%
Net Income (Loss)	(0.7)	(35.2)	9.7	(11.6)	(11.6)	20.7	7.3	(41.0)	(50.7)	6.1	44.9	192.1	290.2
Basic shares outstanding	1.65	17.3	28.434	28.455	28.480	31.004	29.1	33.6	33.8	34.0	34.2	34.5	34.7
Diluted shares	1.65	17.3	32.775	28.455	28.480	35.549	29.1	33.6	33.8	37.3	37.6	37.9	38.1
GAAP EPS Figures	**2012A**	**2013E**	**1Q14E**	**2Q14E**	**3Q14E**	**4Q14E**	**2014E**	**2015E**	**2016E**	**2017E**	**2018E**	**2019E**	**2020E**
Basic EPS	$ (0.72)	$ (2.03)	$ 0.34	$ (0.41)	$ (0.41)	$ 0.67	$ 0.25	$ (1.22)	$ (1.50)	$ 0.18	$ 1.31	$ 5.57	$ 8.36
Diluted EPS	$ (0.72)	$ (2.03)	$ 0.30	$ (0.41)	$ (0.41)	$ 0.58	$ 0.25	$ (1.22)	$ (1.50)	$ 0.16	$ 1.19	$ 5.07	$ 7.61
Non-GAAP EPS	**2012A**	**2013E**	**1Q14E**	**2Q14E**	**3Q14E**	**4Q14E**	**2014E**	**2015E**	**2016E**	**2017E**	**2018E**	**2019E**	**2020E**
Basic		$ (1.94)	$ 0.36	$ (0.39)	$ (0.39)	$ 0.69	$ 0.33	$ (1.10)	$ (1.35)	$ 0.34	$ 1.49	$ 5.77	$ 8.60
Diluted		$ (1.94)	$ 0.31	$ (0.39)	$ (0.39)	$ 0.60	$ 0.33	$ (1.10)	$ (1.35)	$ 0.31	$ 1.36	$ 5.25	$ 7.82

Source: JMP Securities LLC and Epizyme SEC filings

APPENDIX A – BIOGRAPHIES

SENIOR MANAGEMENT

Robert J. Gould, Ph.D. has served as a director since March 2008 and President and Chief Executive Officer since March 2010. Prior to joining Epizyme, from November 2006 to March 2010, Dr. Gould served as Director of Novel Therapeutics at The Broad Institute of MIT and Harvard, or Broad, a research institute. Prior to that, Dr. Gould was Vice President, Licensing and External Research, Merck Research Laboratories, at Merck & Co., Inc., or Merck, a healthcare company, where he held a variety of leadership positions during his tenure of over 20 years. Dr. Gould received a B.A. from Spring Arbor College and a Ph.D. from The University of Iowa and undertook post-doctoral studies at The Johns Hopkins University. We believe that Dr. Gould's detailed knowledge of our company and his over 30 years in the pharmaceutical and biotechnology industries, including his roles at Broad and at Merck, provide a valuable contribution to our board of directors.

Robert A. Copeland, Ph.D. has served as Executive Vice President and Chief Scientific Officer since September 2008. Prior to joining Epizyme, from January 2003 to September 2008, Dr. Copeland was Vice President, Cancer Biology, Oncology Center of Excellence in Drug Discovery, at GSK, a pharmaceutical company. Before joining GSK, Dr. Copeland held scientific staff positions at Merck Research Laboratories of Merck and Bristol-Myers Squibb Company, a biopharmaceutical company, and a faculty position at the University of Chicago Pritzker School of Medicine. Dr. Copeland received a B.S. in chemistry from Seton Hall University, a Ph.D. in chemistry from Princeton University and did post-doctoral studies as the Chaim Weizmann Fellow at the California Institute of Technology.

Jason P. Rhodes has served as Executive Vice President, Chief Financial Officer, and Treasurer since March 2013 and previously served as Executive Vice President, Chief Business Officer and Treasurer from March 2010 to March 2013. Prior to joining Epizyme, from July 2007 to March 2010, Mr. Rhodes served as Vice President, Business Development at Alnylam Pharmaceuticals, Inc., or Alnylam, a biopharmaceutical company. Prior to Alnylam, he was a founder and partner with Fidelity Biosciences, Fidelity Investments' biopharma venture capital group. Mr. Rhodes received a B.A. from Yale University and an M.B.A. from the Wharton School of the University of Pennsylvania.

Eric E. Hedrick, M.D. has served as the Chief Medical Officer since May 2012. Prior to joining Epizyme, Dr. Hedrick served as Vice President, Oncology Development, at Pharmacyclics, Inc., or Pharmacyclics, a biopharmaceutical company, from August 2010 to April 2012, and Interim Chief Medical Officer from May 2011 to April 2012. From October 2009 to August 2010, Dr. Hedrick was an independent drug development consultant, including consulting with Pharmacyclics. From November 2000 to September 2009, Dr. Hedrick held a variety of positions at Genentech, Inc., or Genentech, a biotechnology company, including Medical Director, Group Medical Director and clinical scientist. Prior to his time at Genentech, Dr. Hedrick was an Associate Attending Physician at Memorial Sloan-Kettering Cancer Center where he focused on clinical research in non-Hodgkin lymphoma, myelodysplastic syndromes, multiple myeloma and hematopoietic growth factors. He is a board-certified medical oncologist who was formerly a fellow and staff physician on the Hematology Service at Memorial Sloan Kettering Cancer Center. Dr. Hedrick received a B.A. in biology from Boston University and an M.D. from the University of Maryland.

BOARD OF DIRECTORS

Carl Goldfischer, M.D. has served as a director since September 2009. Dr. Goldfischer has served as an Investment Partner and Managing Director of Bay City Capital LLC, or Bay City Capital, serving as a member of the board of directors and executive committee, and has been with the firm since January 2000. Prior to joining Bay City Capital, Dr. Goldfischer was Chief Financial Officer of ImClone Systems Incorporated, a biopharmaceutical company. Since 2004, Dr. Goldfischer has served on the board of directors of EnteroMedics Inc., a publicly traded medical device company. He has previously served on the board of directors of two other publicly traded companies, MAP Pharmaceuticals, Inc. from 2004 to 2011 and Poniard Pharmaceuticals, Inc. from 2000 to 2012. Dr. Goldfischer received a B.A. from Sarah Lawrence College and an M.D. with honors in Scientific Research from Albert Einstein College of Medicine. We believe that Dr. Goldfischer's extensive finance and investment experience, his experience as an executive and his service on the board of directors of numerous public and privately held companies allow him to be a key contributor to our board of directors.

Thomas O. Daniel, M.D. has served as a director since May 2012. Dr. Daniel has served as President, Research and Early Development of Celgene, since December 2006. Prior to joining Celgene, he served as the Chief Scientific Officer of, and a member of the board of directors at, Ambrx Inc., a biotechnology company focused on discovering and developing protein-based therapeutics. Dr. Daniel previously served as Vice President, Research at Amgen Inc., a biotechnology company, where he was Research Site Head of Amgen Washington and Therapeutic Area Head of Inflammation. Dr. Daniel received an M.D. from the University of Texas, Southwestern, and completed medical residency at Massachusetts General Hospital. We believe that Dr. Daniel's extensive experience in the pharmaceutical industry, his status as an officer of our collaboration partner, Celgene, and his scientific knowledge make him a valuable member of our board of directors.

David M. Mott has served as a director since December 2009. Mr. Mott has served as a general partner of New Enterprise Associates, Inc., an investment firm focused on venture capital and growth equity investments, since September 2008, where he leads the healthcare investing practice. From 1992 until 2008, Mr. Mott worked at MedImmune, Inc., or MedImmune, a biotechnology company and subsidiary of AstraZeneca Plc, or AstraZeneca, and served in numerous roles during his tenure, including Chief Financial Officer, President and Chief Operating Officer, and most recently as Chief Executive Officer from October 2000 to July 2008. During that time, Mr. Mott also served as Executive Vice President of AstraZeneca from June 2007 to July 2008 following AstraZeneca's acquisition of MedImmune in June 2007. Prior to joining MedImmune, Mr. Mott was a Vice President in the healthcare investment banking group at Smith Barney, Harris Upham & Co. Inc. Mr. Mott received a B.A. from Dartmouth College. Mr. Mott also serves as the Chairman of the Board of Directors of TESARO, Inc., or TESARO. We believe that Mr. Mott's extensive experience in the life sciences industry as a senior executive and venture capitalist, as well as his service on the boards of directors of other life sciences companies, provide him with the qualifications and skills to serve as a director of our company.

Richard F. Pops has served as a director since September 2008. Mr. Pops has served as Chief Executive Officer of Alkermes plc, or Alkermes, a publicly traded biopharmaceutical company since 1991. Mr. Pops has been a director of Alkermes since February 1991 and has been Chairman of the Board of Directors since April 2007. Since 1998, Mr. Pops has served on the board of directors of Neurocrine Biosciences, Inc., a publicly traded biopharmaceutical company. He has previously served on the board of directors of two other publicly traded biopharmaceutical companies, Sirtis Pharmaceuticals, from 2004 until 2008, and CombinatoRx, Incorporated, from 2001 until 2009. Mr. Pops received a B.A. in economics from Stanford University. We believe that Mr. Pops' leadership experience, including as chief executive officer of a public pharmaceutical company, his business judgment and his industry knowledge provide him with the qualifications to serve as a director of our company.

Beth Seidenberg, M.D. has served as a director since February 2008. Dr. Seidenberg has been a partner at Kleiner Perkins Caufield & Byers, a venture capital firm, since May 2005, where she has primarily focused on life sciences investing. Dr. Seidenberg was previously the Senior Vice President, Head of Global Development and Chief Medical Officer at Amgen, Inc., a biotechnology company. In addition, Dr. Seidenberg was a senior executive in research and development at Bristol Myers Squibb Company, a biopharmaceutical company, and Merck. Dr. Seidenberg received a B.S. from Barnard College and an M.D. from the University of Miami School of Medicine and completed her post-graduate training at The Johns Hopkins University, George Washington University and the National Institutes of Health. Dr. Seidenberg serves on the board of directors of TESARO. We believe that Dr. Seidenberg's extensive experience in the life sciences industry as a senior executive and venture capitalist, as well as her training as a physician, provide her with the qualifications and skills to serve as a director of our company.

Kazumi Shiosaki, Ph.D. has served as a director since July 2011 and previously served as Epizyme's President and Chief Executive Officer and as a director from November 2007 until March 2010. Dr. Shiosaki has also served as Interim President and Chief Executive Officer of Mitokyne, Inc., a biotechnology company, since May 2011. Dr. Shiosaki has served as a Managing Director with MPM Asset Management LLC, or MPM, a venture capital firm, since 2003. Prior to joining MPM, Dr. Shiosaki was Senior Vice President of Drug Discovery at Millennium Pharmaceuticals, Inc., a pharmaceutical company. Previously, she worked on drug discovery programs in a number of therapeutic areas at Abbott, including neuroscience, cardiovascular and infectious disease. Dr. Shiosaki received a B.S. from Whitman College and a Ph.D. in Synthetic Chemistry from the University of California, Berkeley. We believe that Dr. Shiosaki's broad experience in the life sciences industry as a venture capitalist and senior executive and her research knowledge provide her with the qualifications and skills to serve as a director of our company.

APPENDIX B - THE EPIGENETICS REVOLUTION: EXPLOITING A VAST NEW AREA OF CANCER BIOLOGY IN PURSUIT OF BETTER OUTCOMES

Executive Summary

The Basic Science of Epigenetics

Epigenetics is defined as the investigation of those alterations in the genetic program that are not due to base changes in the DNA sequences, but rather ancillary modifications of the hereditary message. Epigenetic mechanisms are now recognized to play a fundamental role in gene regulation and expression. The current model of hereditary control envisions a dynamic interaction between the genome (base pairs sequences), the epigenome (extragenomic modification) and environmental interaction. These three inputs are believed to play back and forth in dynamic feedback loops, resulting in the expressed phenotype. This model acknowledges a much more dynamic and plastic concept of the organism, subject to constant change and revision, dependent upon epigenetic and environmental inputs.

Because of this profound change in our entire concept of hereditary control, a vast new area of biological investigation is rapidly unfolding. This paradigm shift has significant implication for every area of the biological sciences, but especially for drug development, with critical opportunities unfolding for understanding and combating disease processes. The examination of many illnesses in a completely new light means there exists a wealth of opportunities to develop new diagnostic and therapeutic approaches.

There is currently much discussion and uncertainty concerning the role of epigenetic variation in the origins and development of various cancers. Due to the relatively limited knowledge of the serviceable chemistries and lack of widespread assay availability, oncology has emerged as the most active area of epigenetic drug development. But despite many unanswered questions, there are already FDA approved therapeutics on the market, such as Vidaza and Dacogen, and many more in clinical trials.

Cancer and mental dysfunction are two extremely important areas of investigation in which epigenetic modification have been demonstrated to play critical roles. Other pathological states known or suspected to have an epigenetic basis include autoimmune disorders, cardiovascular disease, obesity, and diabetes. Whereas these conditions have excited much interest within the scientific community, there are many unanswered questions regarding the precise mechanisms by which epigenetic changes are reflected in a range of different pathological states. For the purposes of this report, we will focus solely on the oncologic applications of the study of epigenetics.

Leading Companies Active in Epigenomics

There are a number of large and small companies that are pursuing epigenetic models of drug development. Those which have especially excited our interest and will be covered in this document are the following:

1. Acetylon Pharmaceuticals
2. Astex Pharmaceuticals
3. Chroma Therapeutics
4. Constellation Pharmaceuticals Ltd.
5. Epizyme
6. Merck
7. MethylGene Inc
8. Novartis AG
9. RaNA Therapeutics
10. Syndax
11. Tensha Therapeutics

Outlook for epigenetics R&D

Epigenetics today finds itself at a turning point, with many unanswered questions and a proliferation of opportunities for products based on the constant flow of new research findings. These discoveries are revolutionizing our vision of what constitutes the genetic regulatory systems that govern the phenotypes of living system.

In our view, the companies profiled are the current leaders in the understanding of the biology and have the highest odds of bringing novel epigenetic-based therapies to market.

However, we recognize that this is an ongoing and rapidly changing enterprise and that years may be required for a full understanding of the genome, epigenome, and the role of environmental influences in their complex interactions. Since so much of the phenotypic expression is governed by epigenomic forces, we anticipate that a massive research effort will be required in order to develop pharmaceutical agents of precise specificity, without unacceptable side effects.

The field is moving forward at a rapid pace, and the next few years should see startling advances and tremendous investment opportunities, in our opinion.

Introduction

Epigenetics constitutes a challenge to the long-held paradigm of DNA base pair sequences as the prime determinant of the phenotype. Epigenetic mechanisms are now recognized to play a highly significant role in gene regulation and expression, and a new vision, based on a dynamic interaction between the genome and the epigenome, is emerging. The new discoveries promise a wealth of investment opportunities for diagnostic and therapeutic products in the pharma industry, as well as other areas. This report will describe the leading companies now pursuing epigenetic-based technologies.

Epigenetics is defined as the investigation of the control of the organism's phenotype (physical characteristics) by mechanisms not coded in the DNA. The predominant model of genetic information packaging has long been based on the concept of a linear code of base pairs (i.e., A, C, T, and G). This code is translated into RNA and then into protein; these segments constitute the structural genes. It was assumed that the regulation of these structural elements was governed by controller genes that turned groups of structural genes on and off. While this model has been confirmed in some limited cases in higher organisms, epigenetic control appears to be a much more significant regulatory system. It is recognized that about half the structural genes are regulated by epigenetic signals.

The concept of epigenetics is not new, dating back to the 1940s. But its understanding at the molecular level is quite recent. The sequencing of the human genome and related investigations has revealed that about half of the structural genes in higher organisms are preceded by "CpG islands." These are repeats of the bases cytosine-guanine, and they can be modified by chemical reactions that affect the ability to control the structural genes to which they are adjacent. When methyl group are added to the cytosines, the ability of the structural genes to produce protein is blocked. Methylation can involve either the addition (hypermethylation) or the removal (hypomethylation) of methyl groups. In either case, the normal flow and processing of genetic information may be interrupted. This is the best understood of the epigenetic regulatory mechanisms. The hypomethylating agent (HMA) class of drugs (Dacogen and Vidaza) are approved by the FDA for cancer treatment and are based on the concept of blocking the methylation reaction.

Whereas methylation studies are the most advanced, there are other important mechanisms, not as well understood, by which genes are regulated epigenetically.

Histones are proteins that complex with DNA and respond to epigenetic signaling. Although DNA is usually portrayed as a linear tape, in fact it is actually packaged into a complex three dimensional structure known as chromatin. Although the foundation of chromatin lies in DNA as the carrier of information, it is highly regulated through a network of molecular pathways, concerned with every fundamental activity within the cell, including DNA replication, transcription, cell growth and differentiation, and a host of other functions.

A major component of epigenetic control is through histone complexes, known as nucleosomes. Histones can be modified through various chemical reactions, the most significant being acetylation, deacetylation, methylation, demethylation, phosphorylation, sumoylation, and ubiquination. Various permutations and combinations of these alterations may act as regulatory signals.

Because of its significance in cellular regulatory control, it has long been suggested that processes related to malignancy would be influenced by changes in chromatin architecture. The main part of the DNA sequence remains silenced in a compact chromatin form which makes transcription difficult or impossible. Only a small part of the DNA is used for gene expression in each tissue type. The structure of the chromatin is dictated by epigenetic modifications, including DNA methylation, histone post translational modifications, chromatin remodeling, and non-coding RNAs. Methylation and histone post translational modifications are critical events that play key roles in mammalian development and lineage specification.

This process of chromatin remodeling is now recognized as a key epigenetic mechanism for regulating gene expression. The posttranslational modification of histones is driven by distinct families of enzymes. These include histone deacetylases, protein methyltransferases, and lysine demethylases, whose role is to add or remove functional groups at a variety of residues on histone tails. The resulting "marks" are then recognized by the "reader" proteins that interpret the information and assemble it into complexes that facilitate chromatin remodeling. The reader proteins are able to recruit the factors that initiate mRNA transcription and drive mRNA elongation.

Non-coding RNAs are another group of control elements that are being recognized as having an important role in epigenetic regulation. Although tRNA and ribosomal RNA are long known as important non-coding RNAs, many new classes have recently been discovered and investigated. The most recently identified class is the abundant and versatile long ncRNAs (lncRNAs). These are at least 200 nucleotides in length, although they can be much longer. They exert regulatory signals on adjacent genetic loci. Triggered by epigenetic signals, they can control genomic expression by recruiting transcriptional factors and chromatin modifying complexes.

Another type, the micro RNAs, regulate gene expression by targeting and repressing other RNA classes. A major research effort is aimed at understanding the evolution, cellular expression, and functions of the ncRNAs and their roles in differentiated tissues including the central nervous system and other organs.

Summary of Current State of Epigenetics Basic Science

It is a tautological statement that complex human characteristics, such as disease susceptibility, have a complex basis. With the sequencing of the human genome, a wealth of data became available that allowed not only the linking of different genes, but also their relationships to epigenetic control elements. Using genome wide association studies (GWAS) it is now possible to draw relationships between complex phenotypes and mutations in families of genes. Furthermore, it is possible to search for regulatory genes, many of which have an epigenetic basis.

The investigation of the molecular regulation of individual genes and of gene families is now revealing patterns of expression that are under epigenetic control. These epigenetic features are dynamic. RNA, histones, and transcription factors are constantly turning over, being activated and removed, the whole system responding to environmental inputs.

As these features are defined and elaborated, it is becoming more feasible to design molecules that either enhance or block epigenetic signals. Moreover, this approach serves as model for protocols aimed at development of epigenetically targeted drugs.

The magnitude of the task facing the research community should not be underestimated. Workers in the field constantly emphasize that epigenetics research is in its infancy. The genome contains roughly 30 million CpG sites, hundreds of millions of histone tails that are subject to post translational modification, and at least 2,000 different species of micro RNAs. This means that the complexity of these regulatory systems is immense and unraveling it will require decades. It also means that any epigenetically based drug development will have to focus on specificity in order to reduce the chances of side effects, and prevent interaction with normal, essential systems of regulation.

One promising specific targeting strategy is based on the use of small molecule inhibitors of the BET family bromodomains. These are epigenetic reader proteins that recognize acetylated lysine residues such as those on the N-terminal tails of histones. This recognition allows chromatin remodeling to proceed. Focusing on these regions of the epigenome could be a much more selective approach to obviating the epigenetic dysregulation of specific genes. The favored inhibitors are oligonucleotides, although many companies are working on small molecule inhibitors of BET bromodomains. The intriguing aspect of modulation of BET bromodomains is the potential to influence the oncogene, MYC, which up until now has eluded the industry's ability to target this commonly mutated gene.

Prominent Companies Involved in Epigenetics-Based Product Development

Drug development is on the cusp of a revolution, as the epigenome becomes better understood and as possibilities for new innovative epigenetic drugs become feasible. Many of these advances will come from the biotech rather than the pharma sector, in our view. The biotechs are better attuned to rapid changes in the R&D landscape, and as recent studies demonstrate, their track record in the last few years is far superior to the big pharma companies.

Below we profile some of the most noteworthy companies that focus on epigenetics.

Acetylon Pharmaceuticals

Acetylon is developing selective deacetylase (HDAC) enzyme inhibitors, which may be administered orally, providing enhanced effectiveness and safety compared with currently available alternatives. Acetylon's proprietary "Iterative Biasing Chemistry" drug development platform technology has been adopted to provide the appropriate methodology for discerning small molecule drug structure-activity relationships for selective HDAC inhibition. Acetylon's small molecule drug candidates are designed to inhibit specific enzymes of the HDAC family while producing fewer adverse side effects.

Selective inhibition of HDAC6 may reduce or eliminate the often-severe side effects associated with non-selective HDAC inhibition and may enable the development of optimized treatment regimens, including maximally effective combination drug therapies. The company's first clinical candidate, the selective HDAC6 inhibitor ACY-1215, is targeted for the treatment of hematologic and solid tumor cancer, specifically multiple myeloma patients with relapsed and relapsed-refractory disease.

On December 12, 2012 the company presented preliminary results from a Phase I/II study of ACY-1215 in combination with bortezomib (Velcade®, Takeda Millennium Pharmaceuticals) and dexamethasone. The combination may provide a treatment option for relapsed or relapsed/refractory MM. The company asserts that selective HDAC6 inhibition through ACY-1215 may act favorably on both tumors and bone-forming cells to benefit patients with this condition.

Acetylon also is moving forward with additional patent applications embracing compounds similar to ACY-1215 as well as other molecules. Their HDAC6 inhibitor program is focused on enhancing drug potency and reducing side effects common to HDAC inhibition through selective targeting of the HDAC6 enzyme. Inhibition of HDAC6 versus other isoforms preserves normal gene expression in cells, minimizing patient toxicity.

The rationale for this approach is based on the observation that metabolically active cancers and autoimmune cells produce large amounts of misfolded proteins, and inhibiting HDAC6 increases the generation and accumulation of protein “trash,” triggering self-destruction of diseased cells and leading to regression of disease.

Preliminary results from the first clinical evaluation of ACY-1215 suggest that selective inhibition of HDAC6 with ACY-1215 is well tolerated as a monotherapy at exposures that demonstrate increased acetylation of tubulin, a biomarker of HDAC6 inhibition, versus acetylation of histones, a Class I HDAC inhibitory effect. Continued dose escalation in combination with bortezomib is ongoing.

Bone lesions are a common occurrence in multiple myeloma and are a result of two compounding factors: an increase in myeloma cells inhibits osteoblasts and increases osteoclasts, leading to the metabolic breakdown of bone tissue. Osteoclasts normally act to clear old or decaying bone, but without osteoblasts to rebuild the lost bone, patients are left with bone lesions that can cause severe pain and increased risk of fracture. ACY-1215 was evaluated for its effects on MM bone disease. In both in vitro and in vivo results, ACY-1215 alone, or in combination with bortezomib, decreased markers of bone resorption and increased markers of bone formation (e.g., osteocalcin).

A separate study tested HDAC6 effects on MM cell growth supported by bone marrow stromal cells from either normal or HDAC6 gene knockout mice. BMSC isolated from HDAC6 knockout mice showed a significant increase in osteocalcin and a reduction in MM cell proliferation, versus BMSC with the HDAC6 gene. Together, these data indicate a potential beneficial role of HDAC6 inhibition in MM bone disease.

Current trials include: A Phase I/II, Open-Label, Multi-center Study of ACY-1215 Administered Orally as Monotherapy and in Combination with Bortezomib and Dexamethasone for the Treatment of Relapsed or Relapsed/Refractory Multiple Myeloma.

Phase Ia and Ib: To evaluate the side effects and determine the best dose or oral ACY-1215 as monotherapy, and also in combination with bortezomib and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma.

Phase IIa: To determine the objective response rate of oral ACY-1215 in combination with bortezomib and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma.

Astex Pharmaceuticals (ASTX, MO, $8 price target)

Astex Pharmaceuticals is vigorously pursuing epigenetic-based drug development, basing its technology on the investigation and development of small molecule therapeutics targeted against various cancers. Its main platform is the fragment-based drug discovery tool, Pyramid. The company boasts a pipeline of molecularly-targeted drugs for large pharmaceutical partners and an internal development strategy that runs the gamut of clinical, pre-clinical and early discovery.

Its leading product and source of revenue is DACOGEN® (decitabine), approved for the treatment of AML and MDS. Astex received $70M in royalties on its global sales in 2012, but this number is expected to fall to $55M in 2013 due to loss of U.S. orphan drug exclusivity in May of this year. SGI-110, Astex's next generation hypomethylating agent (HMA), is a differentiated pharmacology play in the HMA space and is expected to enter pivotal trial evaluation by year-end 2013.

Epigenetic regulation through the inhibition of DNA methylation is believed to be a central component to the clinical activity exhibited by hypomethylating agents like Dacogen and SGI-110. Methyl groups at the 5' position of C-phosphate-G dinucleotides (CpG islands) are common at gene promoter sequences and play a key role in the hierarchical regulation of gene expression. Methylated CpG promoter regions recruit methyl-DNA binding proteins and histone deacetylase complexes to promote chromatin condensation and silencing of gene expression. Aberrant DNA methylation has been detected in several cancer types, and groups of genes that are epigenetically silenced by this process are known to include tumor suppressors and cell-cycle regulatory genes (e.g., *Rb, VHL, APC, CDH1, CDKN2A,* and *CDKN2B*) that would normally function to attenuate hyperproliferative cell signaling.

DNA methylation in humans is carried out by any of three DNA methyltransferases (DNMTs; DNMT1, DNMT3a, and DMNT3b), which catalyze the transfer of a donor methyl group from S-adenosyl methionine (SAM) to the cytosine-5' position within a CpG island. Nucleoside analogs like 5-azacytidine (Vidaza) and 5-aza-2'-deoxycytidine (Dacogen and SGI-110), after being converted to 5-azacytidine triphosphate and integrated into newly synthesized DNA, prevent DNMT-mediated methylation due to the substitution of carbon for a nitrogen atom at the 5'-position in the pyrimidine ring. These nucleoside analogs also form stable covalent complexes with DNMTs and thus deplete the chromatin of DNMTs and DNA methylation. Several studies describe a dose dependent correlation of DNA hypomethylation by azanucleosides with a re-induction of tumor suppressor gene expression and anti-leukemic activity.

Unlike the mono-nucleoside analogs Dacogen and Vidaza, SGI-110 is a dinucleotide, comprising 5-aza-2-deoxycytidine (decitabine) linked to a deoxyguanosine molecule. In this form, the decitabine moiety is largely protected from deamination in vivo, which translates into greater stability while also making the drug amenable to subcutaneous delivery. Pre-clinical studies using xenograft animal models show SGI-110 to be as effective as decitabine at inhibiting DNA methylation, inducing tumor suppressor expression (*CDKN2A*) and slowing tumor growth.

Initial clinical data with SGI-110 show drug to be more stable than decitabine with an approximately four-fold, longer half-life. Recent updates from a continuing Phase I/II study of SGI-110 in relapse/refractory MDS and AML detailed six of 15 patients achieving clinical responses (four with hematologic improvement (HI) and two with marrow CR (mCR)), equating to an overall response rate of 40%, and a median duration of response of 92 days, ranging from 28-126 days. Of note, clinical responses were observed in patients that had received prior HMA therapy (Dacogen and/or Vidaza), implying superior efficacy to these earlier agents which have thus far failed to elicit responses in a post-HMA treatment setting.

The Phase II expansion portion of the trial, initiated in June 2012, is currently underway and is slated to enroll approximately 150 patients with intermediate or high-risk MDS, or AML. Patients are being randomized to one of three dosing arms (a BED of 60mg/m^2 daily for five days of a 28-day cycle, an MTD of 90mg/m^2 daily for five days of a 28-day cycle, and a third arm of 60mg/m^2 for ten days daily of a 28-day cycle) to allow for more comprehensive evaluation of SGI-110's safety/efficacy profile leading into a pivotal study. Phase II results from the AML expansion cohort are anticipated by yearend 2013.

Chroma Therapeutics

Chroma was founded in 2001 with a focus on development of next-generation HDAC inhibitors for cancer, undisclosed chromatin targets for cancer and other HDAC inhibitors for inflammation. The privately-held biotechnology company is evaluating small molecule drugs for the treatment of high-prevalence cancers and inflammatory disorders.

The company conducted a phase I study of CHR-2797 (tosedostat), an orally active aminopeptidase inhibitor in refractory myeloma patients. It functions by depriving the tumor cells of amino acids needed for tumor protein synthesis. This compound is the first synthetic aminopeptidase inhibitor to demonstrate promising activity in adult acute myelogenous leukemia. CHR-2797 has demonstrated encouraging clinical activity, in particular in elderly/refractory AML patients.

Lancet Oncology recently published results from the OPAL Phase 2 study of tosedostat in elderly patients. This trial was jointly conducted by Cell Therapeutics (CTIC, NR) and Chroma, treating relapsed or refractory acute myeloid leukemia (AML). Tosedostat resulted in a disease control rate of 51%. Subset analyses suggested the greatest benefit occurred in the difficult-to-treat patients with prior myelodysplastic syndrome (MDS) or those that had received prior hypomethylating therapy (HMA). Adverse events were manageable. The company states that additional studies of tosedostat including combination with hypomethylating agents and low-dose cytarabine in patients with high-risk myelodysplastic syndromes and AML are in the works.

Tosedostat is a metalloenzyme-inhibitor, and initially demonstrated marked in vitro cytotoxicity in AML samples and strong synergy with Cytarabine (Ara-C) in primary acute myeloid leukemia (AML) cells. Ara-C is also referred to as cytosine arabinoside because it consists of a cytosine base and an arabinose sugar. It is considerably less cytotoxicity to the normal marrow progenitor population. Molecular studies of its mechanism of action revealed that CHR-2797 inhibited the intrinsic nuclear, cytoplasmic and cell surface aminopeptidase function of AML blasts in a dose-dependent manner.

More recently, Chroma announced that GSK approved the progression of Chroma's macrophage-targeted HDAC inhibitor, CHR-5154, towards human clinical trials subject to regulatory approval, triggering an undisclosed milestone payment from GSK.

The company announced in January 2013 that its collaboration with GSK has been extended to enable their Epinova Discovery Performance Unit to apply Chroma's ESM technology to a novel GSK epigenetic target. Chroma will receive an upfront cash payment and is eligible to receive milestones and royalties based on compounds arising from this element of the collaboration.

Constellation Pharmaceuticals, Ltd.

This epigenetically-focused biotech pursues small molecule therapeutics for the treatment of cancer and inflammatory, immunological, and various other disorders. Constellation's product discovery engine targets both the enzymes that modify the dynamic structure of chromatin (writers and erasers) and other proteins that interact with chromatin (readers) to control gene expression. The company's goal is the restoration of normal gene expression through chromatin modulation by highly selective and specific inhibitors promises to be a powerful avenue for the development of important new medicines against a broad range of diseases.

It is widely recognized that drug development in this field is directed towards the identification of small molecules that inhibit the activities of proteins (epigenetic regulators) that add, remove or recognize various chemical modifications (or marks) on specific DNA sites or chromosomal proteins. These marks play a key role in determining whether a gene is on or off. As previously explained, epigenetic regulators are often referred to as writers (histone methyltransferases which add modifications catalysing the addition of methyl marks to histone proteins). A second category is erasers (histone demethylases that reverse histone methylation by removing modifications). Yet a third group is readers (proteins that bind to specific recognition domains, typically methyl or acetyl marks, on chromatin).

The company's research into chromatin readers demonstrated that MYC transcription can be suppressed using small molecule inhibitors of the BET family of chromatin inhibitors. Members of the BET family, including BRD2, BRD3, BRD4, and BRDT modulate gene expression by recruiting transcriptional regulators to specific genomic locations. MYC is a master regulator of diverse cellular functions and has long been considered a compelling therapeutic target because of its role in many human malignancies. Constellation scientists showed rapid, potent, and dose-dependent suppression of MYC gene expression using inhibitors of BET bromodomains. By inhibiting the transcription of selected genes involved in growth control, proliferation is blocked, followed by the death of targeted cancer cells.

During 2012, Constellation entered into an agreement with Genentech, a member of the Roche Group (RHHBY, NC). Under the terms of the arrangement, Constellation receives committed funding of $95 million, comprising an upfront payment and research funding for a three-year collaboration period. Constellation will be eligible for substantial development and commercialization milestone payments as well as up to double-digit royalties on commercial sales of multiple products by Genentech. Additionally, Constellation will retain exclusive development and commercialization rights to selected programs emerging from the collaboration, for which payments would be due to Genentech upon the successful commercialization of such products.

The parties will establish a research collaboration addressing multiple epigenetic target classes. Constellation will retain independent strategic direction, operational management and exclusive rights to programs outside of the collaboration scope, including its two most advanced programs that are focused on the development of inhibitors of the BET chromatin reader and EZH2 chromatin writer proteins. Genentech has a future option to acquire all outstanding shares of Constellation based on pre-negotiated terms, which include a significant initial acquisition payment plus contingent value rights payments based on the future successful development and commercialization of multiple products by Genentech. Genentech's option to acquire Constellation includes the BET and EZH2 programs, as well as other programs outside the collaboration scope.

Constellation scientists have demonstrated that transcription of the MYC oncogene can be suppressed using small molecule inhibitors of the BET family of chromatin adapters. MYC is a master regulator of diverse cellular functions and has long been considered a compelling therapeutic target because of its role in many human malignancies including hematologic and solid tumors. Also, continued research by Constellation on chromatin-modifying enzymes has resulted in significant progress towards developing small molecule inhibitors of the histone lysine methyltransferase EZH2. This enzyme functions as part of a chromatin-associated protein complex implicated in the repression of gene expression. Recent cancer genomic sequencing studies have identified recurrent mutations in the EZH2 encoding genomic locus in a subset of human cancers. In addition, numerous epidemiological data sets linking increased EZH2 expression to late stage disease with poor prognosis suggest a prominent role for EZH2 in human malignancies.

Epizyme, Inc.

The company boasts a vigorous R&D program covering small molecule histone methyltransferase inhibitors, aimed at developing personalized therapeutics for the treatment of patients with epigenetically-defined cancers. These molecules are a class of epigenetically-targeted enzymes, believed to be associated with various diseases. The company recognizes personalized therapeutics as a basis for profiling cancer patients, in order to achieve more effective therapy. The two most advanced programs focus on the widely investigated histone methyltransferases, DOT1L and EZH2. The deregulated expression of the latter gene has been linked to soft tissue sarcomas, making it a likely candidate for therapy epigenetic inhibitors.

The company is looked upon as one of the leaders in the field. It was founded in 2007 by Dr. Robert Horvitz, a Nobel Prize winning member of the MIT faculty and Dr. Yi Zhang of The University of North Carolina. They are building a product pipeline of small molecule inhibitors directed to specific enzymes within the 96-member HMT target class. The management team has 58 INDs and seven marketed products in its pipeline, and claims to have raised $54M in two rounds from venture capital firms including Kleiner Perkins Caulfield and Byers, MPM Capital, Bay City Capital, NEA, Astellas Venture Management, and Amgen Ventures. The company has also raised $45M from partnerships with GSK, Eisai, the Multiple Myeloma Research Foundation, and the Leukemia and Lymphoma Society. To date, Epizyme has entered into therapeutic collaborations with Celgene, Eisai and GSK that have provided it with approximately $120 million in non-equity funding through December 31, 2012.

Epizyme recently announced the achievement of pre-clinical milestones in its alliance with GlaxoSmithKline (GSK), triggering $4M in milestone payments. Epizyme and GSK entered a worldwide strategic alliance in January 2011 to discover, develop, and market novel small molecule therapeutics targeting histone methyltransferases.

The GSK alliance leverages Epizyme's discovery platform, including its proprietary biology, biochemistry, chemical library, expertise, and intellectual property, to discover and develop HMT therapeutics against the set of targets included in the collaboration. Under the terms of the agreement, Epizyme received an upfront payment of $20M and will also receive research funding. Epizyme is eligible to receive more than $630M in total milestone payments if pharmaceuticals are commercialized for all targets in the collaboration. Additionally, Epizyme is eligible to receive up to double-digit royalties on net sales of products resulting from the alliance. For each target in the collaboration, Epizyme will be primarily responsible for research up to development candidate selection, and GSK will be solely responsible for development and commercialization.

The HMT class of epigenetic enzymes contains 96 members, many of which have strong genetic associations with cancer and other serious diseases. Targeting histone methyl transferases with small molecule inhibitors offers an alternative therapeutic approach to controlling pathways of disease-causing gene expression.

An interesting facet of Epizyme's technology is its potential to influence several cancer-related genes with a single small molecule, including genes that have evaded previous drug regimens.

Epizyme's pact with Eisai brought $6 million at the front end. Eisai also agreed to fund all R&D costs for drugs involved in the deal through human proof-of-concept studies. That partnership focuses on molecules against the EZH2 enzyme, which play a role in certain forms of lymphoma and other cancers. It is known that the EZH2 protein activates growth promoting genes in advanced prostate cancer, which may represent another possible opportunity for therapeutic intervention.

A Phase I trial for Epizyme's DOT1L inhibitor EPZ-5676 was initiated in September 2012. According to the company's website, EPZ-5676 is the first HMT inhibitor (HMTi) to enter human clinical development. The trial involved MLL-r, a group of acute leukemias.

In April 2013, Epizyme signed an agreement with Abbott to develop a molecular companion diagnostic test for use with EPZ-5676. Using its proprietary fluorescence in situ hybridization (FISH) technology Abbott will design a test to detect MLL genetic alterations that lead to the oncogenic function of DOT1L. Epizyme will use Abbott's FISH-based test to help identify eligible patients for its DOT1L inhibitor.

MLL-r is an aggressive subtype of two of the most common forms of acute leukemia, acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), caused by a chromosomal translocation involving the MLL gene. The five-year overall survival rate for adult patients with the MLL-r subtype of AML is extremely low, ranging from approximately 5 to 24 percent. MLL-r occurs in both an adult population and an infant/pediatric population. At this time, there are no approved therapies specifically indicated for MLL-r.

Merck

Merck & Co., Inc. is a global health care giant that manufactures prescription medicines, vaccines, biologic therapies, animal health, and consumer care products, marketed directly and through its joint ventures.

Merck markets the anti-cancer therapeutic, Zolinza for the treatment of patients with advanced cutaneous T-cell lymphoma who manifest progressive, persistent, or recurrent disease subsequent to prior systemic therapies. Zolinza was the first drug in its class to reach the market in 2006. It is a member of a class of compounds that inhibit histone deacetylases, and manifests a broad spectrum of epigenetic activities. CTCL is a rare disease, making Zolinza a minor drug for Merck.

The drug has shown promise in a Phase III trial involving multiple myeloma patients, potentially opening up a lucrative new market for the drug. However, Phase III trials of the drug in mesothelioma were unsuccessful, although Merck is still carrying out other studies in this indication.

In addition to the improvement in progression-free survival, Zolinza achieved a significant improvement in overall response and there was a trend towards improved overall survival. Zolinza is also in clinical trials for a range of cancers including brain, oropharyngeal, ovarian, liver, prostate and lung cancers, non-Hodgkin's lymphoma, acute myeloid leukemia, and acute lymphoblastic leukemia.

MethylGene Inc (MYG, Bayko, MO, $1 price target)

MethylGene is a Canadian-based biopharmaceutical company pursuing epigenetically targeted drugs for both cancer and infectious diseases. The current focus is on lead molecule MGCD265 for cancer.

MGCD265. As it is known that aberrant chromatin acetylation and deacetylation are involved in the pathogenesis of cancer, compounds that inhibit HDAC activity may behave as anticancer agents. The anticancer activity of HDAC inhibitors is thought to occur through a decrease in transcriptional repression, resulting in inhibition of proliferation, induction of apoptosis, and/or terminal cell differentiation.

MGCD265 is an orally administered cancer therapeutic that inhibits the Met and VEGF receptor tyrosine kinases. The abnormal activation of Met is involved in tumor development, metastasis, and survival and the VEGF kinase is responsible for the inappropriate formation of blood vessels (angiogenesis) that nourish the tumor. In pre-clinical studies, MGCD265 demonstrated nanomolar potency in enzyme and cellular assays and up to 100% of tumor growth inhibition in a broad range of xenograft models.

In the ongoing Phase 1 program, MGCD265 is being administered orally to patients with advanced cancers. The compound has demonstrated a favorable safety profile and can be combined safely with other cancer therapeutics such as docetaxel (Taxotere®) and erlotinib (Tarceva®). These therapeutics were selected for combination studies based on preclinical data that demonstrated the combination of MGCD265 and erlotinib and of MGCD265 and docetaxel showed greater anti-tumor activity compared to each drug administered alone.

RTKs are key kinases involved in cancer, angiogenesis (a process whereby new blood vessels are formed to nourish the tumors), tumor cell metastasis, tumor development, and survival. Met expression is elevated and associated with tumorigenesis in several solid tumor indications including non-small cell lung cancer (NSCLC), gastric, prostate, colorectal, bladder, breast, renal, hepatocellular, and ovarian cancers. Phase I/II studies of single agent MGCD265 and combinations with erlotinib or docetaxel are currently underway. More than 200 patients have been treated to date in clinical studies of both single-agent and combination therapy with docetaxel or erlotinib.

In the ongoing Phase I program, MGCD265 is being administered orally in patients with advanced cancers. The compound has demonstrated a favorable safety profile and can be combined safely with other cancer therapeutics such as docetaxel (Taxotere®) and erlotinib (Tarceva®). These therapeutics were selected for combination studies based on preclinical data that demonstrated the combination of MGCD265 and erlotinib and of MGCD265 and docetaxel showed greater anti-tumor activity compared to each drug administered alone.

Novartis AG

Panobinostat (LBH589) is one of the company's lead epigenetic products. This orally available Pan-DAC inhibitor crosses the blood-brain barrier, enabling it to target epigenetic and multiple oncogenic pathways. In vitro studies have shown multiple effects, including decreased oncoprotein expression (e.g., Bcr-Abl, HER-2), decreased angiogenesis, induction of apoptosis, induction of cell-cycle arrest, and decreased tumor cell motility and invasion.

Phase Ib/II studies of panobinostat monotherapy and in combination with chemotherapy and/or targeted therapy are ongoing in relapsed/refractory Hodgkin's lymphoma (HL), MM, AML/MDS, and other hematological malignancies. Phase III trials have started global enrollment in relapsed MM (PANORAMA-1) and post–transplant HL maintenance (PATH).

LBH589 (panobinostat) is an orally available HDAC inhibitor that crosses the blood–brain barrier and is currently in phase III clinical trials for several types of cancer. It restores cholesterol homeostasis in cultured NPC1 mutant fibroblasts to almost normal levels within 72 h when used at 40 nM.

RaNA Therapeutics

The company was founded by Dr. Jeannie T. Lee, based on technology developed in her laboratory at Harvard. Lee's investigations demonstrated a large number of long non-coding RNA regions that interact with the regulatory complex PRC2. Additional studies demonstrated that it is possible to activate single gene expression by specifically blocking this interaction.

The non-coding RNAs (lncRNAs) do not encode proteins but rather are committed to performing a variety of important regulatory functions. These include regulation of gene expression, cell differentiation, and development through acting on mRNA transcription.

The lncRNAs are subject to epigenetic deregulation. It is known that that DNA methylation modulates the expression of tumor suppressor miRNAs miR-124 and miR-137 in anaplastic astrocytoma and glioblastoma125. The lncRNAs are also subject to epigenetic regulation by histone and chromatin modification, and some investigators have suggested that disease-linked abnormalities in ncRNA activity are associated with deregulation of these processes. Perturbations in factors responsible for modulating ncRNA metabolism and function can also lead to pathology.

The RaNA discovery program seeks to modulate disease-associated long non-coding RNA (lncRNA), thereby restoring normal expression of individual targeted genes. The technology platform is based on thousands of gene-associated lncRNA's that contain binding regions for epigenetic regulatory proteins such as PRC2. Lead products are designed to specifically block the binding of the transcriptional repressor complex PRC2 to individual lncRNA regions, thus inducing the expression of the associated target gene. The ultimate epigenetic target of the lncRNA product candidate is EZH2.

These lncRNAs far outnumber the ~20,000 protein-coding genes, and thus represent an enormous increase in the "target space" available for drug development. It is the regulatory mechanisms, modulated by ncRNA, that RaNA leverages to discover and develop new therapeutic drugs.

RaNA's technology platform is built upon a proprietary database of tens of thousands of gene-associated lncRNA's and other ncRNAs and the sequences through which they interact with the Polycomb Repressive Complex 2 (PRC2). This family of proteins was first discovered in Drosophila, where it was determined that their function is to remodel chromatin in order that epigenetic silencing may occur.

PRC2 normally represses gene expression at thousands of sites across the genome. During its transcription, an lncRNA that contains one of these PRC2-recognizing sequences is "tethered" to the chromosome at one end through RNA polymerase II. Because of this "tethering" to a specific chromosomal locus, the binding of the lncRNA to PRC2 usually only represses an individual neighboring mRNA. Since each PRC2-associated lncRNA intersects with PRC2 through distinct sequences, RaNA scientists are able to efficiently design and develop synthetic oligonucleotide antagonists that specifically block the binding of PRC2 to an individual lncRNA region, thus de-repressing the expression of a single mRNA in order to produce increased amounts of the specific protein, and thereby achieve a therapeutic outcome.

Data indicate that RaNA's oligonucleotides show excellent bioavailability after subcutaneous injection in saline solution and have tissue half-lives of three weeks. The company has demonstrated selective upregulation of EPO mRNA and protein both in vitro and in vivo, and has data showing epigenetic histone modifications consistent with the proposed mechanism of action and a lack of effect on the expression of unrelated genes.

miRNAs, for example, are another class of short non-coding RNAs that have recently been shown to regulate the expression of large sets of genes in a coordinated fashion. Humans and other vertebrates make several thousand miRNAs divided into a large number of families, each of which can regulate the expression of hundreds or even thousands of different mRNAs in complex ways that are only partially understood. The effect of an miRNA on each of these genes individually is usually very modest, often no more than a 20-30% change in the level of expression, but in combination, these changes can dramatically influence the overall cellular biology.

The company's platform is based on genome-wide database of the interaction regions between PRC2 and lncRNAs (and other PRC2-associated RNAs) which permits the design of specific oligonucleotides that will selectively block the recruitment of PRC2 to individual lncRNA. In many cases destroying the lncRNA can also increase the expression of a neighboring gene, but RaNA scientists have discovered that the optimal effects are usually achieved by steric-blocking oligonucleotide designs.

Syndax

Based in Waltham, MA, the company pursues epigenetic-based cancer therapies. It was founded in 2005 on concepts developed by Dr. Ronald Evans of the Salk Institute. The long-term goal is to build epigenetic strategies to overcome the problem of resistant or refractory disease states. Acquired resistance to cancer therapeutics is a long-standing problem in cancer treatment and is responsible for the failure of many treatment protocols.

Its important intellectual property is the patent rights to entinostat, an oral, selective histone deacetylase (HDAC) inhibitor.

Syndax is using a combination approach with entinostat to epigenetically modulate the development of drug tolerance to cancer drugs. Two such drugs include endocrine agents that block the production of estrogen. Estrogenic hormones are known to drive tumor growth in estrogen receptor positive breast cancers. Another class of agents is the tyrosine kinase inhibitors. Erlotinib (trade name Tarceva) is a reversible tyrosine kinase inhibitor, used to treat lung and pancreatic cancer. It acts on the epidermal growth factor receptor, which competes with growth factors that stimulates tumor proliferation in non-small cell lung cancer.

In both cases epigenetic changes in these tumor types can be reversed by entinostat. This compound showed clinical activity in Phase I and demonstrated promise in combination with other approved cancer therapies - a well-established development strategy in the oncology world. Entinostat's pharmacokinetic properties, convenient oral dosing and HDAC selectivity are all positive qualities. It has been the subject of Phase II trials, in combination with conventional targeted therapies.

Last year, a randomized phase II trial of erlotinib with and without entinostat in patients with advanced non-small-cell lung cancer who progressed on prior chemotherapy was reported. Erlotinib combined with entinostat did not improve the outcomes of patients in the overall study population when compared with erlotinib monotherapy. There are a number of clinical trials currently underway including a phase II study conducted by the NCI combining Entinostat with azacytidine.

Tensha Therapeutics

This small virtual company is engaged in the development of low molecular weight bromodomain inhibitors directed toward cancer treatment and other disorders. The company's scientific founder, Dr. James Bradner, MD, an investigator at the Dana-Farber Cancer Institute, is one of the most prolific researchers of small molecule inhibitors of BET bromodomain proteins that are important for cancer cell growth. Tensha has an exclusive license to the technology from Dana-Farber. Tensha uses an "open source" approach to the licensing of the probe compound, JQ-1.

In pioneering studies, as discussed in the introduction, the BET family of bromodomains are epigenetic reader proteins that recognize acetylated lysine residues such as those on the N-terminal tails of histones. This recognition allows chromatin remodeling to proceed. Focusing on these regions of the epigenome could be a much more selective approach to obviating the epigenetic dysregulation of specific genes. The company's lead program is directed toward patients with BRD4-NUT midline carcinoma, myelomas, and related diseases.

In September 2011, the company achieved $15M in financing to advance its program from HealthCare Ventures, a life science venture capital firm investing in preclinical and early clinical stage, "Focused Companies." The company has not reported significant activities since that time.

Bradner and his colleagues continue to publish on the bromodomain family. They recently demonstrated that epigenetic reader, BRD4, is a promising target in the treatment of acute myelogenous leukemia. Inhibition of BRD4 using BRD4-specific RNAi or JQ1, a BET bromodomain inhibitor that blocks BRD4-binding to acetylated histones, showed profound antileukemic effects in AML mouse models as well as in various human AML cell lines and in primary leukemic cells obtained from

AML patients. Their studies show that a small molecule inhibitor, JQ1, leads to growth inhibition and apoptosis in human AML stem and progenitor cells. The authors argue that inhibition of BRD4 is a promising strategy that should be pursued in clinical trials.

Bradner is also a cofounder of Syros Pharmaceuticals, a company that pursues a class of epigenetic regulators known as superenhancers. This class of keep normal cells functioning properly. In malignant cancer cells, super-enhancers upregulate cancerous gene production, leading to potentially fatal tumors.

Company Description

Epizyme (EPZM) is a biopharmaceutical company, based in Cambridge, Massachusetts, focused on the discovery, development, and commercialization of personalized therapeutics for epigenetically-defined cancers. The company's technology is focused on the development of small molecule drugs specifically targeted against the individual members of the 96-member histone methyltransferase (HMT) class of enzymes. To date, the company has entered into strategic collaborations with Celgene, Eisai, and GSK regarding specific products, as well as the underlying technology platform.

Investment Risks

Clinical. Drug development is an inherently risky business. As clinical trials always carry a risk of failure, Epizyme's assets (EPZ-5676, EPZ-6438, or future products), may fail to demonstrate clinically meaningful levels of efficacy in ongoing or future trials. Further, it is unclear whether resistance pathways may develop to the epigenetic mechanisms being targeted.

Regulatory. The ability of Epizyme or its partners to market its drugs is dependent upon those drugs obtaining approval from the U.S. FDA and foreign regulatory authorities. Failure to achieve approval or delays in the timeline to approval could lead to substantial decrease in the company's share price.

Competitive. Epigenetics is an increasingly competitive field and Epizyme will face competition both from companies focused in the space, as well as players targeting related mechanisms. As such, there is no assurance that Epizyme's product will be competitive or differentiated from other drugs.

Commercialization. Epizyme has stated its plans to retain U.S. commercial rights to its products and develop a commercial infrastructure to market those products. The company has limited commercial experience and infrastructure in place. As such, the company will face significant expenses developing or acquiring these resources.

Reimbursement. There is no guarantee that Epizyme, or its partners, will garner adequate reimbursement for its products. Failure to obtain adequate levels of reimbursement could negatively impact the company's share price.

Partners. Epizyme has formed development and commercial partnerships with Celgene, Eisai, and GSK. Epizyme is highly dependent upon these partnerships to provide non-dilutive sources of capital. Celgene and Eisai are critical to the development and commercialization of Epizyme's clinical stage assets. Changes to or terminations of these partnerships could affect Epizyme's shares negatively.

Financial. Post-IPO, we estimate that the company will end 2Q13 with approximately $160MM in cash and cash equivalents. While the company has guided that even excluding any milestones payments from Celgene, Eisai, or GSK (which we expect) it has adequate resources to fund the company into 2015, we wholly expect the company to revisit the capital markets to further fund clinical development of its assets, develop a commercial infrastructure in the U.S., and to identify other assets using its platform technology and expertise. We currently forecast that the company will conduct secondary offerings in 2014 and 2015 before reaching profitability in 2017. While we view this as common for similar stage biotechnology companies, the risk of dilution may create an overhang at times.

JMP FACTS AND DISCLOSURES

Analyst Certification:

The research analyst(s) who prepared this report does/do hereby certify that the views presented in this report are in accordance with my/our personal views on the securities and issuers discussed in this report. As mandated by SEC Regulation AC no part of my/our compensation was, is or will be directly or indirectly related to the specific views or recommendations expressed herein. This certification is made under the obligations set forth in SEC Regulation AC. Any other person or entity may not use it for any other purpose. This certification is made based on my/our analysis on the date of this report's publication. I/We assume no obligation to update this certification to reflect any facts,circumstances or events that may subsequently come to my/our attention. Signed Michael G. King and Carter L. Gould

JMP Securities Disclosure Definitions:

JMP Securities currently makes a market in the securities of Epizyme, Inc., ARIAD Pharmaceuticals, Inc., Astex Pharmaceuticals, Inc., Celgene Corporation, MethylGene Inc. and Pharmacyclics, Inc.

JMP Securities was manager or co-manager of a public offering for Epizyme, Inc. in the past 12 months.

JMP Securities Investment Opinion Definitions:

Market Outperform (MO): JMP Securities expects the stock price to outperform relevant market indices over the next 12 months.

Market Perform (MP): JMP Securities expects the stock price to perform in line with relevant market indices over the next 12 months.

Market Underperform (MU): JMP Securities expects the stock price to underperform relevant market indices over the next 12 months.

JMP Securities Research Ratings and Investment Banking Services: (as of June 24, 2013)

JMP Rating	Regulatory Equivalent	# Co's Under Coverage	*% of Total*	Regulatory Equivalent	# Co's Under Coverage	*% of Total*	# Co's Receiving IB Services in Past 12 Months	*% of Co's With This Rating*
MARKET OUTPERFORM	Buy	233	*60.99%*	Buy	233	*60.99%*	74	*31.76%*
MARKET PERFORM	Hold	143	*37.43%*	Hold	143	*37.43%*	20	*13.99%*
MARKET UNDERPERFORM	Sell	6	*1.57%*	Sell	6	*1.57%*	0	*0%*
TOTAL:		382	*100%*		382	*100%*	94	*24.61%*

Stock Price Chart of Rating and Target Price Changes:

Note: First annotation denotes initiation of coverage or 3 years, whichever is shorter. If no target price is listed, then the target price is N/A. In accordance with NASD Rule 2711, the chart(s) below reflect(s) price range and any changes to the rating or price target as of the end of the most recent calendar quarter. The action reflected in this note is not annotated in the stock price chart. Source: JMP Securities.

In order to obtain these (6 or more) stock price charts or additional applicable disclosures and information concerning JMP's recommendations of companies under coverage mentioned in this report, please contact JMP Securities at (877) 263-1333 or visit www.jmpsecurities.com

JMP Disclaimer:

JMP Securities LLC (the “Firm”) compensates research analysts, like other Firm employees, based on the Firm’s profitability, which includes revenues from the Firm’s institutional sales, trading, and investment banking departments as well as on the quality of the services and activities performed that are intended to benefit the Firm’s institutional clients. These data have been prepared by JMP Securities LLC for informational purposes only and are based on information available to the public from sources that we believe to be reliable, but we do not guarantee their accuracy or completeness. Any opinions and projections expressed herein reflect our judgment at this date and are subject to change without notice. These data are neither intended nor should be considered as an offer to sell or a solicitation or a basis for any contract for the purchase of any security or other financial product. JMP Securities LLC, its affiliates, JMP Group LLC, Harvest Capital Strategies LLC, and their respective partners, directors, officers, and associates may have a long or short position in, may act as a market maker for, or may purchase or sell a position in the securities mentioned herein. JMP Securities LLC or its affiliates may be performing, have performed, or seek to perform investment banking, advisory, or other services and may have acted as manager or co-manager for a public offering of securities for any company mentioned herein. The reader should assume that JMP Securities LLC will solicit business from the company covered in this report. Members of our Sales and Trading Department provide oral and/or written market opinions and trading strategies to our clients that reflect their personal opinions about stocks that are the subject of the firm's research reports. Our research analysts discuss trading strategies with clients and complete surveys from clients that sometimes reflect short-term expectations for the price of the securities that are the subject of research reports. Those trading strategies and survey responses are distinct from the analysts' fundamental rating for the stock, which is based upon the analysts' view compared to other stocks under coverage for the relevant time period. JMP Securities LLC is a member of BATS, FINRA, NASDAQ, and SIPC.

Jeffrey H. Spurr
Director of Research
(415) 835-3903

RESEARCH PROFESSIONALS

FINANCIAL SERVICES

Asset Managers
David Trone (212) 906-3525
Chris Ross, CFA (212) 906-3532

Commercial & Specialty Finance
Christopher York (415) 835-8965
Kevin Chen (404) 848-7774

Consumer Finance
David M. Scharf (415) 835-8942
Jeremy Frazer (312) 768-1796

Financial Processing & Outsourcing
David M. Scharf (415) 835-8942
Jeremy Frazer (312) 768-1796

Insurance
Matthew J. Carletti (312) 768-1784
Christine Worley (312) 768-1786

Investment Banks & Brokers
David Trone (212) 906-3525
Chris Ross, CFA (212) 906-3532

Mortgage Finance
Steven C. DeLaney (404) 848-7773
Trevor Cranston, CFA (415) 869-4431
Charter Robinson (757) 613-8955
Benjamin Zucker (212) 906-3529

HEALTHCARE

Biotechnology
Liisa A. Bayko (312) 768-1785
Heather Behanna, Ph.D. (312) 768-1795
Jason N. Butler, PhD (212) 906-3505
Christopher T. Radom, PhD (212) 906-3519
Michael G. King, Jr. (212) 906-3520
Carter L. Gould (212) 906-3522
Eric Joseph (212) 906-3514
John L. Newman, PhD (212) 906-3510
Caroline Palomeque (212) 906-3509

Healthcare Services & Facilities
Peter L. Martin, CFA (415) 835-8904
Aaron Hecht (415) 835-3963
Arthur Kwok (415) 835-8908

Medical Devices
David Turkaly (212) 906-3563
John Gillings (212) 906-3564

Medical Devices & Molecular Diagnostics
J. T. Haresco, III, PhD (415) 869-4477
Ralph Fong (415) 835-8916

REAL ESTATE

Housing & Land Development
Peter L. Martin, CFA (415) 835-8904
Aaron Hecht (415) 835-3963
Bharathwajan Iyengar (415) 835-3902

Lodging & Property Services
William C. Marks (415) 835-8944
Whitney Stevenson (415) 835-8948

REITs: Healthcare
Peter L. Martin, CFA (415) 835-8904
Aaron Hecht (415) 835-3963
Arthur Kwok (415) 835-8908

REITs: Office, Industrial, & Diversified
Mitch Germain (212) 906-3546
Peter Lunenburg (212) 906-3537

TECHNOLOGY

Communications Equipment & Internet Security
Erik Suppiger (415) 835-3918
Christopher Slaymaker (415) 835-3920

Internet & Digital Media
Ronald V. Josey III (212) 906-3528
John Dessouki (212) 906-3545

Software
Patrick Walravens (415) 835-8943
Peter Lowry (415) 869-4418
Greg McDowell (415) 835-3934

Wireless & Cloud Computing Technologies
Alex Gauna (415) 835-8998
Michael Wu (415) 835-8996

ADDITIONAL CONTACTS

Thomas R. Wright
Director of Equities
(212) 906-3599

Dan Wychulis
Director of Institutional Sales
(617) 235-8530

600 Montgomery Street, Suite 1100
San Francisco, CA 94111
www.jmpsecurities.com