Epizyme (EPZM)

Initiating Coverage with an OUTPERFORM Rating and $37 Price Target -- Highly Meaningful Therapeutics Targeting HMTs

- **Advances in genetically defining sub-sets of cancer patients have identified members of the family of histone methyltransferase (HMT) proteins as key drivers of malignancy.** EPZM's small molecule drug discovery platform seeks to marry the appropriate HMT antagonist with the genetically definable malignancy.
- **Epizyme's lead product candidate, EPZ-5676, an intravenous drug that inhibits DOT1L, is currently in a Phase I study in patients with acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) with the mixed lineage chromosomal rearrangement (MLL-r subtype).** Interim data from this 2-stage Phase I trial is expected in H2:13.
- **Epizyme's second product candidate, EPZ-6438, an oral drug that inhibits EZH2 is also in a Phase I study for a subtype of non-Hodgkin's lymphoma.** Interim data is expected by YE:13.
- **The company's collaborations with Celgene, Eisai and GlaxoSmithKline have provided Epizyme with a strong cash balance and support going forward, while at the same time, EPZM retains 100% of US rights to '5676 and has a 50/50 co-promotion option for '6438.**
- **As a result of the cause and effect link between the oncogenic HMT driver and malignancy, we would expect early evidence of deep and durable efficacy, potentially in even just a few genetically pre-defined patients, to lead to significant appreciation of EPZM's shares as investors price in clinical, regulatory and market success.**
- **Initiating coverage of Epizyme with an OUTPERFORM rating and $37 price target.** Our price target of $37/share is derived from applying 8x and 15x multiples to our 2019 estimated sales and royalty revenues respectively, discounted by 35% annually (fully-diluted share count, assumes an increase of 2 million additional shares for future financings). We note that with positive data, a decline in our discount rate from 35% per year to 20% per year yields a potential value in 12 months of $66/share.

FYE Dec	2012A	2013E			2014E		
REV	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	--	$8.9A		N/AA	$0.0E		N/AE
Q2 Jun	--	6.0E		N/AE	0.0E		N/AE
Q3 Sep	--	0.0E		N/AE	25.0E		N/AE
Q4 Dec	--	10.0E		N/AE	15.0E		N/AE
Year*	**$45.2A**	**$24.9E**		**N/AE**	**$40.0E**		**N/AE**
Change	--	-45%			61%		
	2012A	2013E			2014E		
EPS	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	--	($0.33)A		N/AA	($0.65)E		N/AE
Q2 Jun	--	(0.42)E		N/AE	(0.68)E		N/AE
Q3 Sep	--	(0.62)E		N/AE	0.17E		N/AE
Q4 Dec	--	(0.30)E		N/AE	(0.21)E		N/AE
Year*	**($0.03)A**	**($1.67)E**		**N/AE**	**($1.37)E**		**N/AE**
P/E	--	--			--		
Change	--	-4998%			18%		

Consensus estimates are from Thomson First Call.
** Numbers may not add up due to rounding.*

June 26, 2013

Price
$27.00

Rating
OUTPERFORM

12-Month Price Target
$37

Gregory R. Wade, Ph.D.
(415) 274-6863
greg.wade@wedbush.com

David M. Nierengarten, Ph.D.
(415) 274-6862
david.nierengarten@wedbush.com

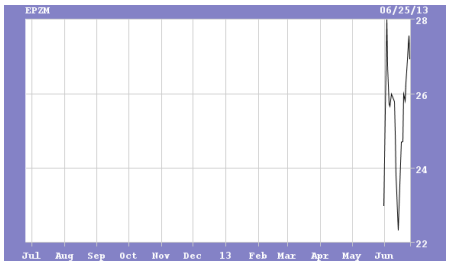
Christopher N. Marai, Ph.D.
(415) 274-6861
christopher.marai@wedbush.com

Company Information

Shares Outst (M)	26.4
Market Cap (M)	$728.5
52-Wk Range	$18.60 - $30.86
Book Value/sh	$-31.49
Cash/sh	$3.22
Enterprise Value (M)	$643.5
LT Debt/Cap %	0.0
Cash Burn (M)	$43.5

Company Description

Epizyme, Inc., is based in Cambridge, MA and is focused on the development of histone methyl transferase inhibitors in genetically defined cancers. The company has two candidates in Phase I testing: EPZ-5676 for MLL-r AML and ALL and EPZ-6438 for a subtype of NHL.



Source: Thomson Reuters

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Investment Thesis

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

Valuation

Our price target of $37/share is derived from applying 8x and 15x multiples to our 2019 estimated sales and royalty revenues respectively, discounted by 35% annually. We project 2019 US and global EPZ-5676 sales and royalties of $280 million and $33.7 million respectively, derived from 85-95% peak penetration into just the approximately 4800 MLL-r AML/ALL patients. We project EPZM's share of 2019 US and global EPZ-6438 sales and royalties of $239.5 million and $38.4 million respectively, derived from 95% peak penetration into just the approximately 12000 lymphoma patients with EZH2-driven malignancies. We note that with positive data, a decline in our discount rate from 35% per year to 20% per year yields a potential value in 12 months of $66/share (fully-diluted share count, assumes an increase of 2 million additional shares for future financings).

Our valuation does not take into account the potential for expanded use of EPZ-5676 and EPZ-6438, any success from the company's proprietary pipeline, or potential milestone payments / royalties related to the partnerships with Celgene and GSK.

Risks

Risks to the achievement of our price target include clinical, regulatory or market failure for EPZ-5676 and/or EPZ-6438.

Key points

- HMT's have been identified as the key oncogenic drivers in genetically definable sub-sets of malignancies with un-met medical need.
- Pre-clinical studies suggest EPZM's highly selective small molecule HMT inhibitors have potent anticancer effects.
- EPZ-5676, an intravenous drug that inhibits DOT1L, is currently in a Phase I study in patients with acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) with the mixed lineage chromosomal rearrangement (MLL-r subtype). Interim data from this 2-stage Phase I trial is expected in H2:13.
- Epizyme's second product candidate, EPZ-6438, an oral drug that inhibits EZH2 is also in a Phase I study for a subtype of non-Hodgkin's lymphoma. Interim data is expected by YE:13.
- As a result of the cause and effect link between the oncogenic HMT driver and malignancy, we would expect early clinical evidence of deep and durable efficacy, potentially in even just a few genetically pre-defined patients, to lead to significant appreciation of EPZM's shares as investors price in clinical, regulatory and market success.
- EPZM retains 100% of US rights to '5676 (with Celgene having licensed ex-US rights) and has a 50/50 US co-promotion option for '6438 with Eisai. The company could receive up to mid-double digit royalties on ex-US sales of those product candidates.

MILESTONES

H2:13 Begin second stage of the Phase I/II study of EPZ-5676 in AML/ALL patients with MLL-r
H2:13 Interim data for the Phase I study of EPZ-5676 in the AML/ALL setting
H2:13 Interim data from the Phase I study of EPZ-6438 in the NHL setting
2014 Final data for the Phase I/2 study of EPZ-5676 in the MLL-r setting
H1:14 Final data for the Phase I study of EPZ-6438 in the NHL setting
H2:14 Begin pivotal Phase II trial for EPZ-5676 in adults with MLL-r
Q1:15 Begin pivotal Phase II/III trial for EPZ-6438 in EZH2-driven NHL
Q2:15 Begin pivotal Phase II trial for EPZ-5676 in children with MLL-r
H2:15 Data from pivotal Phase II trial for EPZ-5676 in adults with MLL-r
H2:15 Data from pivotal Phase II/III trial for EPZ-6438 in EZH2-driven NHL
H2:16 File NDA for EPZ-5676
H1:17 File NDA for EPZ-6438

Epizyme, Inc. Overview

Epizyme, Inc., based in Cambridge, Massachusetts, is the first company to begin clinical testing of inhibitors for HMT enzymes. The company has identified 20 HMTs (of 96) with oncogenic potential as attractive targets for therapeutic discovery and potential development. The company's lead product candidates include EPZ-5676, in Phase I for a subtype of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), and EPZ-6438, in Phase I/II for a subtype of NHL. Epizyme has established partnerships for their lead candidates, and is also collaborating on developing companion tests for each their drug candidates.

Exhibit 1: Product Development Table

Product	Indication/Field	Stage of Development	Partner	Companion Test Collaborator
EPZ-5676	Mixed lineage rearranged leukemia (MLL-r)	Phase I	Celgene	Abbott
EPZ-6438	Subtype of non-Hodgkin lymphoma (NHL)	Phase I/II	Eisai	Roche
3 GSK Collaboration Targets	Oncology	Pre-clinical	GSK	unspecified
WHSC1	Myeloma	Pre-clinical	None (Multiple Myeloma Research Foundation research funding)	unspecified

Source: Epizyme

Epigenetics and HMT inhibition – A new direction in oncology, with strong parallels to kinase inhibition

Epigenetics is the study of changes in the regulation of gene activity and expression, independent of gene sequence. Recent oncology drug discovery has focused significant attention on cellular signal transduction mediated by growth and survival factors with many new drugs targeting the inhibition of extracellular growth factors, their receptors, and the intracellular proteins (often kinases) that transduce (and regulate) these signals to the cells' nucleus.

While many growth and survival signaling pathways are regulated by kinases, another layer of regulation is mediated at the gene transcription level. In order for the genes to be transcribed into mRNA (which is then translated into protein), chromosomal DNA has to be physically accessible to the large complex of transcriptional machinery. This requires de-condensation of the normally tightly packaged chromatin, via modifications of the histone proteins and DNA itself. These modifications include methylation, acetylation, and phosphorylation, among others. Mutations in epigenetic proteins, associated proteins or even alterations to the chromatin substrate can drive the proliferation of cancer cells. Much of the focus so far in developing epigenetic drugs has been the targeted inhibition of histone deacetylase (HDAC) or DNA methyltransferase (DNMT) enzymes. Epizyme is focused on the 96 member histone methyl transferase family of proteins, some of which have been associated with genetically identifiable malignancies.

Exhibit 2: Epigenetic Drugs Approved by FDA

Product	Marker	Indication/Field	Approval Date	Developer
Istodax (romidepsin)	HDAC	peripheral T-cell lymphoma	June 2011	Celgene
		cutaneous T-cell lymphoma	Nov. 2009	
Zolinza (vorinostat)	HDAC	cutaneous T-cell lymphoma	Oct. 2006	Merck
Dacogen (decitabine)	DNMT	myelodysplastic syndrome	May 2006	Eisai
Vidaza (azacitidine)	DNMT	myelodysplastic syndrome	May 2004	Celgene

Source: Nature Biotechnology

HMT inhibition - Getting specific

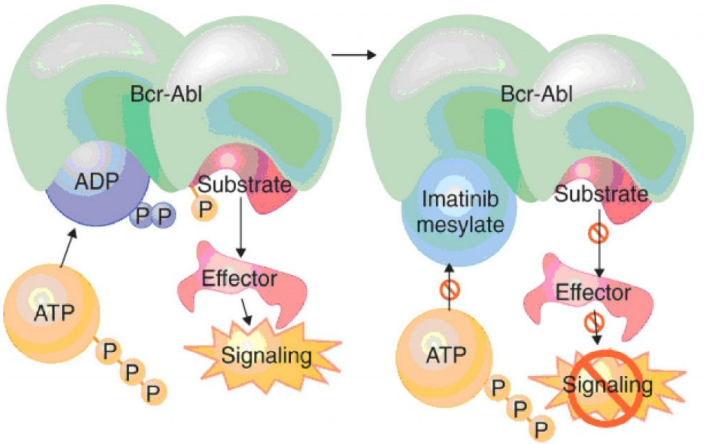
Much like the research into kinase inhibition has moved from less-specific, general kinase inhibitors that block multiple signaling pathways to those that target specific mutations in kinases that arise in cancer subsets, Epizyme has moved the field from more general epigenetic inhibition of HDAC/DNMTs to much more specific inhibition of HMTs that are critical to the growth of subsets of

cancers. DNMTs modify DNA by incorporating methyl groups to available cytosines (the "C" of the DNA code letters A, T, C, G) on DNA strands while HDACs target any lysine residues on histone proteins.

In contrast, HMTs target specific residues on specific histone tails. Certain cancers are "addicted" to signals that are generated via genes activated by aberrant histone methylation, and by inhibiting those HMTs responsible, it is expected that these pathways would not be turned on. Thus EPZM's drug candidates have the potential to "switch off" these pathways "at the source," the mRNA transcription level, rather than attempting to reduce the activity of an already-expressed kinase.

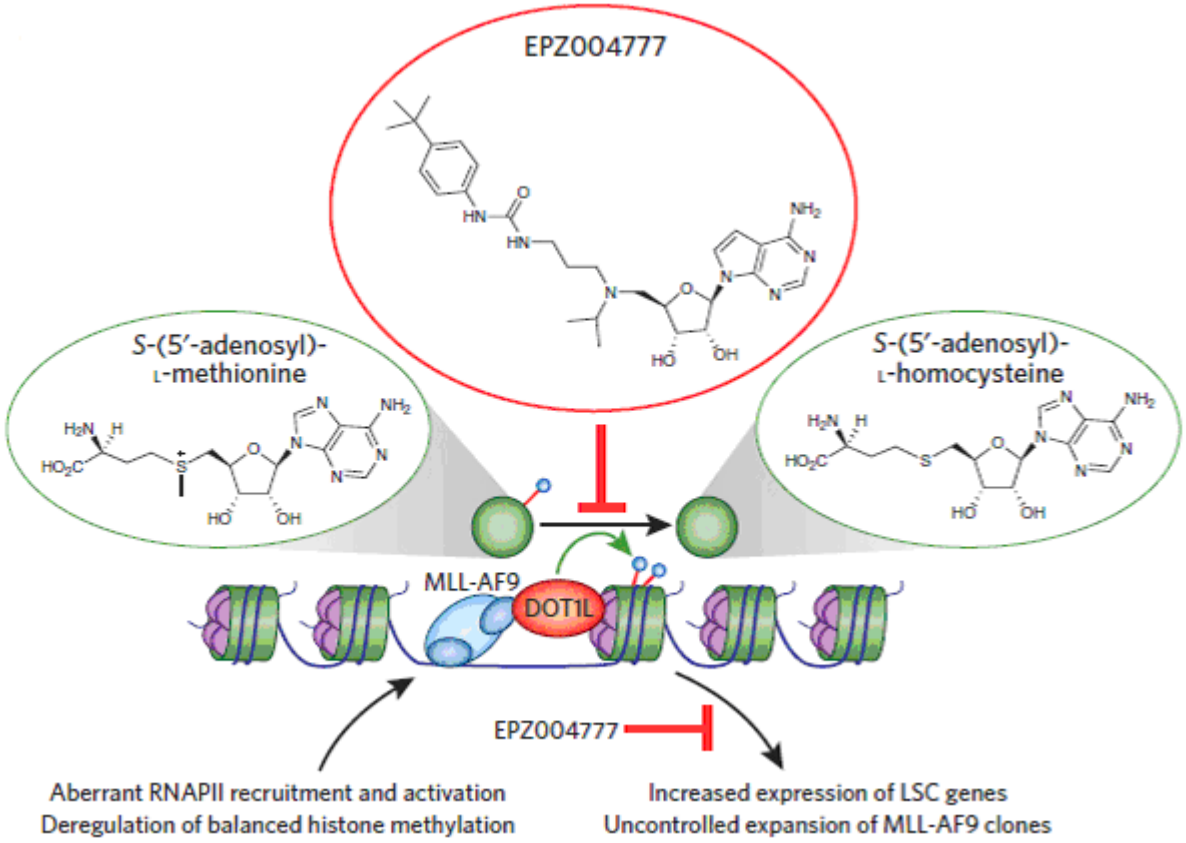
To continue to draw upon the parallels with kinase inhibitor development, kinase enzymes use the universal phosphate donor, ATP, to phosphorylate various chemical groups on biological molecules. Most kinase inhibitors build specificity from adding chemical groups to an ATP mimic so that it resembles the enzyme's substrate. Similarly, HMTs use a universal methyl donor, S' Adenosyl Methionine (SAM) to methylate the substrate. However, while all kinase inhibitors act by binding to the ATP pocket, Epizyme's platform technology has used various inhibition strategies including, but not limited to binding/blocking the SAM binding pocket of HMTs. Epizyme has also created molecules that bind to the substrate pocket and also at non-catalytic (allosteric) sites to inhibit specific HMTs.

Exhibit 3: Mechanism of a Kinase Inhibitor (imatinib)



Source: Goldman, L., & Ausiello, D. (2008). The Chronic Leukemias. Cecil Medicine: 23rd Edition. (p. 1401).

Exhibit 4: HMT Action Compared



Source: Travers, J., Blagg, J. and Workman, P. (2011). Epigenetics:Targeting leukemia on the DOT. Nature Chemical Biology, 7 (10). Page 664.

Comparison with Kinase Inhibitors

The success of highly selective kinase inhibitors that treat kinase-driven malignancies offers the best parallel to the potential success EPZM's HMT's may achieve.

Novartis' Gleevec (imatinib) was approved in 2001 to treat patients with chronic myeloid leukemia (CML) who are Philadelphia chromosome positive (Ph+). Gleevec, a tyrosine kinase inhibitor (TKI) that targets the Bcr-Abl protein at the Philadelphia chromosome, has since been approved for additional cancers including metastatic gastrointestinal stromal tumors (GIST) and Ph+ ALL. Gleevec's unprecedented disease control and long-term safety caused this drug to grow to over $1B in sales as the prevalent population of CML patients expanded annually (due to the improvement in overall survival mediated by this therapy). Other treatments that have since launched that are intended to treat patients resistant or intolerant to Gleevec include Novartis' Tasigna (nilotinib), Bristol-Myers' Sprycel (dasatinib) and Pfizer's Bosulif (bosutinib). Parallels between the CML market and the potential large CLL population that might achieve long-term disease control with a specific Bruton's tyrosine kinase inhibitor, ibrutinib, currently under development have led investors to ascribe a near $6B market capitalization to Pharmacyclics (PCYC, Outperform), for just half of the global economics for its targeted therapy.

Exhibit 5: Sales and Development of Notable Kinase Inhibitors

Product	Target	Indication	2012 US Sales	First approved	IND filed	Developer
Gleevec (imatinib)	Bcr-Abl	CML and other cancers	$1698 M	5/2001	4/1998	Novartis
Tarceva (erlotinib)	EGFR	NSCLC and pancreatic cancer	$612 M	11/2004	8/2002	OSI/Roche
Sprycel (dasatinib)	Bcr-Abl	CML and Ph+ ALL	$404 M	6/2006	3/2003	Bristol-Myers
Tasigna (nilotinib)	Bcr-Abl	Ph+ CML	$351 M	10/2007	4/2004	Novartis
Xalkori (crizotinib)	ALK	NSCLC	$81 M	8/2011	12/2005	Pfizer
Zelboraf (vemurafenib)	BRAF	Melanoma	$120 M	8/2011	10/2006	Daiichi Sankyo and Roche
Bosulif (bosutinib)	Bcr-Abl	Ph+ CML	$6 M	9/2012	4/2004	Pfizer
CO-1686	EGFR	NSCLC		N/A	1/2012	Clovis

Source: company annual reports, Symphony Health Solutions

Epizyme has licensed exclusive rights to patents related to HMTs (based on research conducted by Epizyme co-founder Professor Yi Zhang) from the University of North Carolina.

Other companies focused on developing HMT inhibitors include CellCentric, GSK and Constellation Pharmaceuticals. All of their products are still in preclinical development, and Epizyme is the only company to take an HMT inhibitor into the clinical phase.

Exhibit 6: Other Companies Targeting HMTs

Company	Target / Drug	Stage	Partnership
CellCentric (UK)	Undisclosed	preclinical	Out-licensed to Takeda Pharmaceuticals in Feb. 2010 for potentially more than $200 million in fees, milestones and royalties.
GSK (UK)	EZH2 / GSK126	preclinical	-
Constellation (US)	Undisclosed	preclinical	Partnered with Genentech, Constellation received $95 million in fees and research funding plus undisclosed milestones and royalties
EpiTherapeutics (Denmark)	Undisclosed	preclinical	Partnered with Abbott Laboratories for undisclosed amount

Source: Katsnelson, A. "An Epic Search." The Scientist. April 2010. Page 76; company reports

EPZ-5676

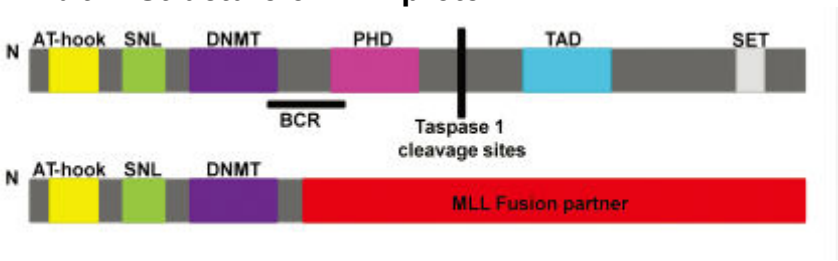
Epizyme's lead product candidate, EPZ-5676, is an IV administered small molecule inhibitor of the DOT1L HMT. DOT1L, which methylates histone H3 at lysine 79 (H3K79), has been associated with the progression of MLL-r, a chromosomal rearrangement found in ~22% of AML patients. Epizyme is collaborating with Abbott to develop a companion test for MLL-r AML.

EPZ-5676 is currently being evaluated in a US Phase I open-label, multicenter trial with two stages. The first stage is a three week dose-escalation study in patients with hematological malignancies (including some with MLL-r), and the second stage is an expansion phase testing the maximum tolerated dose (MTD) identified in the first stage in only MLL-r patients. The first stage began in September 2012 and the second stage is expected to begin in H2:13.

Disease

Mixed lineage (or myeloid/lymphoid) rearranged leukemia (MLL-r) is an aggressive form of the disease that occurs when there are rearrangements involving the MLL gene at the 11q23 chromosome. This rearrangement can be associated with both AML and ALL. A translocation in MLL results in the amino-terminal of the MLL gene fusing to the carboxy-terminal portion of the fusion partner gene.

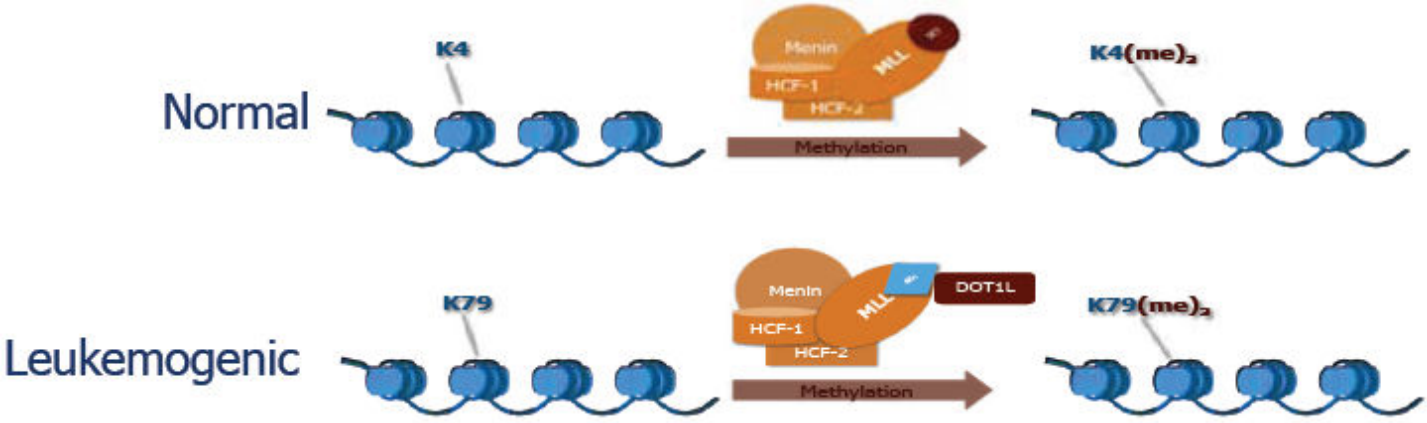
Exhibit 7: Structure of MLL protein



Source: Journal of Clinical and Experimental Hematopathology. Vol. 50, No.2

The MLL-fusion protein binds to a variety of complexes that increase gene expression. The MLL-fusion protein also recruits DOT1L, a histone methyltransferase that binds actively transcribing RNA polymerase II. DOT1L catalyzes the methylation of H3K79, leading to increased expression of leukomogenic genes. These genes appear to be required for the leukemic cells to proliferate, thus DOT1L's activity also appears to be required for the progression of MLL-r leukemia. Interestingly, DOT1L remains unmutated. Due to the role DOT1L plays in leukemic transcription, inhibition of DOT1L in patients with MLL-r is expected to lead to decreased cell proliferation.

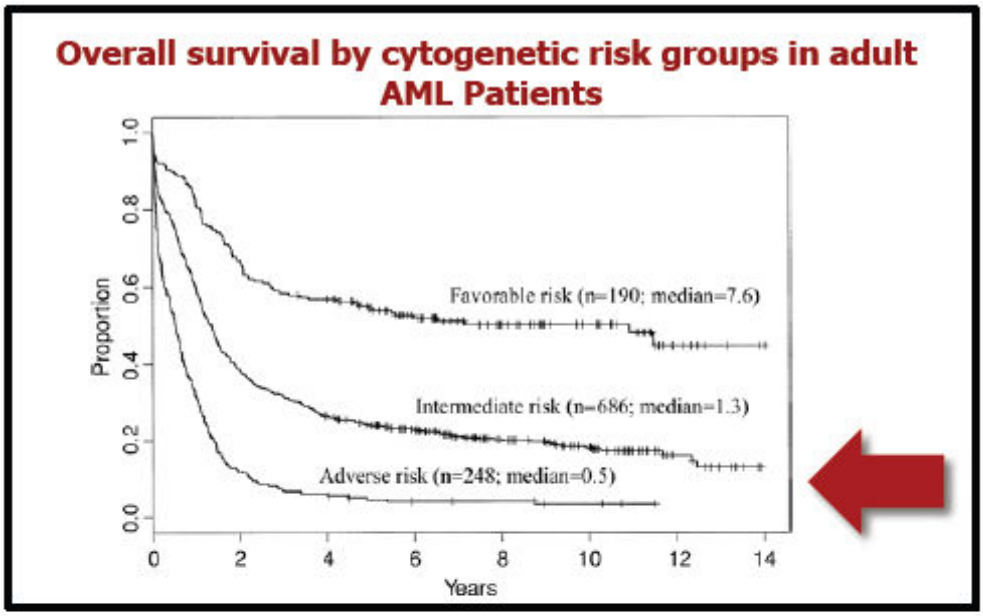
Exhibit 8: Histone Methylation in MLL-r Leukemia

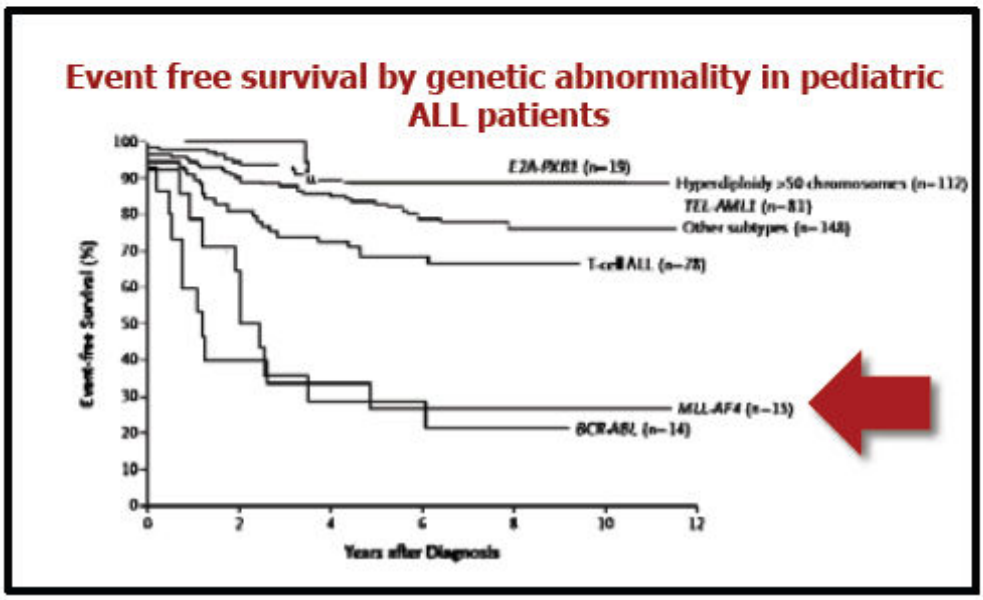


Source: Epizyme

MLL rearrangement is associated with poor prognosis, with the five-year overall survival rate for adult AML MLL-r patients in the range of 5 to 24% (vs. ~25% for AML overall). The five-year event-free survival rate in pediatric patients with the MLL-r subtype of ALL is about 27 percent, compared to an >90% five-year survival rate for children with ALL without the rearrangement. This inferior prognosis points to the unmet need for a focused treatment specifically targeted to the MLL-r patient population.

Exhibit 9: ALL/AML Survival Rates





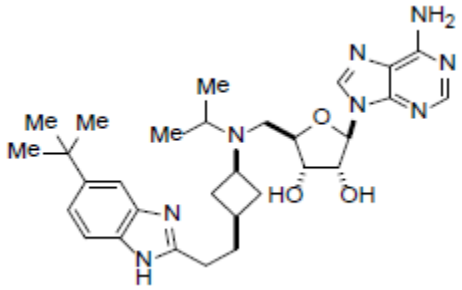
Source: Epizyme

Competition

Currently there are no approved therapies specifically indicated for patients with MLL-r AML/ALL. The disease is currently treated with chemotherapeutics approved for patients with relapsed or refractory leukemia. There are many drugs prescribed for relapsed/refractory ALL, including Clolar (clofarabine) in children. For relapsed or refractory AML, mitoxantrone, etoposide, cytarabine (MEC) and regimens combining these agents are commonly used.

An estimated 48,610 new cases of leukemia are expected to be diagnosed in the US in 2013, with AML comprising 30% (14,590 cases) and ALL comprising 13% (6,070 cases). The ALL/AML case ratio in children under 15 years old is 4:1, approximately the reverse of the ratio in adults. The treatment goal for ALL is complete remission through chemotherapy, and the goal for AML is to induce a complete response and then perform an allogeneic bone marrow transplant if the patient is fit enough and a suitable donor is available.

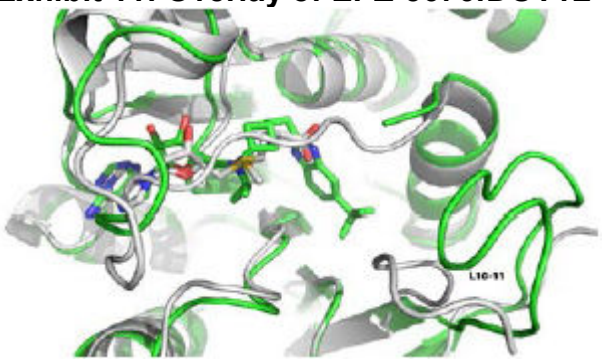
Exhibit 10: Chemical Structure of EPZ-5676



Source: Epizyme

EPZ-5676
EPZ-5676 is an S-adenosyl methionine (SAM) analog that binds to DOT1L, inducing a conformational change that extends the compound binding pocket to include novel recognition elements beyond the SAM binding site.

Exhibit 11: Overlay of EPZ-5676:DOT1L (green) and SAM:DOT1L (gray) crystal structures

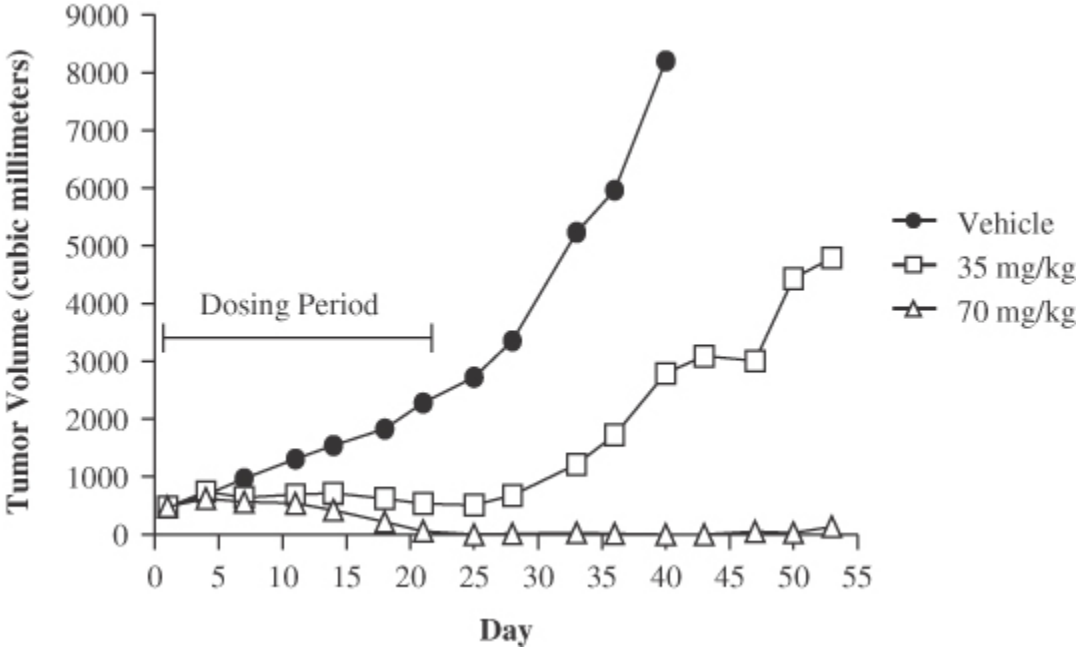


Source: Epizyme

In vitro studies of cell lines that included the MLL-r gene rearrangement reveal that EPZ-5676 selectively inhibits the DOT1L-associated methylation in a concentration dependant manner while having no effect on other histone methyl markers. EPZ-5676 also inhibits proliferation and killed cells containing the MLL-r abnormality while having minimal effect on cells without the alteration.

In a xenograft study in nude rats with tumors established from human MLL-r cells implanted subcutaneously, administration of EPZ-5676 resulted in significant tumor growth inhibition. Rats received 35 and 70 mg/kg per day for 21 days via continuous IV. In comparison with the control group, animals treated at the 35 mg dose had tumor stasis that continued for up to seven days past discontinuation of drug treatment. For the 70 mg group, nine of the 10 animals had tumors reduced to undetectable volumes by the end of treatment, and eight of the nine animals had no tumor regrowth through 32 days after treatment (see below).

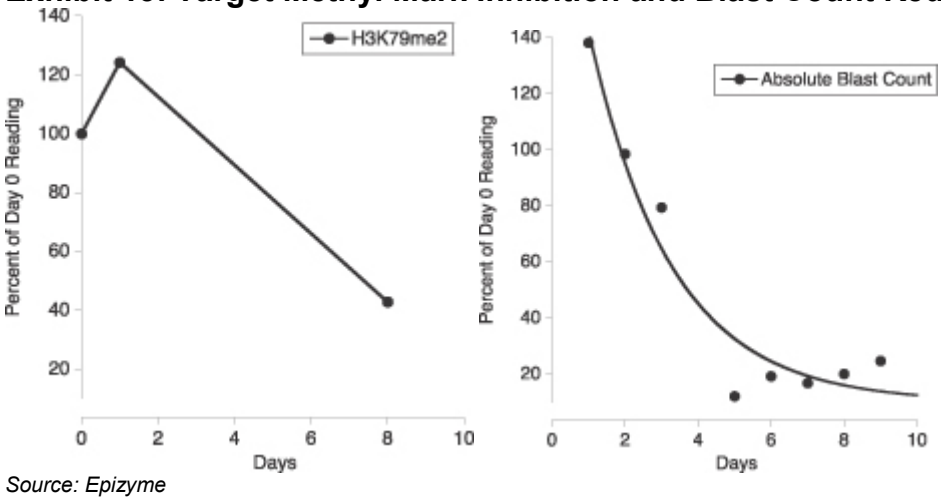
Exhibit 12: Median Tumor Volume



Source: Epizyme

Initial data from the Phase I trial of EPZ-5676 showed that partial inhibition of DOT1L (target methyl mark H3K79me2) was observed after treatment in one patient with ALL and the MLL-r subtype who received 24 mg/m2/day. By the fifth day of treatment the patient experienced a 90% reduction in circulating leukemic blast count in the blood and a resolution of leukemia-related fevers.

Exhibit 13: Target Methyl Mark Inhibition and Blast Count Reduction



Source: Epizyme

Treatment was terminated on day 10 in the patient due to disease progression. Given the incomplete methyl mark inhibition by day 8, and the lack of adverse events, we believe that higher doses of '5676 should have a more complete inhibition of DOT1L and a more lasting reduction of blasts. As expected, the three other patients that completed dosing who did not have the MLL-r rearrangement showed no clinical effect.

Market

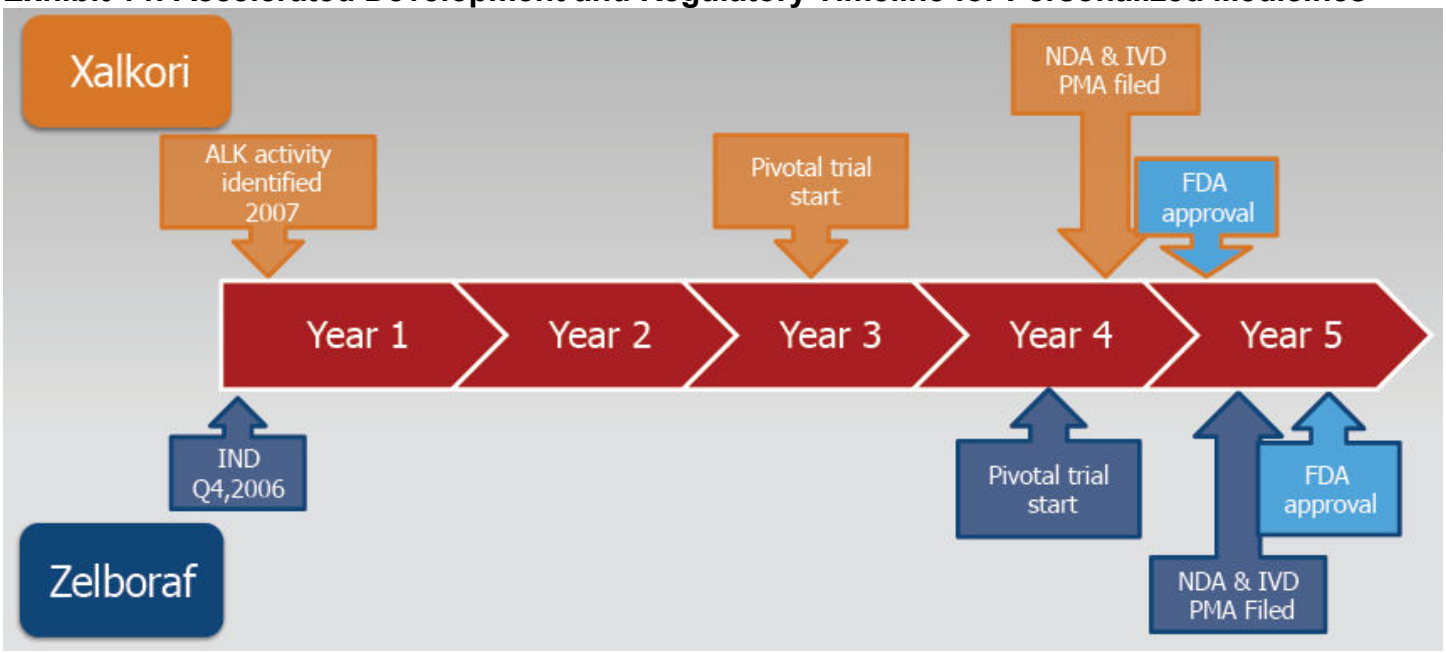
About 10% percent of patients with AML and ALL have structural alterations of 11q23, which leads to MLL-r. A report commissioned by Epizyme found that the total annual incidence of MLL-r in major pharmaceutical markets is about 4,900 patients.

We project that EPZ-5676 will be priced at an annualized per patient cost of $150,000. This is at the high-end of recent oncology therapies, but is feasible considering the focused patient set and our expectation for deep and durable disease control.

First-in-class molecularly targeted therapies tend to achieve high peak penetration rates in a short time frame, with the most recently approved therapies having the most rapid rate of adoption. There is a high awareness of MLL-r among oncologists, and leukemia patients that have the MLL-r subtype are routinely identified with existing technologies commonly used in clinical settings. As a result, we project EPZ-5676 will reach a peak US market penetration of 85% within a year, which is similar to Zelboraf's adoption rate.

Development
Epizyme plans to begin a global Phase II pivotal trial for EPZ-5676 in mid-2014 potentially leading to an NDA filing in H2:16. This timeline would be similar to the accelerated approval pathway taken by Pfizer for Xalkori, which was approved within five years of entering clinical testing. Xalkori was approved based on efficacy established in the Phase II 'PROFILE 1005' trial in 261 patients with NSCLC and a mutated ALK gene. About 5% of NSCLC patients have a mutated ALK gene, or an annual incidence of 5,000.

Exhibit 14: Accelerated Development and Regulatory Timeline for Personalized Medicines



Source: Thomson Reuters Pharma

EPZ-6438

EPZ-6438 is an oral small molecule inhibitor of the enhancer of zeste homolog 2 (EZH2) HMT. EZH2, which methylates histone 3 at Lys 27 (H3K27), has been implicated in NHL, malignant rhabdoid tumors (MRT) and other solid tumors. In particular, EZH2 is associated with two types of NHL: follicular lymphoma (FL) and diffuse large B-cell lymphoma of germinal-center origin (DLBCL). There are currently no approved therapies indicated for cancer associated with the EZH2 point mutation. The company is collaborating with Roche and Eisai to develop a companion test for EZH2 sensitivity in patients with DLBCL/FL .

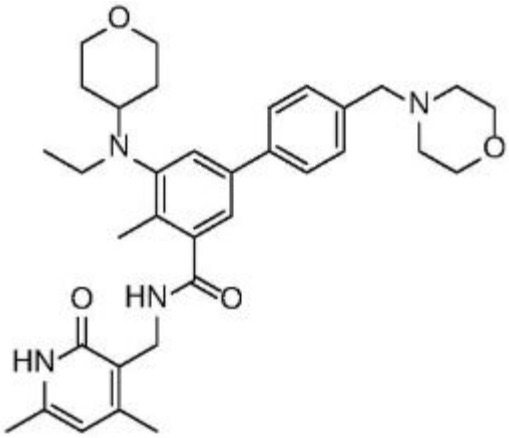
A two-stage Phase I/II trial has begun enrolling patients with NHL who have the EZH2 point mutation. The Phase I portion will be an open-label dose-escalation study of EPZ-6438 administered twice-daily to determine MTD in cancer patients, including (but not exclusive to) NHL patients with the EZH2 mutation. The Phase II portion will be a two-stage trial with the primary endpoint to assess the objective response rate of EPZ-6438 in patients with the EZH2 point mutation who have relapsed or refractory DLBCL or FL. In the first stage all patients will be administered the MTD identified in the Phase I portion, and in the second stage, patients will be randomized 2:1 to receive either EPZ-6438 or the existing standard of care.

Disease and Treatment.
DLBCL is the most common form of NHL, accounting for 30% of newly diagnosed cases in the US. This aggressive hematologic malignancy can develop in any part of the body. In contrast, FL is a slow-growing tumor, and accounts for about 25% of new NHL cases. About one-third of FL cases will transform into a more aggressive form of lymphoma.

There is no therapy approved specifically for NHL cancer associated with the EZH2 mutation. Patients with DLBCL are typically treated with multi-agent chemotherapy, most commonly Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, prednisone and occasionally etoposide. Patients with FL can also be treated with multi-agent chemotherapy, although Rituxan alone is typically sufficient for an initial, if not as durable response. Patients with relapsed/refractory DLBCL or FL are usually treated with high dose chemotherapy and an allogeneic stem cell transplant, if available and the patient is a candidate. The five year overall survival rate for patients with relapsed/refractory NHL who are not eligible for stem cell transplant ranges from 10 to 15%.

Malignant rhabdoid tumor (MRT) is a rare (~150 patients per year in the US) childhood cancer often presenting first in the brain or kidney at less than two years of age. This very aggressive cancer has an estimated event-free survival below 20% with current treatment regimens consisting of intensive chemotherapy and radiation therapy.

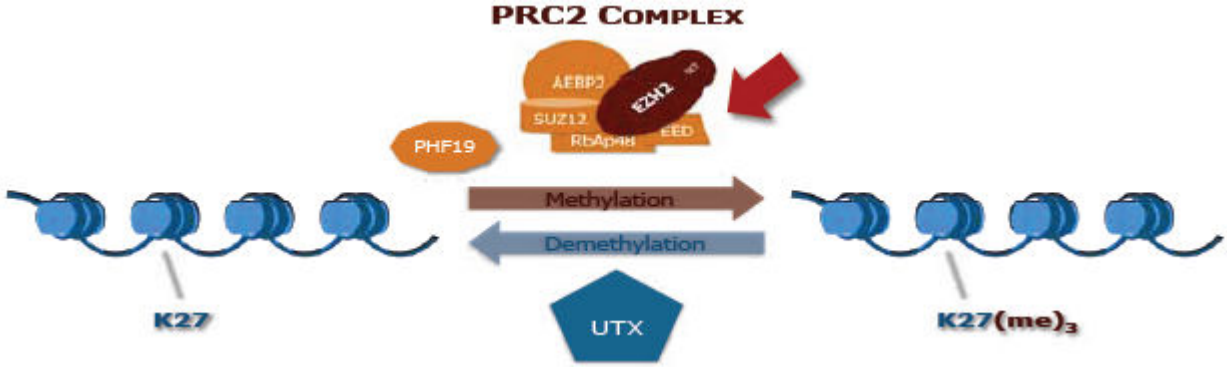
Exhibit 15: Structure of EPZ-6438



Source: Epizyme

EPZ-6438 inhibits EZH2 in a manner competitive with SAM and is highly selective, displaying a 35-fold selectivity versus EZH1 and a >4,500-fold greater affinity vs. all other HMTs tested. EZH2 is the catalytic subunit of the polycomb repressive complex 2 (PRC2), which regulates chromatin structure. Excess EZH2 leads to hypermethylation of H3K27 and lymphomagenesis.

Exhibit 16: Histone Methylation with EZH2

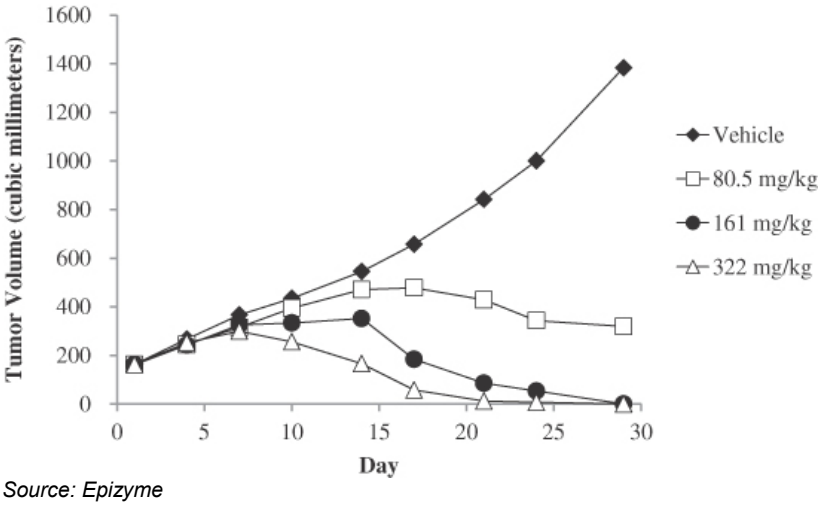


Source: Epizyme

In vitro analysis of NHL cell lines with the EZH2 point mutation showed that EPZ-6438 selectively inhibited the targeted EZH2-associated methylation in a concentration dependent manner, without affecting other histone methyl marks. EPZ-6438 inhibited proliferation, and killed cells containing the oncogenic EZH2 mutation, while leaving other cells unaffected.

In a xenograft study in mice with tumors established from human EZH2 associated NHL cells implanted subcutaneously, administration of EPZ-6438 resulted in significant tumor growth inhibition. Mice received 80.5 mg/kg, 161 mg/kg or 322 mg/kg of EPZ-6438 (orally) for 28 days. Tumors were not detectable in the 161 and 322 mg/kg groups by day 28.(see below).

Exhibit 17: Median Tumor Volume



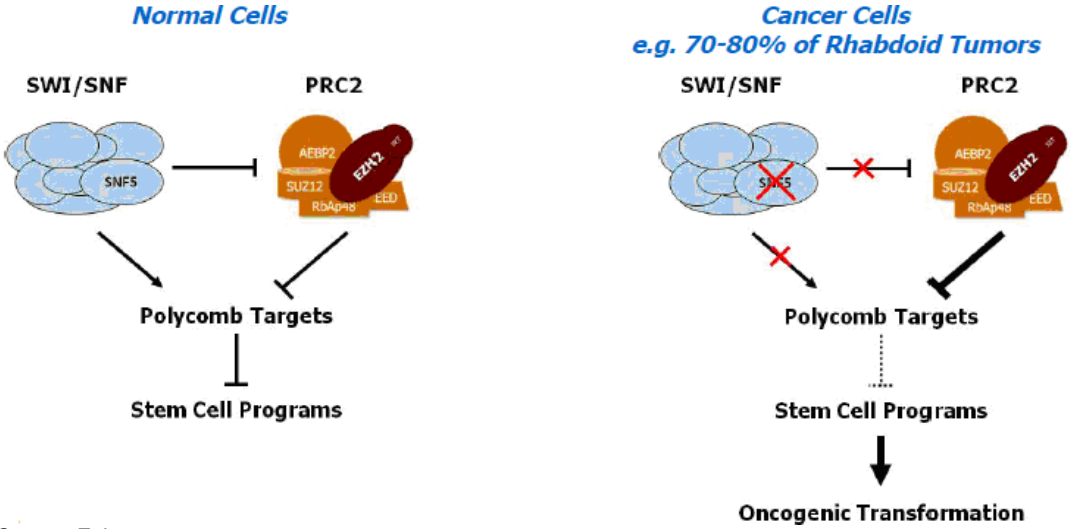
Source: Epizyme

In a separate mouse model assessing EPZ-6438 administered twice-daily at 322 mg/kg for 28 days, tumors were undetectable by the end of treatment on day 28 and no tumor regrowth was observed in any of the animals through the end of study on day 91.

EZH2 and MRT

Nearly all MRT patients have an inactivated SMARCB1 gene, which is a core component of the SWI/SNF chromatin remodeling complex. SMARCB1 plays a role in regulating EZH2 methylation, and the absence of SMARCB1 function leads to decreased expression of cell cycle inhibitors and tumor suppressors.

Exhibit 18: SWI/SNF and PRC2

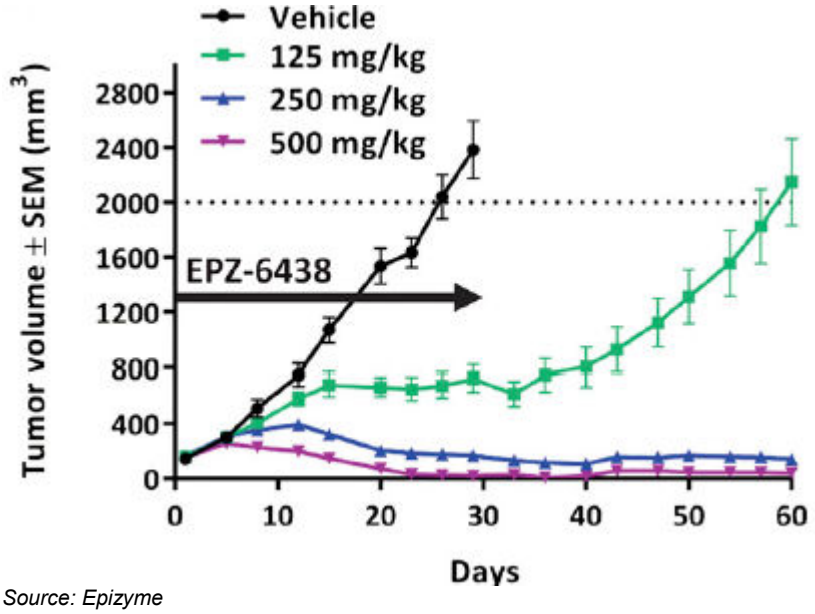


Source: Epizyme

EPZ-6438 selectively inhibited methylation associated with EZH2 in a concentration dependant manner without affecting other histone methyl marks in *in vitro* studies of MRT cell lines with an SMARCB1 deletion. EPZ-6438 inhibited proliferation and killed cells containing the SMARCB1 deletion while leaving other cells unaffected.

EPZ-6438 resulted in significant tumor growth inhibition in a xenograft study in 16 mice with tumors established from human SMARCB1-deleted MRT cells implanted subcutaneously. Mice received EPZ-6438 (orally) 125 mg/kg, 250 mg/kg or 500 mg/kg orally twice daily for 21 days, with half of the mice continuing to receive treatment for an additional seven days. Mice in the 125 mg/kg group had an 80% reduction while mice in the 250 and 500 mg/kg groups had a >=90% reduction in methyl mark levels compared to the control group at day 21. The mice receiving the two higher doses had no detectable tumor by the end of the 28 day period. Furthermore, no tumor growth was observed in any of the mice receiving 250 or 500 mg/kg by the end of the study on day 60.

Exhibit 19: Median Tumor Volume



Source: Epizyme

Market
The annual incidence rate of FL and DLBCL in major markets is approximately 54,000 patients, and of these it is estimated 12,000 carry the EZH2 point mutation.

Development
The company plans for proof-of-concept for EPZ-6438 to be established in 2014, with a potential Phase II/III registration to follow. An NDA filing for EPZ-6438 could come as early as H1:17 if the clinical program advances as anticipated.

Collaboration with GSK

Epizyme entered into a collaboration with GSK in January 2011 to discover, develop and commercialize novel HMT inhibitors. GSK was granted exclusive worldwide license rights to three inhibitors.

Exhibit 20: Collaborations

Product	Partner	Terms
DOT1L (includes EPZ-5676)	Celgene (100% ex-US rights)	Epizyme received $65 million upfront and $25 million in sale of equity, and is eligible for $160 million in development/regulatory milestones. Epizyme is also eligible for a ~ 5% to 15% royalty on ex-US sales
EZH2 (includes EPZ-6438)	Eisai (100% worldwide rights); Epizyme retains option for 50% of the US economics (if exercised, future milestones reduced by half and US royalty payments terminated, plus 25% of prior development costs become creditable by Eisai against future milestone payments)	Epizyme received $3 million upfront and $16.5 million in research funding and milestones through 2012, and is eligible for $86 million in additional development/regulatory milestones and $115 million in sales milestones. Epizyme is also eligible for a ~5% to "low double digit" royalty on US sales and ~ 5% royalty on ex-US sales
3 HMT inhibitors	GSK (100% worldwide rights)	Epizyme received $20 million upfront and $11.7 million in research funding and milestones through 2012, and is eligible for $360 million in additional development/regulatory milestones and $270 million in sales milestones. Epizyme is also eligible for a ~5% to "low double digit" royalty on worldwide sales.
All other targets	Celgene retains option (until July 2015) for 100% of ex-US rights	If the options are exercised Epizyme is eligible for $165 million in fees and development/regulatory milestones for each target Celgene selects

Epizyme has also entered into a research agreement with the Multiple Myeloma Research Foundation to develop HMT inhibitors targeting WHSC1 for myeloma. Epizyme received $0.2 million upfront and $0.1 million in milestones through 2012, and is eligible for an additional $0.7 million in milestones. The Foundation is entitled to receive a 3% royalty on any products developed under the agreement, up to a four-times multiple of the total funding the Foundation provides to Epizyme.

Exhibit 22: Management

Title	Biography
Robert J. Gould, PhD. **CEO and President**	President and CEO since March 2010. Prior to joining Epizyme he was Director of Novel Therapeutics at the Broad Institute of MIT and Harvard from November 2006 to March 2010. Prior to that he was VP of Licensing and External Research at Merck's Merck Research Laboratories. 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.
Robert A. Copeland, PhD. **EVP and CSO**	EVP and CSO since September 2008. Prior to joining Epizyme he was VP of Cancer Biology at GSK's Oncology Center of Excellence in Drug Discovery from January 2003 to September 2008. Prior to that he held scientific staff positions at Merck and Bristol-Myers Squibb, 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 postdoctoral studies as the Chaim Weizmann Fellow at the California Institute of Technology.
Jason P. Rhodes. **EVP, CFO and Treasurer**	EVP, CFO and Treasurer since March 2013. Previously served as EVP, CBO and Treasurer from March 2010 to March 2013. Prior to joining Epizyme he was VP of Business Development at Alnylam Pharmaceuticals from July 2007 to March 2010. Prior to that 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, MD. **CMO**	CMO since May 2012. Prior to joining Epizyme he was VP of Oncology Development from August 2010 to April 2012 and Interim CMO from May 2011 to April 2012 at Pharmacyclics. Prior to that he was an independent drug development consultant from October 2009 to August 2010. From November 2000 to September 2009 he held a variety of positions at Genentech, including Medical Director, Group Medical Director and clinical scientist. Prior to that he was an Associate Attending Physician at Memorial Sloan-Kettering Cancer Center focusing on clinical research in non-Hodgkin lymphoma, myelodysplastic syndromes, multiple myeloma and hematopoietic growth factors. Dr. Hedrick 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.

Exhibit 23: Model

6/25/2013
Ticker: (EPZM:Nasdaq)
Epizyme, Inc

WEDBUSH
PAC GROW LIFE SCIENCES

Gregory R. Wade, Ph.D.
415-274-6863

Epizyme, Inc (EPZM)
in thousands except per share data

	2012A	Q1A	Q2E	Q3E	Q4E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
Revenues:													
Net Product Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0	$78,726	$324,500	$519,702	$644,826
Other Revenues	$0	0	0	0	0	0	0	0	0	10,453	45,565	72,180	89,834
Royalties	$45,222	8,882	6,000	0	10,000	24,882	40,000	25,000	40,000	60,000	0	0	0
Total Revenues	**45,222**	**8,882**	**6,000**	**0**	**0**	**24,882**	**40,000**	**25,000**	**40,000**	**149,180**	**370,065**	**591,882**	**734,660**
Cost and Expenses:													
Cost of Sales	0	0	0	0	0	0	0	0	0	3,936	16,225	25,985	32,241
R&D	38,482	13,361	13,762	14,312	15,028	56,463	66,368	73,909	80,002	86,597	93,735	101,462	109,825
SG&A	7,508	2,998	3,049	3,101	3,154	12,301	13,927	15,897	18,946	40,573	92,304	133,296	159,572
Total Operating Expenses	**45,990**	**16,359**	**16,811**	**17,413**	**18,181**	**68,764**	**80,295**	**89,806**	**98,948**	**131,106**	**202,263**	**260,743**	**301,639**
Operating Income (Loss)	(768)	(7,477)	(10,811)	(17,413)	(18,181)	(43,882)	(40,295)	(64,806)	(58,948)	18,074	167,802	331,139	433,022
Net Interest Income (Expense)/Other Income	67	(20)	(344)	(165)	(209)	(739)	1,309	843	1,053	(432)	741	5,222	7,717
Income Before Income Taxes	(701)	(7,497)	(11,155)	(17,579)	(18,391)	(44,621)	(38,986)	(63,964)	(57,895)	17,643	168,543	336,361	440,739
Provision for Income Taxes	1	0	0	0	0	0	252	149	0	2,365	8,933	131,181	171,888
Net Income (Loss)	(702)	(7,497)	(11,155)	(17,579)	(18,391)	(44,621)	(39,238)	(64,112)	(57,895)	15,278	159,610	205,180	268,851
GAAP EPS	**(0.03)**	**(0.33)**	**(0.42)**	**(0.62)**	**(0.30)**	**(1.67)**	**(1.38)**	**(2.14)**	**(1.89)**	**0.50**	**5.17**	**6.62**	**8.65**
Total Shares Outstanding	21,448	22,502	26,444	28,415	28,440	26,450	28,503	29,590	30,678	30,778	30,878	30,978	31,078
Cash Burn	44,154	0	0	0	0	(43,548)	(38,280)	(63,300)	(57,215)	16,019	160,693	206,622	270,626
Cash Balance	97,981	85,047	156,443	138,924	130,590	130,590	89,928	120,003	62,274	63,289	172,107	336,958	402,658

Covered companies mentioned

COMPANY	TICKER	RATING	PRICE	PRICE TARGET
Pharmacyclics	PCYC	OUTPERFORM	$79.30	$165

Analyst Biography

Gregory Wade, Ph.D.

Greg is a Managing Director and joined Wedbush in March 2009 from Pacific Growth Equities where he was a Senior Research Analyst covering emerging Pharmaceutical and Biotechnology companies. He started at Pacific Growth in February 2000 as a Research Associate and became an Analyst in 2004. Prior to Pacific Growth Equities, Greg was a Director in the business development group at ISIS Pharmaceuticals and prior to that was with Procyon BioPharma in London, Canada. While completing his Ph.D. in Physiology at the University of Western Ontario Greg worked as an Associate at the venture capital company Helix Investments Canada where he focused on early stage investments in life science companies.
Greg's team includes Drs. David Nierengarten (Analyst) and Chris Marai (Senior Research Associate) and together they cover 30+ companies focused on antibiotics, rare diseases, prostate cancer, hematology/oncology, gastrointestinal disorders, vaccines, biodefense and drug/device combinations.
Greg's Edge: Greg's edge comes from the breadth and duration of his tenure on the sell-side. Coverage of nearly 60 different companies over 13 years provides him with a measured perspective and industry and key opinion leader contacts help to inform his view.

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

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Investment Rating System:
Outperform: Expect the total return of the stock to outperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.
Neutral: Expect the total return of the stock to perform in-line with the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.
Underperform: Expect the total return of the stock to underperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.

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

Rating Distribution (as of March 31, 2013)	**Investment Banking Relationships (as of March 31, 2013)**
Outperform:51% Neutral: 44% Underperform: 5%	Outperform:18% Neutral: 2% Underperform: 0%

The Distribution of Ratings is required by FINRA rules; however, WS' stock ratings of Outperform, Neutral, and Underperform most closely conform to Buy, Hold, and Sell, respectively. Please note, however, the definitions are not the same as WS' stock ratings are on a relative basis.

The analysts responsible for preparing research reports do not receive compensation based on specific investment banking activity. The analysts receive compensation that is based upon various factors including WS' total revenues, a portion of which are generated by WS' investment banking activities.

Wedbush Equity Research Disclosures as of June 26, 2013

Company	Disclosure
Epizyme	1,3,5,7
Pharmacyclics	1,5,6,7,10

Research Disclosure Legend
1. WS makes a market in the securities of the subject company.
2. WS managed a public offering of securities within the last 12 months.
3. WS co-managed a public offering of securities within the last 12 months.
4. WS has received compensation for investment banking services within the last 12 months.
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10. The research analyst, a member of the research analyst's household, any associate of the research analyst, or any individual directly involved in the preparation of this report has a long position in the common stocks.
11. WS or one of its affiliates beneficially own 1% or more of the common equity securities.
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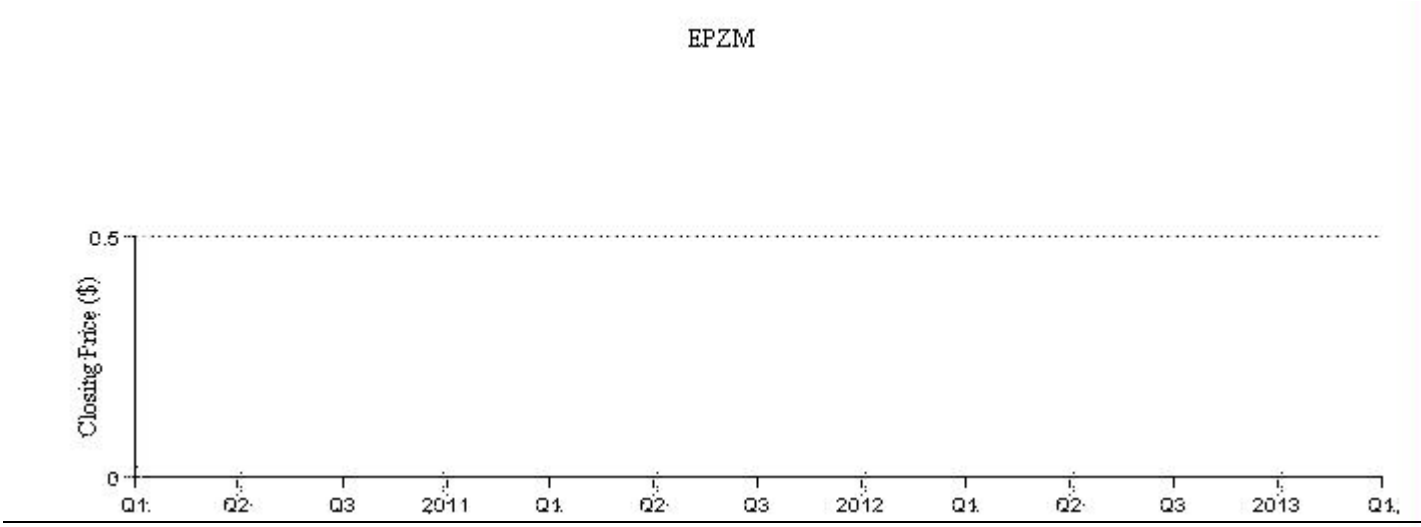
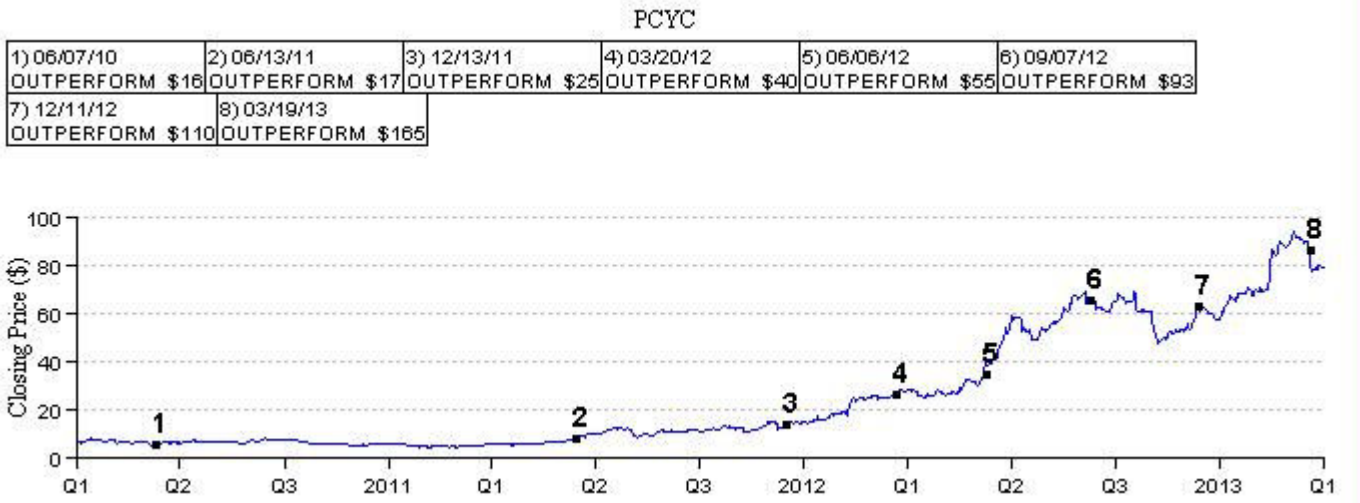
Wedbush disclosure price charts are updated within the first fifteen days of each new calendar quarter per FINRA regulations. Price charts for companies initiated upon in the current quarter, and rating and target price changes occurring in the current quarter, will not be displayed until the following quarter. Additional information on recommended securities is available on request.





* WS changed its rating system from (Strong Buy/Buy/Hold/Sell) to (Outperform/ Neutral/Underperform) on July 14, 2009.
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CORPORATE HEADQUARTERS (213) 688-8000

Gregory R. Wade, Ph.D. (415) 274-6863

WEDBUSH

EQUITY RESEARCH DEPARTMENT

(213) 688-4529

DIRECTOR OF RESEARCH
Mark D. Benson (213) 688-4435

MANAGER, RESEARCH OPERATIONS
Ellen Kang (213) 688-4529

RETAIL AND CONSUMER

Consumer Products
Rommel T. Dionisio (212) 938-9934
Kurt M. Frederick, CFA CPA (415) 274-6822

Footwear, Apparel and Accessories
Corinna Freedman (212) 668-9876
Alicia Reese (212) 938-9927

Healthy Lifestyles
Kurt M. Frederick, CFA CPA (415) 274-6822

Restaurants
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John Garrett, CFA (213) 688-4523

Specialty Retail: Softlines
Betty Chen (415) 273-7328
Alex Pham (415) 273-7315

RETAIL/CONSUMER MARKET RESEARCH

Gabriella Santaniello (213) 688-4557

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Min Xu (212) 938-9925

Environmental Services / Building Products
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Christopher N. Marai, Ph.D. (415) 274-6861

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Semiconductors
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Ryan Jue, CFA (415) 263-6669

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Gregory R. Wade, Ph.D. (415) 274-6863
David M. Nierengarten, Ph.D. (415) 274-6862
Christopher N. Marai, Ph.D. (415) 274-6861

Emerging Pharmaceuticals
Liana Moussatos, Ph.D. (415) 263-6626
Richard Lau (415) 274-6851
Christopher N. Marai, Ph.D. (415) 274-6861

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