June 25, 2013

OUTPERFORM

Reason for report:

INITIATION

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HEALTHCARE EQUITY RESEARCH

EPIZYME, INC.

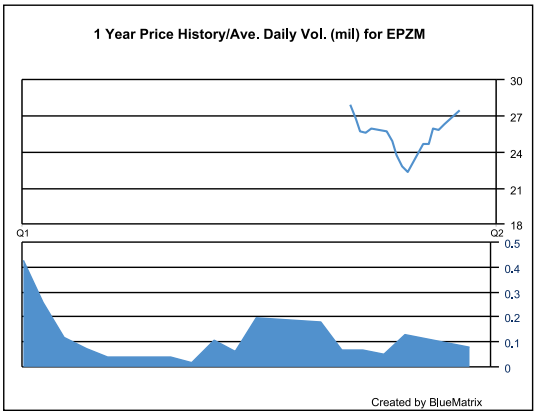
A Leader in Epigenetics - Initiate at Outperform

• **Bottom Line:** We are initiating coverage of EPZM with an Outperform rating and $34 12-month price target. EPZM is a clinical stage biotechnology company focused on epigenetic treatments for cancer and has a proprietary platform for developing inhibitors of histone methyltransferases (HMTs), an important class of enzymes that control gene expression and is associated with tumorgenesis.

• **Epigenetics represents an important new direction for new cancer treatment and EPZM's has a leading platform for development of HMT inhibitors.** The historical approach of targeting individual signaling pathways has often yielded modest efficacy, except in limited circumstances. This has resulted in the pursuit of alternative strategies such as epigenetics, which is supported by impressive survival benefit in a currently marketed epigenetic drug as well as recent findings linking mutations affecting the epigenetic complexes and cancer. HMTs have emerged as an attractive class of epigenetic targets due to both mutational evidence and drug-ability. EPZM scientists characterized the 96 members of the class, and EPZM has a leading intellectual property position in this area. EPZM has prioritized 20 HMTs for development and currently has 23 HMTs in screen today. The strong partnerships signed with CELG (OP), GSK (MP) and Eisai provide validation of this platform, which we believe is a valuable asset and could provide a sustainable engine for new compounds.

• **Two clinical programs could potentially generate proof of principle data in the next 12 months.** EPZ-5676 is a DOT1L inhibitor for the treatment of MLL-r, a subtype of leukemias with particularly poor prognosis. Pre-clinical models have demonstrated tumor eradication, without re-growth, post washout of the drug. Biological activity was seen in the 1st MLL-r patient dosed in the Phase I dose escalation, with a decrease in blast counts prior to CNS relapse. Though the agent is administered through a continuous IV infusion, our conversation with MEDACorp key opinion leaders (KOLs) suggest that the unmet medical need is high and if the agent is effective, dosing will not be a problem. Early efficacy data from the trial will be available in the 2H:13. EPZ-6438 is an orally dosed inhibitor of EZH2, which is implicated in the development of lymphomas as well as major solid tumors. Preclinical models by both EPZM and GSK have demonstrated the efficacy of EZH2 inhibition in lymphomas, with lack of tumor re-growth, post cessation of dosing. Phase I dosing has recently begun, and an early assessment of efficacy will be available in 1H:14.

Key Stats:	**(NASDAQ:EPZM)**
S&P 600 Health Care Index:	**988.12**
Price:	**$27.55**
Price Target:	$34.00
Methodology:	DCF with 11% discount rate
52 Week High:	$30.86
52 Week Low:	$15.00
Shares Outstanding (mil):	28.4
Market Capitalization (mil):	782.4
Book Value/Share:	0.00
Cash Per Share:	$5.34
Dividend (ann):	$0.00
Dividend Yield:	0.0%



Dec Yr	1Q	2Q	3Q	4Q	FY Rev	1Q	2Q	3Q	4Q	FY EPS	P/E
2012A	--	--	--	--	$45.2	--	--	--	--	(0.72)	NM
2013E	$8.9A	$13.0	$9.0	$10.0	$40.9	(4.27)A	(2.80)	(0.27)	(0.24)	(7.59)	NM
2014E	--	--	--	--	$60.0	--	--	--	--	(0.60)	NM
2015E	--	--	--	--	$35.0	--	--	--	--	(1.47)	NM

Source: Company Information and Leerink Swann LLC Research
Revenues in $MM
GAAP EPS

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The Healthcare Investment Bank™

Epizyme – Initiation of Coverage

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Epizyme Overview

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- EPZM is a platform-based epigenetics company with first in class in development for protein methyltransferase inhibitor for genetically defined tumors (MLL-r and EZH2) and is associated with tumorgenesis.
  - EPZM has 12 more targets in pre-clinical development
- Impressive partnerships signed at the pre-clinical stage with 2 companies familiar with the epigenetics field (CELG and Eisai)
- Marquee pure play epigenetics company

Investment Thesis

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- We are initiating coverage of EPZM with an Outperform rating and $34 12-month price target. EPZM is a clinical stage biotechnology company focused on epigenetic treatments for cancer and has a proprietary platform for developing inhibitors of histone methyltransferases (HMTs), an important class of enzymes that controls gene expression.

- Epigenetics represents an important new direction for new cancer treatment and EPZM's has a leading platform for development of HMT inhibitors. The historical approach of targeting individual signaling pathways has often yielded modest efficacy except in limited circumstances. This has resulted in pursuit of alternative strategies such as epigenetics which is supported by impressive survival benefit in a currently marketed epigenetic drug as well as recent findings linking mutations affecting the epigenetic complexes and cancer. HMTs have emerged as an attractive class of epigenetic targets due to both mutational evidence and drug-ability. EPZM scientists characterized the 96 members of the class, and it has a leading intellectual property position in this area. EPZM has prioritized 20 HMTs for development and currently has 23 HMTs in screen today. The strong partnerships signed with CELG, GSK and Eisai provide validation of this platform.

Investment Thesis (Cont.)

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- Two clinical programs could potentially generate proof of principle data in the next 12 months. EPZ-5676 is a DOT1L inhibitor for the treatment of MLL-r, a subtype of leukemias with particularly poor prognosis. Pre-clinical models have demonstrated tumor eradication, without re-growth, post washout of the drug. Biological activity was seen in the 1st MLL-r patient dosed in the Phase I dose escalation, with a decrease in blast counts prior to CNS relapse. Though the agent is administered through a continuous IV infusion, our conversation with MEDACorp key opinion leaders (KOLs) suggest that the unmet medical need is high and if the agent is effective, dosing will not be a problem. Early efficacy data from the trial will be available in the 2H:13. EPZ-6438 is an orally dosed inhibitor of EZH2, which is implicated in the development of lymphomas as well as major solid tumors. Preclinical models by both EPZM and GSK have demonstrated the efficacy of EZH2 inhibition in lymphomas, with lack of tumor re-growth, post cessation of dosing. Phase I dosing has recently begun, and an early assessment of efficacy will be available in 1H:14.

Valuation

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- Our valuation on EPZM is $34 a share based on a DCF for EPZ-5676 and EPZ-6438 with an 11% discount rate. We believe this discount rate is appropriate as we use probability weighted sales for the products. We also include $60M of cash at the end of 2014 and $300M in technology value.

Risks to Valuation

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- Pre-clinical models may not accurately predict for clinical benefit
- Human safety and efficacy of EPZ-5676 or EPZ-6438 are unknown due to early stage of development. Dosing of EPZ-5676 (continuous infusion) is not optimal and human dosing requirement of EPZ-6438 remains to be determined.
- Competition from GSK or other companies focused on these targets could negatively impact EPZM's revenues
- Competition from other agents for MLL-r or other hematological malignancies could limit the revenues of EPZM's products
- Commercial uptake may be limited by reimbursement, access or dosing concerns for EPZ-5676 and EPZ-6438

Broad Discovery Platform Behind Lead Candidates Targeting DOT1Li and EZH2i

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Compound	Target	Phase	Partner
EPZ-5676	DOT1L inhibitor	I	CELG
EPZ-6438	EZH2 Inhibitor	I	Eisai
GSK targets	Undisclosed	Pre-clinical	GSK
Platform	Various - 23 HMT in screen today	Pre-clinical	

Source: Company Reports

Proof-of-Concept Data Over the Next 12-18 Months

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Timing	Event
2H 2013	Early assessment of therapeutic effects of EPZ-5676 in MLL-r leukemias
2H 2013	Initiate expansion cohort of EPZ-5676
1H 2014	Early assessment of therapeutic effects of EPZ-6438 for mutated EZH2 subtype of NHL
2014	Initiate Phase II clinical trial of EPZ-6438

Source: Company Reports

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EPIZYME HAS A LEADING PLATFORM IN EPIGENETICS -- A PROMISING AREA FOR CANCER DRUG DEVELOPMENT

What is Epigenetics?

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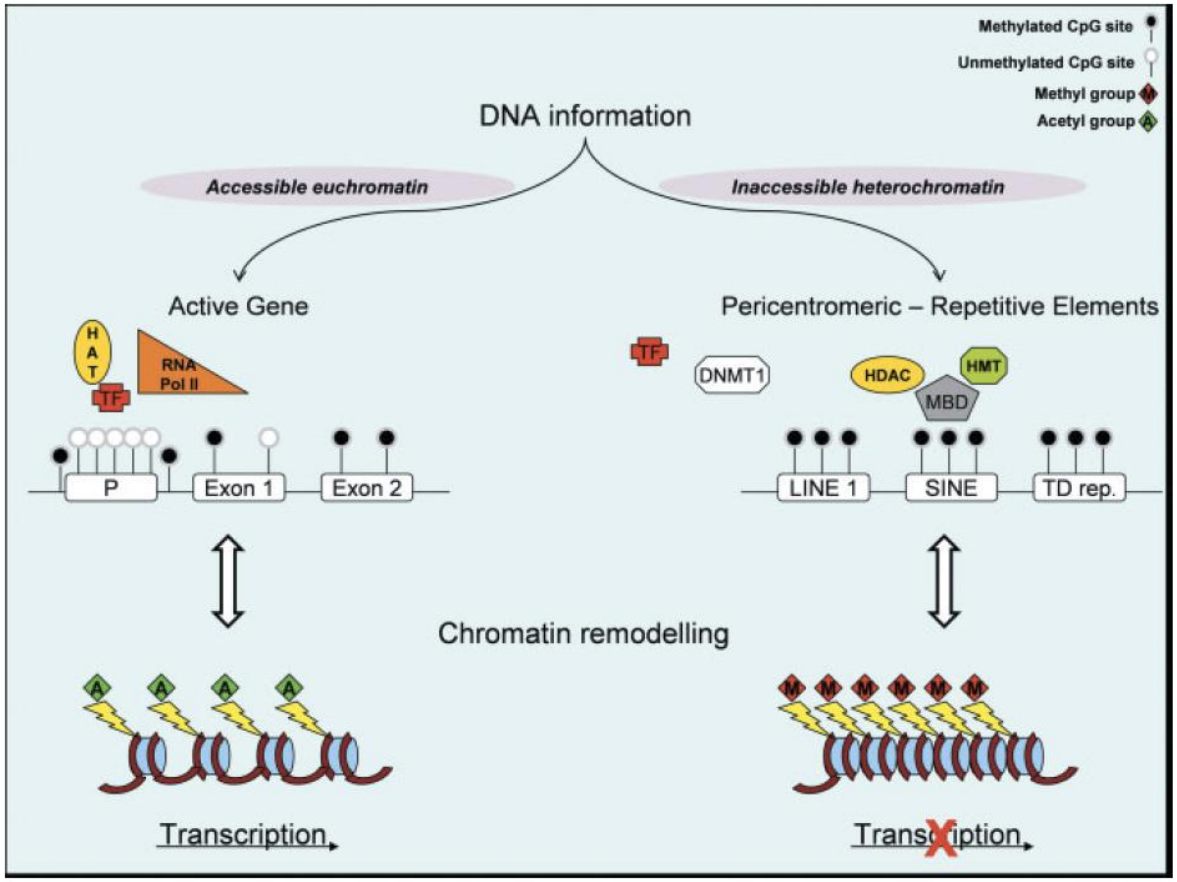
- Epigenetics is the alteration of gene expression with no underlying modification in the genetic sequence
  - A classic example is cellular differentiation. A single fertilized cell egg, changes into multiple cell types by activating some genes while inhibiting others
  - Examples of epigenetic modifications include DNA methylation and histone modification

DNA is Packaged In Nucelosomal Building Blocks that Determine its Accessibility to the Nuclear Environment and Transcriptional Status



- (*Left) Transcriptionally active genes are marked by methylation-free promoters and an open, highly acetylated* chromatin configuration that allows access to transcription factors and polymerase II (pol II).
- (*Right) Repetitive elements are silenced by high levels of DNA methylation,* specific histone lysine methylation, and a closed chromatin state.
- A switch from active to inactive chromatin characterizes some genes in cancer cells.

Source: Taby, Ca Cancer J Clinic Cancer 2010

HAT indicates histone acetyltransferase; TF, transcription factor; RNA pol II, RNA pol II; DNMT1, DNA methyltransferase 1; HDAC, histone deacetylase; MBD, methyl-CpG binding protein; HMT, histone methyltransferase; P, gene promoter; LINE 1, long interspersed nuclear element 1; SINE, short interspersed nuclear element; TD rep, tandem repeats.

Epigenetic Mechanisms Include DNA Methylation, Post-Translation Histone Modifications and Noncoding RNAs

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- DNA methylation
  - Covalent modification of the cytosine ring at the 5' position of the CpG dinucleotide. This process is catalyzed by DNA methyltransferases (DNMTs). CpG sites of high concentration are referred to as "CpG islands" (CGIs). DNA methylation at gene promoter CGIs has been correlated with permanent expression silencing such as that noted in the inactive X chromosome in women. DNA methylation leads to silencing by direct inhibition of transcription factor binding to their relative sites and by recruitment of methyl-binding domain proteins (MDBs). DNA methylation is used to silence expression of endogenous repeats and infecting retrotransposons, keeping them from disrupting normal gene expression.
- Post-translational histone modifications
- Noncoding RNAs

Source: Taby, Ca Cancer J Clin 2010

Epigenetic Mechanisms Include DNA Methylation, Post-Translation Histone Modifications and Noncoding RNAs (Cont.)

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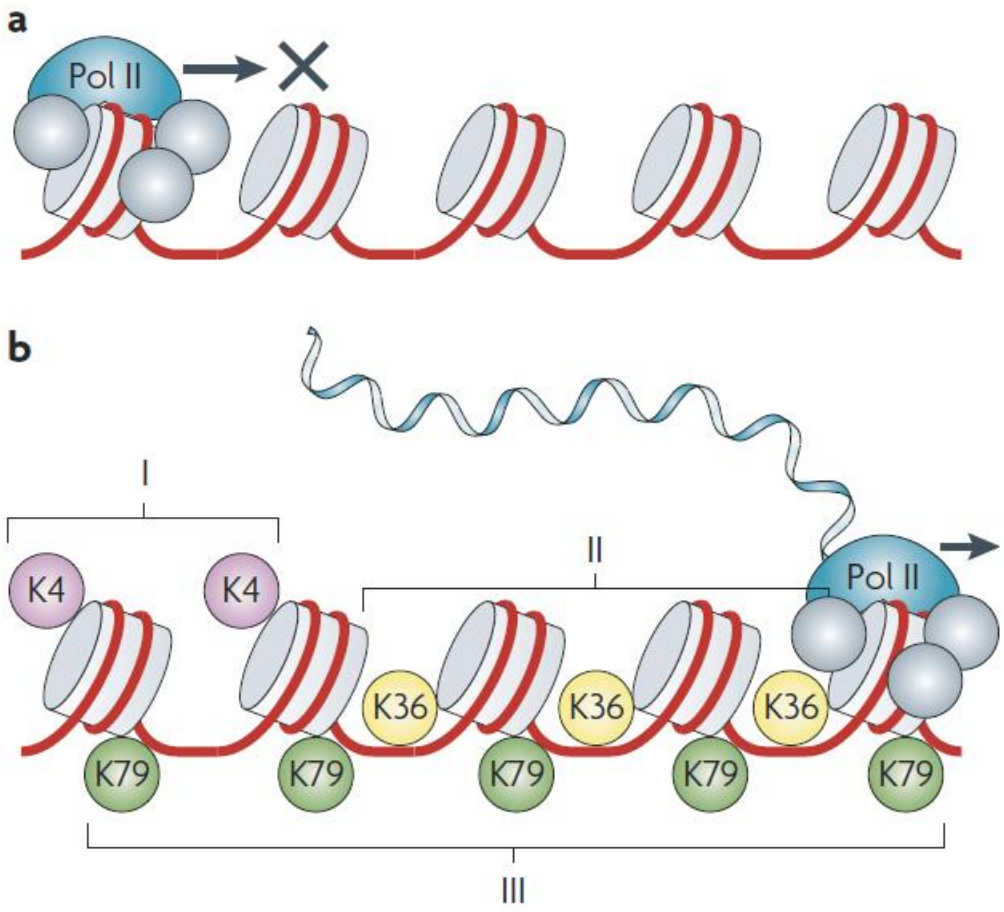
- Post-translational histone modifications
  - Histone modifications fine tune the way DNA is wrapped around chromatin. These modifications include acetylation, methylation, phosphorylation, ubiquitination, sumoylation and ADP ribosylation. Enzymes catalyzing these reactions include histone acetyltransferases, histone deacetylases, histone methyltransferases (HMT) and histone demthylases (HDMT)
  - Histone methylation is associated with transcriptional repression or activation depending on the specific amino acid affected
- Noncoding RNAs
  - Are complementary to the 3' untranslated region of messenger RNA, and lead to their degradation and subsequent inhibition of gene expression

Source: Taby, Ca Cancer J Clin 2010

DNA Transcription is Regulated by Unique Histone Marks on Chromatin



a) RNA polymerase II (Pol II) binds the promoter region of the gene but cannot proceed with transcription in the absence of specific methylation marks (represented by the “X”).

b) Unique histone marks can be found on different regions of a gene, and may impart unique activities.

- RNA transcription may be initiated when a promoter region (I) carries histone H3 lysine 4 (H3K4) methylation marks
- Transcription is extended when an open-reading frame region (II) carries a histone H3 lysine 36 (H3K36).
- Histone H3 lysine 79 (H3K79) methylation marks have a broad distribution across promoter and open reading frame regions (III).

Source: Krivtsov, Nature Review 2007

Epigenetic Aberrations Seen in Multiple Tumor Types

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Type of Cancer	Epigenetic Disruption
Colon cancer	CpG-island hypermethylation (*hMLH1*, *p16^{INK4a}*, *p14^{ARF}*, *RARB2*, *SFRP1*, and *WRN*), hypermethylation of miRNAs (*miR-124a*), global genomic hypomethylation, loss of imprinting of *IGF2*, mutations of histone modifiers (*EP300* and *HDAC2*), diminished monoacetylated and trimethylated forms of histone H4
Breast cancer	CpG-island hypermethylation (*BRCA1*, E-cadherin, *TMS1*, and estrogen receptor), global genomic hypomethylation
Lung cancer	CpG-island hypermethylation (*p16^{INK4a}*, *DAPK*, and *RASSF1A*), global genomic hypomethylation, genomic deletions of *CBP* and the chromatin-remodeling factor *BRG1*
Glioma	CpG-island hypermethylation (DNA-repair enzyme *MGMT*, *EMP3*, and *THBS1*)
Leukemia	CpG-island hypermethylation (*p15^{INK4b}*, *EXT1*, and *ID4*), translocations of histone modifiers (*CBP*, *MOZ*, *MORF*, *MLL1*, *MLL3*, and *NSD1*)
Lymphoma	CpG-island hypermethylation (*p16^{INK4a}*, *p73*, and DNA-repair enzyme *MGMT*), diminished monoacetylated and trimethylated forms of histone H4
Bladder cancer	CpG-island hypermethylation (*p16^{INK4a}* and *TPEF/HPP1*), hypermethylation of miRNAs (*miR-127*), global genomic hypomethylation
Kidney cancer	CpG-island hypermethylation (*VHL*), loss of imprinting of *IGF2*, global genomic hypomethylation
Prostate cancer	CpG-island hypermethylation (*GSTP1*), gene amplification of polycomb histone methyltransferase *EZH2*, aberrant modification pattern of histones H3 and H4
Esophageal cancer	CpG-island hypermethylation (*p16^{INK4b}* and *p14^{ARF}*), gene amplification of histone demethylase *JMJD2C/GASC1*
Stomach cancer	CpG-island hypermethylation (*hMLH1* and *p14^{ARF}*)
Liver cancer	CpG-island hypermethylation (*SOCS1* and *GSTP1*), global genomic hypomethylation
Ovarian cancer	CpG-island hypermethylation (*BRCA1*)

BRCA1 denotes breast-cancer susceptibility gene 1, BRG1 BRM/SWI2-related gene 1, CBP cyclic AMP response-element–binding protein (CREB)–binding protein, DAPK death-associated protein kinase, EMP3 epithelial membrane protein 3, EP300 E1A binding protein p300, EXT1 exostosin 1, EZH2 enhancer of zeste drosophila homologue 2, GSTP1 glutathione S-transferase 1, HDAC2 histone deacetylase 2, hMLH1 homologue of MutL Escherichia coli, ID4 inhibitor of DNA binding 4, IGF2 insulin-like growth factor 2, JMJD2C/GASC1 Jumonji domain-containing protein 2C, MGMT O6-methylguanine–DNA methyltransferase, MLL1 mixed-lineage leukemia 1, MLL3 mixed-lineage leukemia 3, MORF monocytic leukemia zinc finger protein–related factor, MOZ monocytic leukemia zinc finger, NSD1 nuclear receptor binding SETdomain protein 1, RARβ2 retinoic acid receptor β 2, RASSF1A ras association domain family protein 1, SFRP1 secreted frizzled-related protein 1, SOCS1 suppressor of cytokine signaling 1, THBS1 thrombospondin 1, TMS1 target of methylation- induced silencing 1, TPEF/HPP1 hyperplastic polyposis gene 1, VHL von Hippel–Lindau disease, and WRN Werner's syndrome.

Source: Esteller, NEJM 2008

The Methylation Processes Involves Modifications by "Writers," "Erasers," and "Readers"

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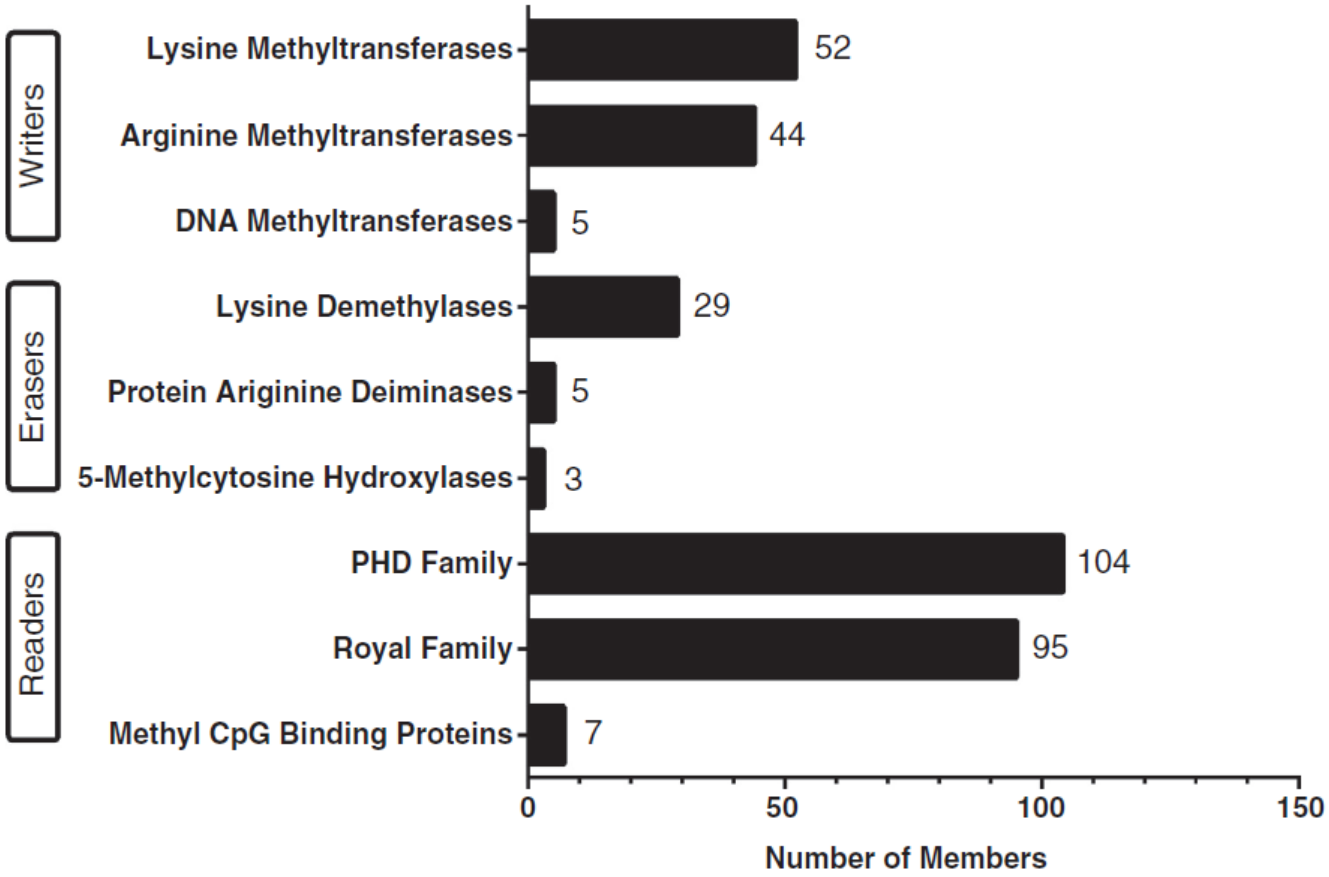
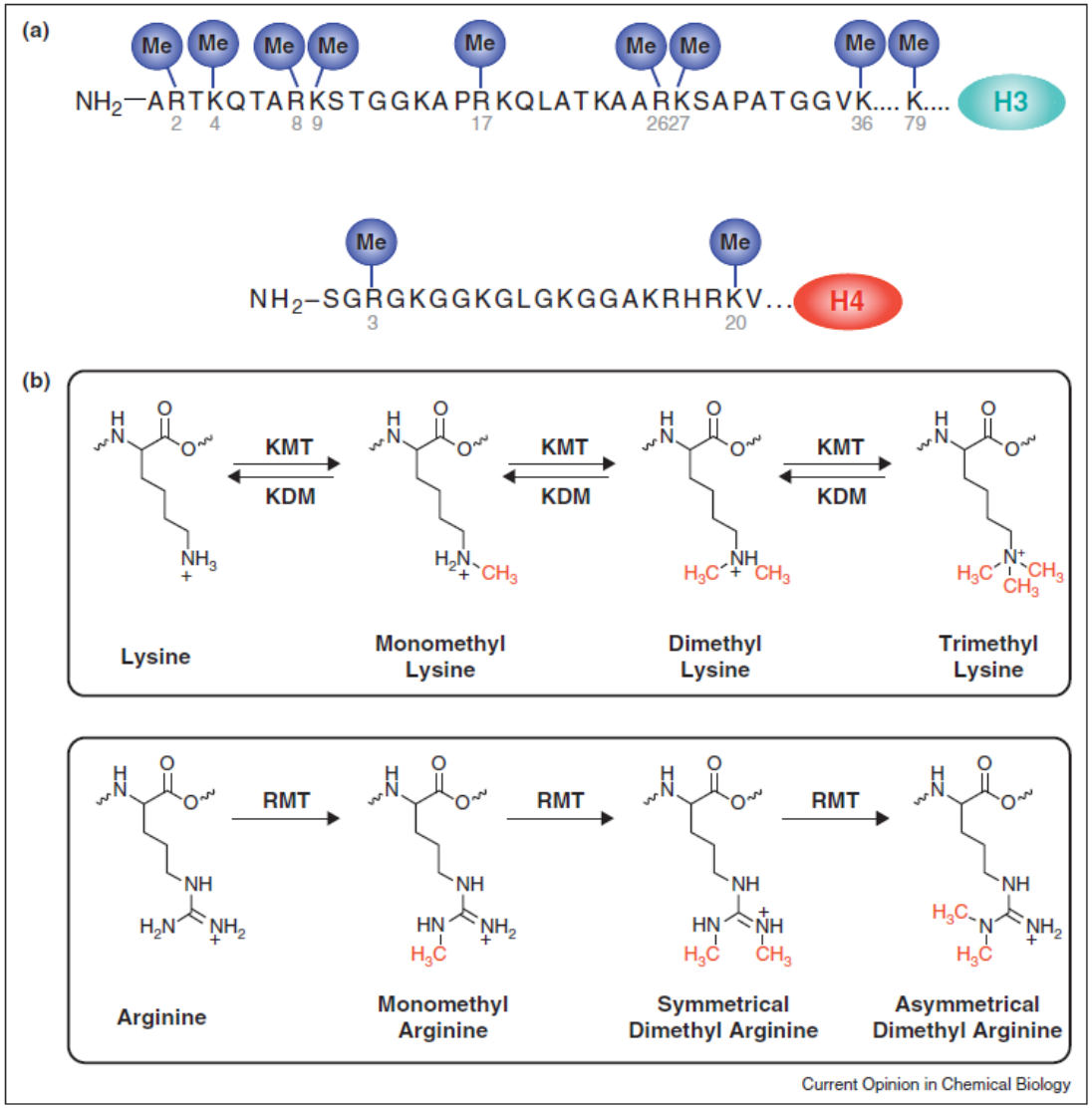
The writers, erasers and readers of the methylome tabulated by protein family within the human genome.



Source: Wigle, Current Opinion in Chemical Biology 2013

Overview of Protein Methylation



a) The location of histone H3 and H4 lysine and arginine methylation sites

b) The 8 potential methylation states of lysine and arginine

Source: Wigle, Current Opinion in Chemical Biology 2013

Genetic Alterations in Writers of the Methylome in Cancer

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Target	Genetic alteration	Disease
Writers		
EZH2	Heterozygous activating mutations occurring at Y641, A677 and A687 that result in hypertrimethylation of H3K27	Lymphoma
	Deletion of miR-101 leads to EZH2 overexpression	Prostate cancer
	Deletion of SNF5 leads to EZH2 dependency	Malignant rhabdoid tumors
DOT1L	11q23 chromosomal translocations fusing MLL1 (without its catalytic SET domain) to DOT1L binding partners such as AF4, AF9, AF-10 and ENL leading to abberant H3K79 methylation. Additionally, CALM-AF10 and SET-NUP214 fusions are known to mistarget DOT1L	Leukemia
NSD1	t(5;11)(q35;p15.5) translocation create NSD1-NUP98 fusions	Acute myeloid leukemia
WHSC1	t(4:14)(p16:q32) chromosomal translocations that places *WHSC1* gene under the control of the *IGH* promoter and results in the overexpression of WHSC1	Multiple myeloma
WHSC1L1	t(8;11)(p11.2;p15) chromosomal translocations fuses WHSC1L1 to NUP98	Acute myeloid leukemia
	8p11–12 focal amplifications	Breast cancer Squamous cell lung cancer
SETDB1	1q21 amplifications	Melanoma
SMYD2	1q32 amplifications	Esophageal squamous cell carcinoma

Source: Wigle, Current Opinion in Chemical Biology 2013

Genetic Alterations in Erasers and Readers of the Methylome in Cancer

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Target	Genetic alteration	Disease
Erasers		
JMJD2C	9p23-24 amplifications t(9;14)(9p24.1q32) translocations creating fusions to *IGH*	Esophageal squamous cell carcinoma Squamous cell lung cancer Medulloblastoma Basal breast cancer
LSD2	6p22 amplifications	Urothelial carcinomas
UTX	Inactivating mutations of UTX lead to pro-oncogenic hypertrimethylation of H3K27 and dependence on EZH2	Multiple blood and solid cancers
Readers		
JARID1A	t(11;21;12)(p15;p13;p13) translocations create fusions of JARID1A PHD domain and NUP98.	Acute myeloid leukemia
PHF23	t(11;17)(p15;13) translocations create fusions of PHF23 PHD domain to NUP98	Acute myeloid leukemia
PHF1	t(1;6)(p34;p21) translocation create MEAF6-PHF1 fusions may misdirect HAT activity towards PHF1 targets	Endometrial stromal sarcoma

Source: Wigle, Current Opinion in Chemical Biology 2013

Representative Genetic Alterations in Human Cancers Affecting the Enzymatic Function of Protein Methyltransferases

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Enzyme	Cancer	Alteration
PKMTs		
DOT1L	Mixed lineage leukemia	Recruited to ectopic sites by MLL translocation
EHMT2	Lung, prostate and hepatocellular carcinoma	Increased expression
EZH2	Non-Hodgkin lymphoma, breast, prostate, colon, gastric, bladder, liver and melanoma	Somatic mutations; amplification
MLL	Leukemia	Translocated
MLL4	Pancreatic, glioblastoma	Amplified
NSD1	Acute myeloid leukemia	Translocated
PRDM14	Breast cancer	Amplified; highly expressed
SMYD3	Breast, liver, colon and gastric cancers	Increased expression
SUV39H1	Colon cancer	Increased expression
WHSC1	Myeloma	Translocated; highly expressed
WHSC1L1	Lung, breast cancer	Amplified
PRMTs		
PRMT5	Lymphoma	Increased expression
CARM1	Breast and prostate cancers	Increased expression
Others		
UTX[a]	Myeloma	Loss-of-function mutation leading to increased H3K27me3

Source: Copeland, Drug Discovery Today 2012

Protein Methyltransferases are Attractive Drug Targets Due to Drug-ability and Association with Cancer Mutations

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Enzyme class	Number of putative human class members	Pros as drug targets	Cons as drug targets	Marketed drugs
Histone acetyltransferases	28	○Some alterations associated with disease ○Examples of small molecule inhibitors	○ No drug-like inhibitors reported ○ Challenging medicinal chemistry	None
Histone deacetylases	18	○ Precedent for potent small molecule inhibitors in clinical use ○ Validated target class for specific cancers	○ Small target class with overlapping biological functions ○ All known inhibitors act through metal chelation, making selectivity challenging ○ To date efficacy has been limited to small number of rare cancers ○ Competitive landscape is crowded with many companies working in this target class	Vorinostat Romidepsin
Protein methyltransferases PKMTs PRMTs	96 52 44	○ Large target class ○ Multiple examples of genetic alterations associated with cancer ○ Multiple examples of drug-like inhibitors	○ No clinical proof of concept to date ○ Few examples of selective SAM competitive inhibitors, especially for PKMTs	None
Lysine demethylases	26	○ Examples of genetic alteration in disease ○ Small molecule inhibitors reported	○ Iron or flavin dependence of catalysis; medicinal chemistry of active-site inhibitors therefore challenging ○ Unclear how much overlap of biological function exists among class members and with other iron-dependent proteins	None
Arginine deiminases	5	○ Disease association reported for some enzymes ○ Small molecule inhibitors reported	○ Small target class ○ Overlapping biological function of class members ○ No drug-like inhibitors reported	None
Kinases	17	○ Well established target class ○ Many examples of drugs in clinical use	○ No enzymes specific to chromatin modification ○ Unclear association with pathogenesis	None (for chromatin modifying kinases)
DNA methyltransferases	5	○ Precedent for potent small molecule inhibitors in clinical use ○ Validated target class for specific cancers	○ Small target class ○ To date efficacy seen in only small group of cancers	Dacogen Vidaza

Source: Copeland, Drug Discovery Today 2012

Select Small Molecule Protein Lysine Methyltransferases (PKMT) Inhibitors

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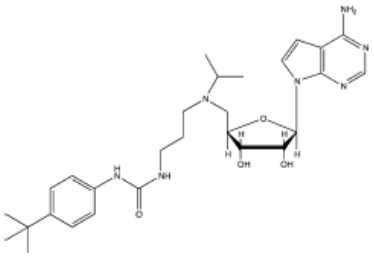
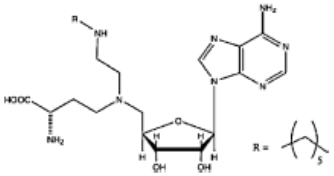
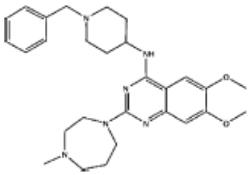
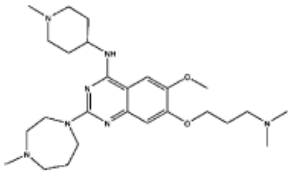
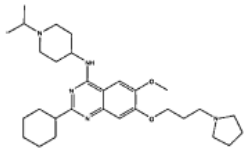
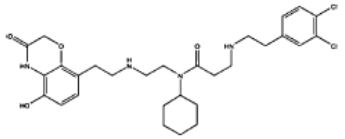
Compound	Structure	Potency and mode of binding	Cellular activity
PKMT inhibitors			
EPZ004777		DOT1L inhibitor, IC_{50} = 0.4 nM. Competitive with SAM	Compound selectively inhibits H3K79 methylation in various cells with IC_{50} < 1 μM and shows selective antiproliferative effects in MLL translocated cells with IC_{50} values between 0.17 and 6.47 μM
Tokyo Medical and Dental University compound 1c of Ref. [23]		SET7/9 inhibitor, IC_{50} = 10 μM Presumed to be competitive with SAM	No cellular activity reported
BIX-01294		Dual EHMT1/2 inhibitor with IC_{50}s of 34 and 133 nM, respectively. Uncompetititve with SAM	Reduced H3K9 me2 levels in MDA-MB231 cells with an IC_{50} of 500 nM. The EC_{50} for cellular toxicity was 2.8 μM
UNC-0224		Dual EHMT1/2 inhibitor with IC_{50}s of 50 and 43 nM, respectively. Noncompetitive with SAM	No cellular activity reported

Compound	Structure	Potency and mode of binding	Cellular activity
PKMT inhibitors			
UNC-0638		Dual EHMT1/2 inhibitor with IC_{50}s of 19 and <15 nM, respectively. Noncompetitive with SAM	Reduced H3K9 me2 levels in MDA-MB231 cells with an IC_{50} of 81 nM. The EC_{50} for cellular toxicity was 11.2 μM
AZ505		SMYD2 inhibitor, IC_{50} = 0.12 μM. Uncompetitive with SAM	No cellular activity reported

Source: Copeland, Drug Discovery Today 2012

Select Small Molecule Protein Arginine Methyltransferases (PRMT) Inhibitors

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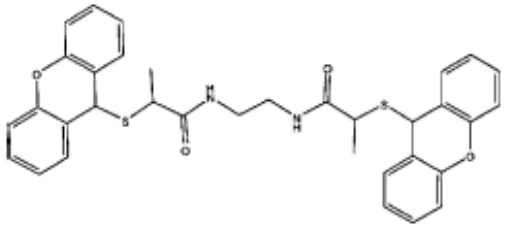
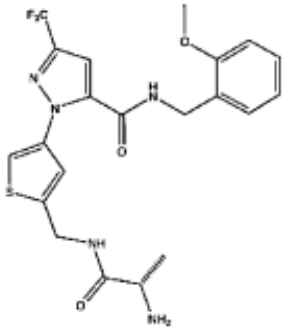
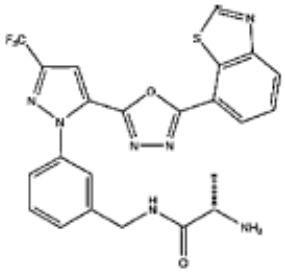
Compound	Structure	Potency and mode of binding	Cellular activity
PKMT inhibitors			
Compound 5 of Ref. [28]		PRMT1 inhibitor, IC_{50} = 55.4 μM. Presumed to be a bisubstrate inhibitor	IC_{50} for inhibition of cellular methylation in HepG2 cells = 150 μM
Methylgene compound 7a of Ref. [29]		CARM1 inhibitor, IC_{50} = 60 nM. Noncompetitive with SAM	No cellular activity reported
Bristol–Myers Squibb compound 7f of Ref. [30]		CARM1 inhibitor, IC_{50} = 40 nM. Noncompetitive with SAM	No cellular activity reported

Source: Copeland, Drug Discovery Today 2012

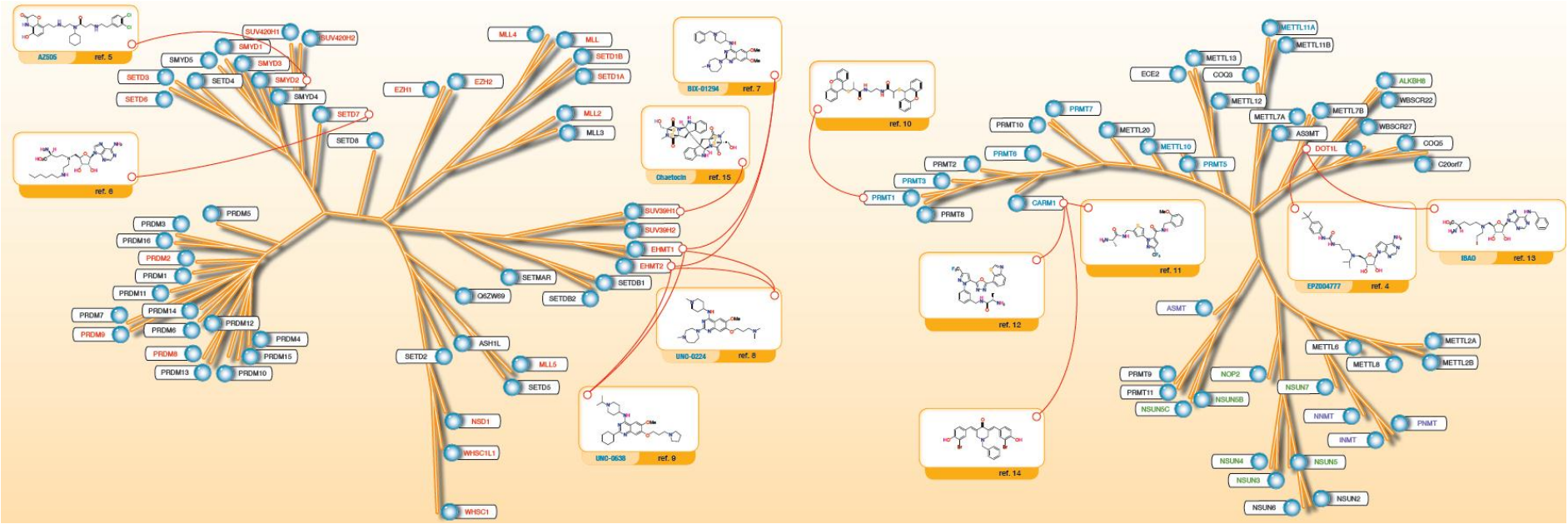
Epizyme Focused on the Large Class of HMTs as Targets to Treat Cancer

LEERINK SWANN

- Epizyme has a proprietary product platform used to create small molecule inhibitors of the 96-member class of enzymes known as histone methyltransferases (HMTs)
  - HMTs are part of the system of gene regulation, known as epigenetics that controls gene expression.
  - Gene alterations can result in changes in the activity of HMTs, making them oncogenic
- Epizyme scientists identified the comprehensive 96-member HMT target class (or HMTome) in 2011
  - 20 HMTs were prioritized for drug discovery based on their potential oncogenic role, clinical need in genetically defined cancers and regulatory pathways for related inhibitors

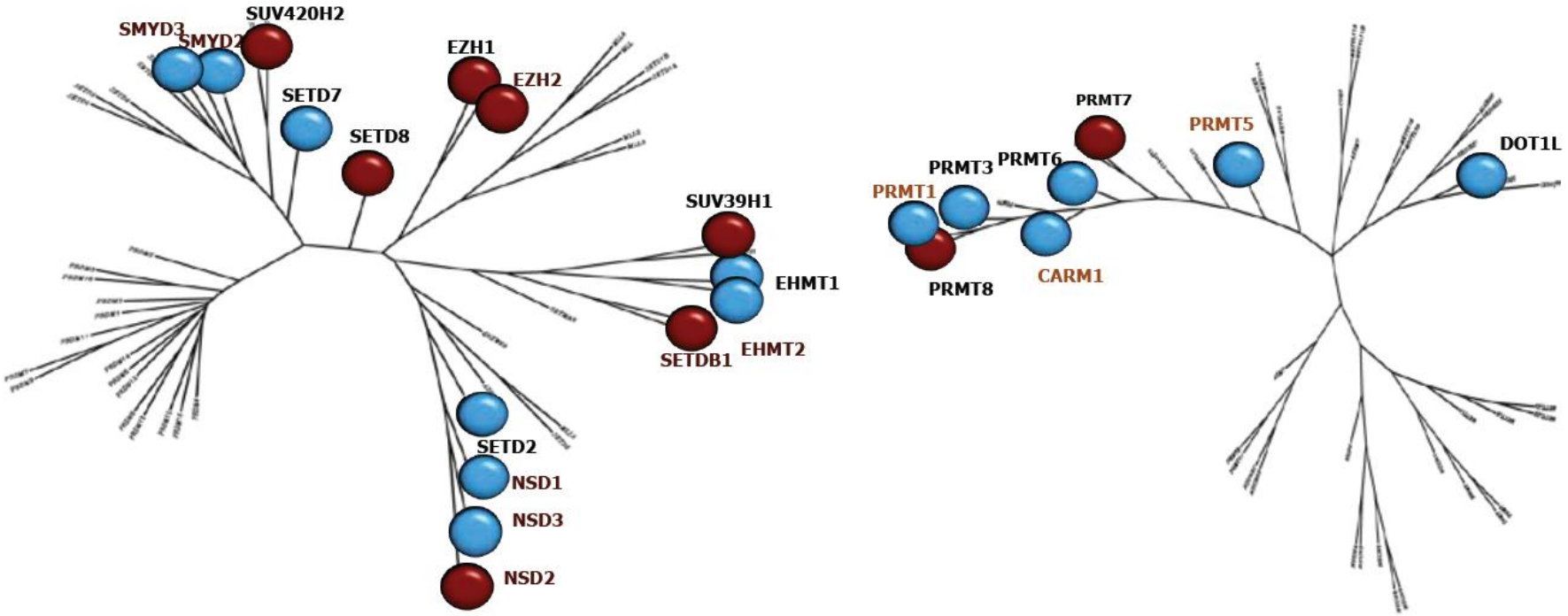
Source: Company Reports

The Human Protein Methyltransferases



Source: Nature Chemical Biology

Epizyme has >200 crystal structures for 14 HMTs



Structure Based Drug Design: Crystal Structures at Epizyme

Source: Company Reports

Epigenetic Competitors (Excluding Histone deacetylase inhibitor [HDAC] and DNA Methyltransferases)

LEERINK SWANN

- GSK, Novartis and Roche/Constellation are also developing epigenetic therapies for cancer
  - In January 2012 Constellation and Genentech (Roche) announced a 3-year collaboration on epigenetics
    - Constellation received $95M in upfront fees and committed R&D funding. Genentech was also given an option to acquire Constellation
    - Constellation is believed to be able to modulate more than one epigenetic target across different families
- PFE, NVS, GSK, LLY are partnered with the Structural Genomics Consortium in the Precompetitive Space

Source: Company Reports, Leerink Swann analysis

Epigenetic Competitors Cont. (Excluding HDAC and DNA methyltransferases)

LEERINK SWANN

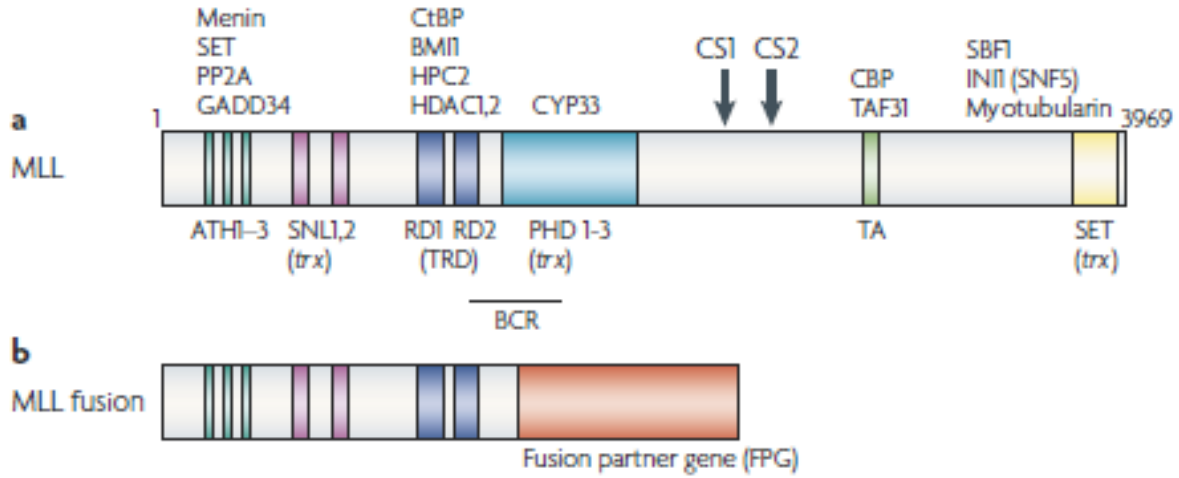
- CellCentric/Takeda signed a deal in February 2010 for an arginine methyltrasferase program
  - Overall deal could be worth >$200M including milestones and royalties.
- Cellzome was acquired by GSK in May 2012 for $99M.
  - GSK previously had signed an agreement in March 2010 to use Cellzome's technology to discover oral small molecules against the BET (bromodomain and extra-terminal) family of proteins and 3 undisclosed epigenetic targets to treat immuno-inflammatory disease
- EpiTherapeutics and ABBV entered a 3-year collaboration in December 2010 for epigenetic oncology targets. Terms were not disclosed.

Source: Company Reports, Leerink Swann analysis

LEERINK SWANN

EPZ-5676 (DOT1L INHIBITOR)

MLL-Rearrangements (MLL-r) Involve the MLL Gene Fused with a Partner Gene and is Constitutively Active due to Fusion with the Partner Gene



a) The mixed lineage leukemia (*MLL) gene is approximately 89 kb long, consists of 37 exons14,* and encodes a 3,969 amino acid nuclear protein with a complex domain structure (unique domains are highlighted). Proteins that bind to specific domains are noted above each domain.

b) Structure of MLL fusion proteins generated by *MLL translocations. A typical MLL* fusion protein contains the N terminus of MLL encoded by the first 8 to 13 exons and the C terminus of one of over 50 fusion partner genes (FPGs).

Source: Krivtsov, Nat Rev Cancer 2007

MLL Role in Normal Hematopoiesis

LEERINK SWANN

- MLL is involved in maintaining epigenetic transcriptional memory at hemeobox (Hox) gene loci
- The SET domain of MLL has histone methyltransferase activity and MLL forms a multi-component complex that specifically methylates lysine 4 on histone 3 (HEk4)
- Homozygous disruption of MLL in mice was lethal
- MLL deficient mice have fetal liver hematopoiesis and Hox gene expression, that was initiated but not maintained.
- Animals with a single normal MLL allele exhibit mild anemia and thrombocytopenia
- MLL is essential of hematopoietic stem cell development

Source: Zhang, Intl J Hematol 2012

The Incidence of MLL-r Partner Genes Varies by Age Group and Acute Lymphoblastic Leukemia (ALL) vs. Acute Myelogenous Leukemia (AML)

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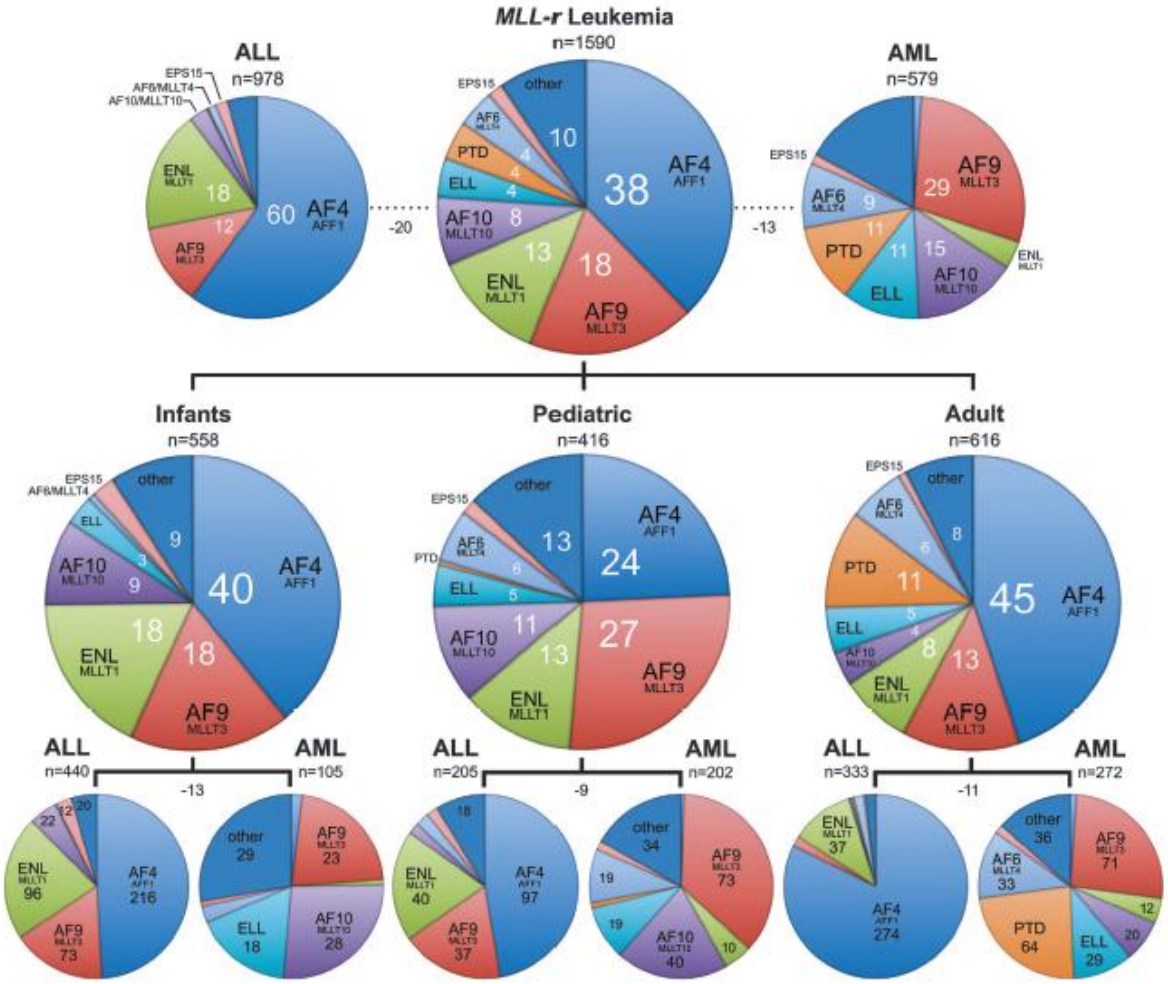

- MLL rearrangements are found in ~5% of ALL ~5-10% of AML and virtually all cases of mixed lineage MLL. It is also found in >70% of infant leukemias
- Fusion partner genes vary by the disease and include AF4 in ALL, AF9 in AML and ENL in both ALL and AML
- AF4 is the most common partner gene in infants and adults, and AF9 is also common in pediatric patients

Source: Krivtsov, Nat Rev Cancer 2007; Meyer, Leukemia 2013

Greater than 80% of MLL Partner Genes are Nuclear, Putative DNA-binding Proteins

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Classification of MLL Partner Genes

	Putative function	Chromosome	Fusion partner	Frequency in leukaemia
Group 1	Nuclear, putative DNA-binding proteins	4q21	*AF4*	>80% of *MLL* rearranged leukaemias
		9p23	*AF9*	
		19p13.3	*ENL*	
		10p12	*AF10*	
		19p13.1	*ELL*	
Group 2	Cytoplasm, presence of coiled-coil oligomerization domain	1q32	*EPS15*	>10%
		17p13	*GAS7*	
		19p13	*EEN*	
		6q27	*AF6*	
		Xq13	*AFX*	
Group 3	Cytoplasm, septin family, interact with cytoskeletal filaments, have a role in mitosis	Xq22	*SEPT2*	>1%
		22q11	*SEPT5*	
		Xq24	*SEPT6*	
		17q25	*SEPT9*	
		4q21	*SEPT11*	
Group 4	Nuclear, histone acetyltransferases	16q13	*CBP*	>1%
		22q13	*P300*	
Group 5	MLL partial tandem duplication of exons 5–11 (MLL–PTD)	11q23	N/A	4–7% of all AML with normal karyotype

AML, acute myeloid leukaemia; CBP, CREB binding protein; MLL, mixed lineage leukaemia; N/A, not applicable; PTD, partial tandem duplication.

Source: Krivtsov, Nat Rev Cancer 2007

MLL-rearrangement is a Common Abnormality of the 11q23 Chromosome, and is Associated with Poor Prognosis

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Prognosis of MLL Patients

Type of 11q23/MLL rearrangement	Adult AML	Adult ALL	Childhood AML	Childhood ALL
t(4;11) (q21;q23) (MLL-AF4)	–	poor	poor	poor
t(6;11) (q27;q23) (MLL-AF6)	poor	–	poor	–
t(9;11) (p23;q23) (MLL-AF9)	controversial (poor/intermediate)	–	controversial (good/intermediate)	poor
t(11;19) (q23;p13.1) (MLL-ELL)	poor	–	intermediate	–
t(11;19) (q23;p13.3) (MLL-ENL)	–	–	intermediate	poor (B-lineage) good (T-lineage)

Source: Tamai, J Clin Exp Hematopathol 2010

DOT1L-Mediated Histone H3K79 Methylation is a Driver of Oncogenesis in MLL-r Leukemia

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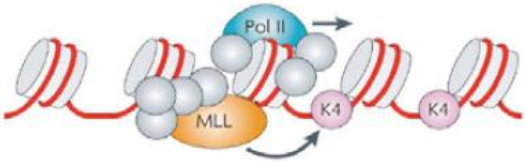
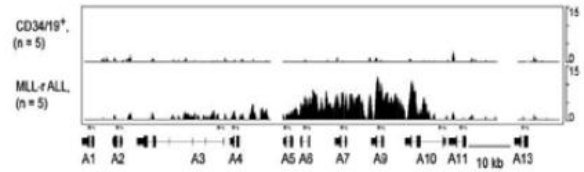
Normal

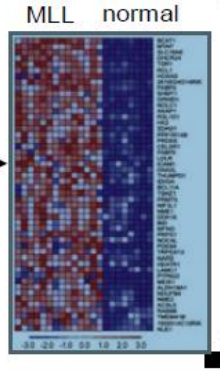


Normal H3K79 methylation



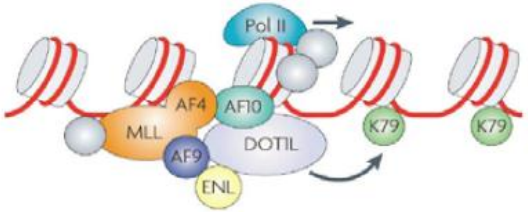
Normal gene expression

Differentiation



Leukemogenesis

MLL-Fusion

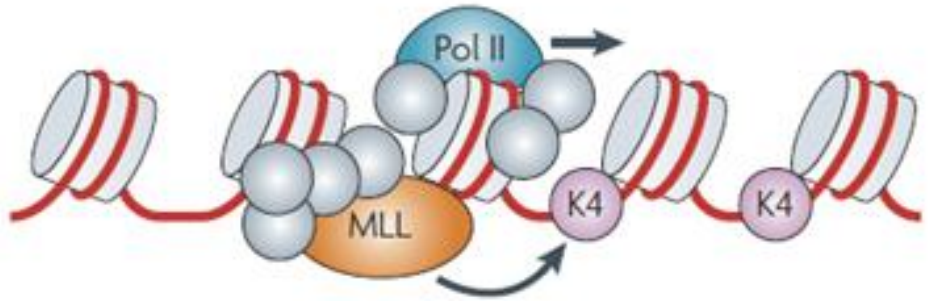


Aberrant H3K79 methylation

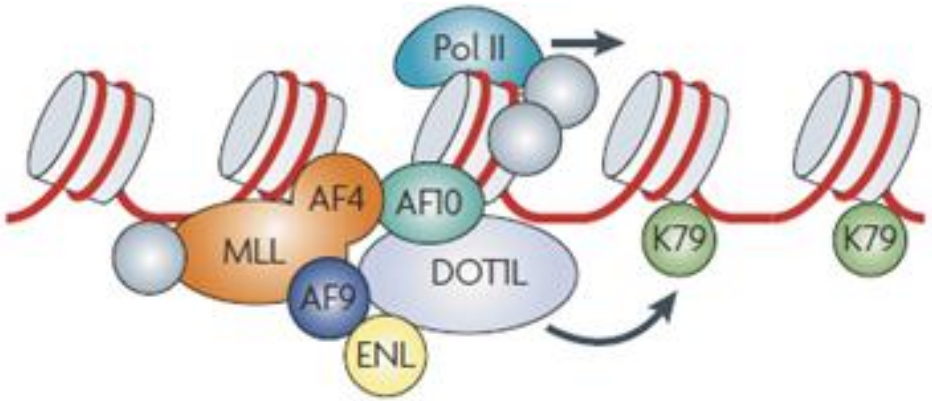
Aberrant gene activation (e.g. HOXA9, MEIS1)

Source: Pollock, ASH 2012

MLL-r Leukemias Recruit DOT1L to Promoters Normally Occupied by MLL leading to Aberrant Expression of Genes



Mixed lineage leukemia (MLL) is a member of a multiprotein complex that mediates methylation of H3K4 within the promoter region of genes occupied by RNA polymerase II. The diagram to the left depicts normal MLL function.



MLL fusion(s) that lack the SET (Su(var)3-9, enhancer-of-zeste, trithorax) domain H3K4 methyltransferase activity may recruit the H3K79 methyltransferase DOT1L. MLL-fusion-mediated recruitment of DOT1L to promoters normally occupied by MLL, (such as the HoxA cluster) allows H3K79 methylation of the HoxA cluster, which may lead to aberrant expression of HoxA cluster genes.

Source: Kritsov, Nature Reviews 2007

MLL-r Leukemias Depend on Chromatin Modifying Complexes such as the DOT1L Complex

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- MLL-r leukemia involves the MLL gene fused to one of at least 79 different partner genes, resulting in the formation of dominantly acting MLL fusion-oncoproteins
- Nuclear proteins such as AF4, AF9, ENL and ELL comprise the vast majority of MLL fusion partners
  - These are components of large, multi-subunit protein complexes that control gene expression
  - One of these complexes is the chromatin modifying DOT1L complex
- For MLL-r leukemias, the constitutive recruitment of these complexes is believed to facilitate sustained expression of MLL-target genes, resulting in leukemic transformation
  - Therefore, targeting DOT1L may allow for treatment of MLL-r leukemias

Source: Deshpande, Blood 2013; Meyer, Leukemia 2013

DOT1L May Be An Important Treatment Target for MLL-r Leukemias

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- The targeting of DOT1L, which is as part of the DOT1L complex recruited in MLL-r leukemia, may be an effective therapeutic strategy
- DOT1L is the only known enzyme to catalyze the methylation of histone 3 at lysine 79 (H3K79)
- Human MLL-r leukemia cells have demonstrated high levels of H3K79 methylation on the MLL fusion genes, suggesting a correlation for DOT1L effects in the disease

Source: Deshpande, Blood 2013

Preclinical Models Suggest a Therapeutic Window for DOT1L in MLL-r

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- MLL-AF9, a subtype of MLL-r, was found to be dependent on DOT1L in vitro and in vivo
  - MLL-AF9 expressed unique patterns of H3K79me2, and most genes did not have any change in expression after loss of DOT1L and H3K79 methylation in pre-clinical models, suggesting that treatment with a DOT1L inhibitor could have a therapeutic window with limited effect on normal cells
- Potential side effects of DOT1L inhibition that were seen from pre-clinical models include reduction in white and red blood cell counts
  - However, knockout mice are born with essentially normal body and organ weights
  - Mice 3-6 weeks of age were found to have DOT1L negative peripheral blood leukocytes, demonstrating that DOT1L is not absolutely required for all hematopoietic cells

Source: Bernt, Cancer Cell 2011

EPZ-5676 is Currently in Phase I

- Intravenously administered small molecule inhibitor of DOT1L
  - Being developed for the treatment of mixed-lineage leukemia rearrangement (MLL-r), an aggressive subtype of the two most common forms of acute leukemia:
    - Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)
- Most advanced product candidate of EPZM
- Currently in Phase I development
- EPZM has US rights, CELG has OUS rights to the compound

Source: Company Reports

EPZ-5676 Chemical Structure

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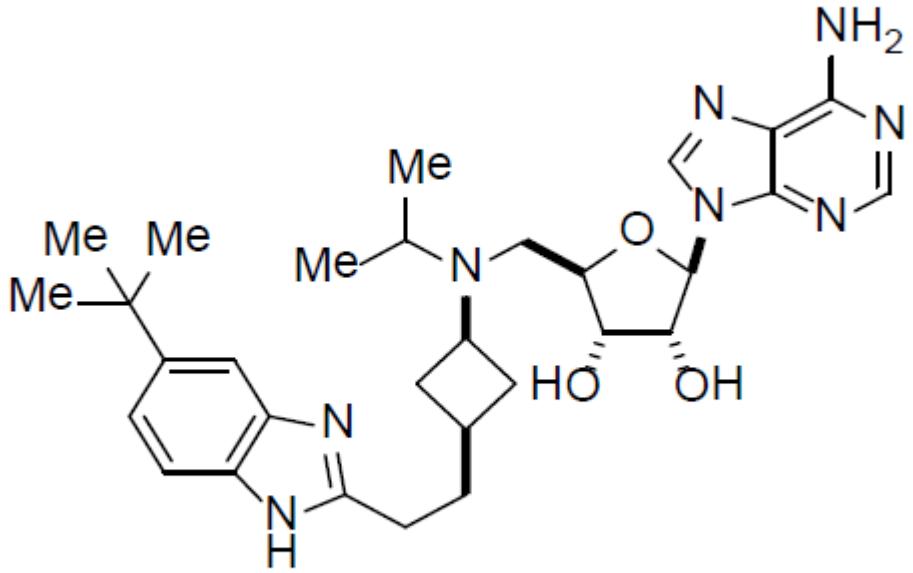
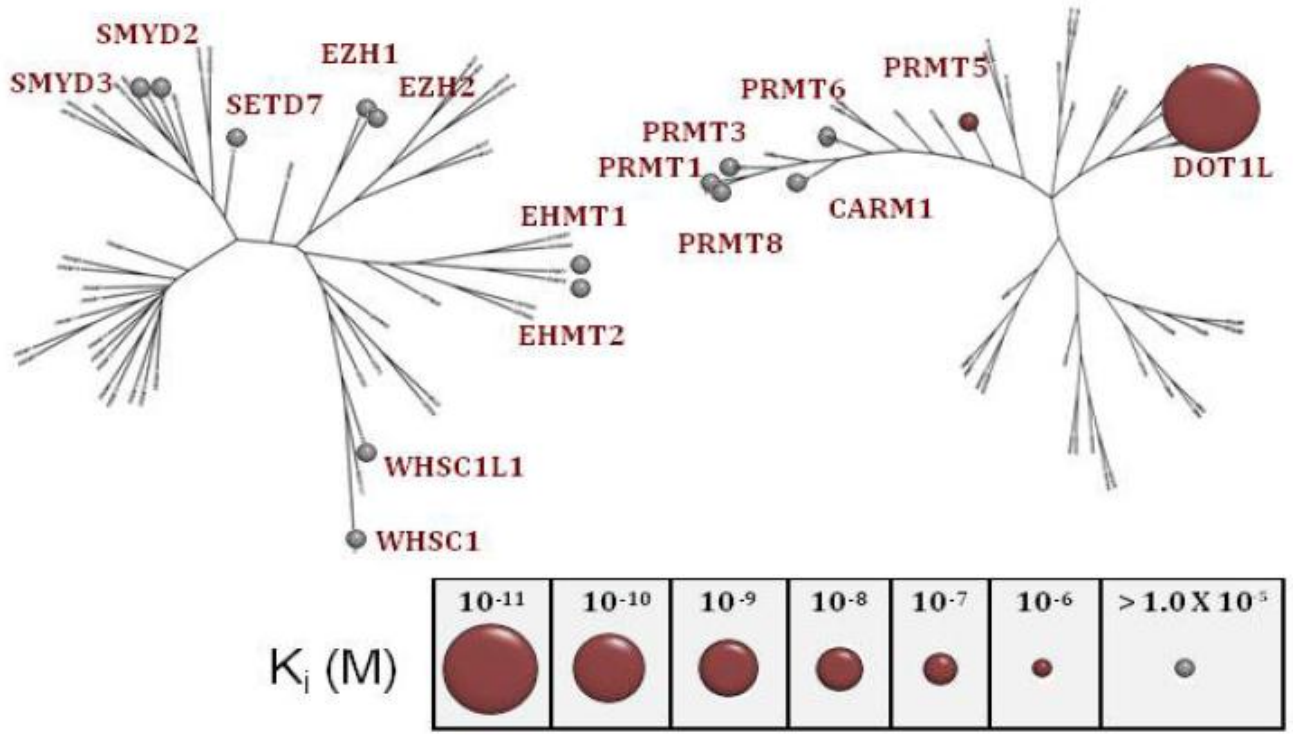
A



Chemical structure of EPZ-5676

Source: Pollack, ASH 2012

EPZ-5676 is Selective for DOT1L



Selectivity profile of EPZ-5676 inhibitory activity (K_i (M)) against representative members of the lysine (left) and arginine (right) enzyme families

Source: Pollack, ASH 2012

EPZ-5676 Continuous IV Infusion for 21 Days Demonstrated Potent Anti-Tumor Activity

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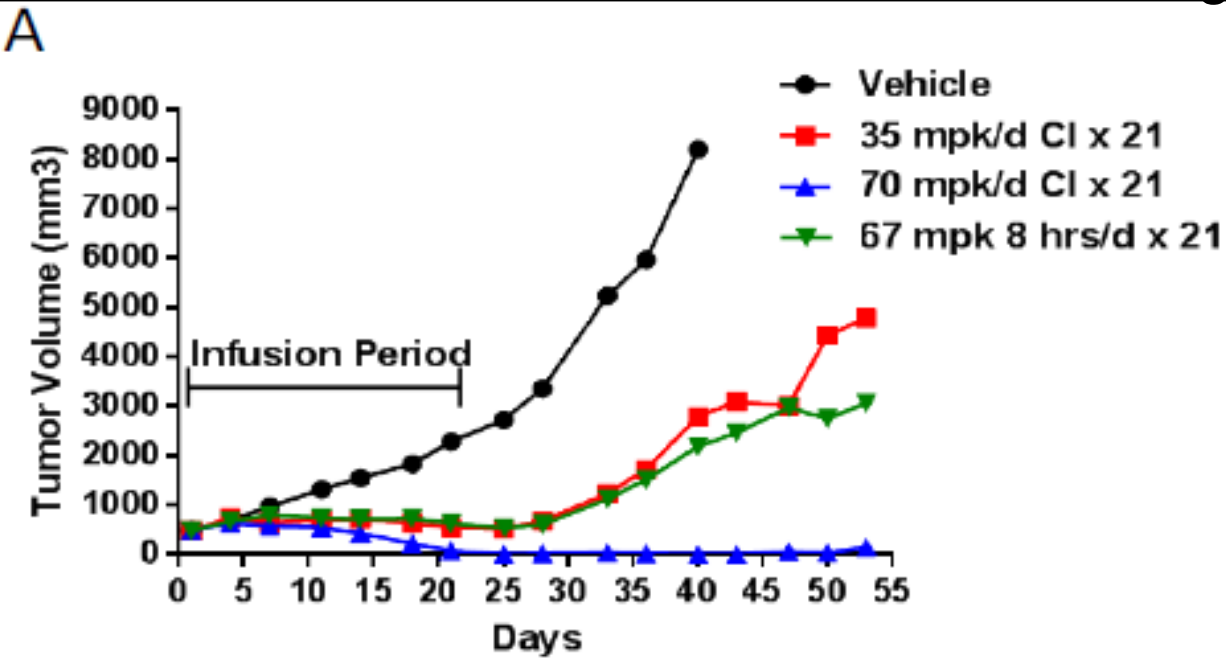
Effects of IV Infusion of EPZ-5676 in a MV4 Nude Rat Xenograft Model



- Continuous infusion at sufficiently high doses resulted on eradication of tumors without re-growth post-cessation of dosing.
- Intermittent dosing at a faster rate of infusion (8 hours per day) resulted in smaller tumor reductions than continuous infusion

Source: Pollack, ASH 2012

Continuous Dosing of EPZ-5676 Is Required for Maximal Efficacy

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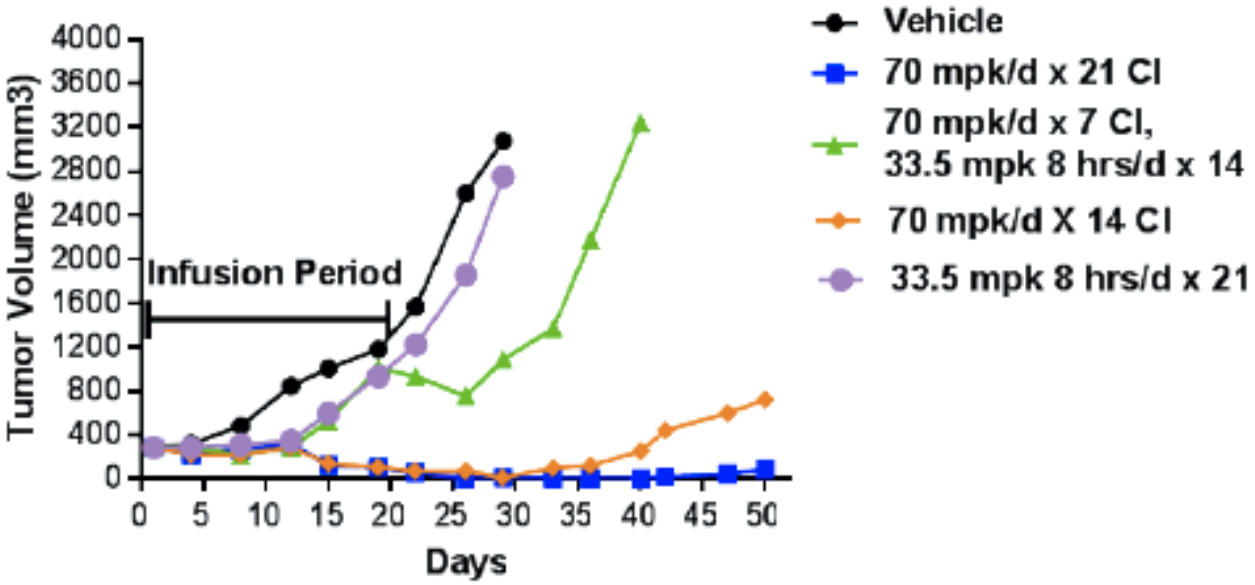
Effects of IV Infusion of EPZ-5676 in a MV4 Nude Rat Xenograft Model



- Continuous infusion at sufficiently high doses (70 mpk/d) resulted on eradication of tumors without re-growth post-cessation of dosing, but dosing for only 14 days resulted in tumor re-growth in ~2 weeks
- Induction continuous dosing, followed by intermittent dosing resulted in temporary reductions in tumor volume

Source: Pollack, ASH 2012

EPZ-5676 Resulted in Decreased H3K79me2 Levels for Xenograft Rats

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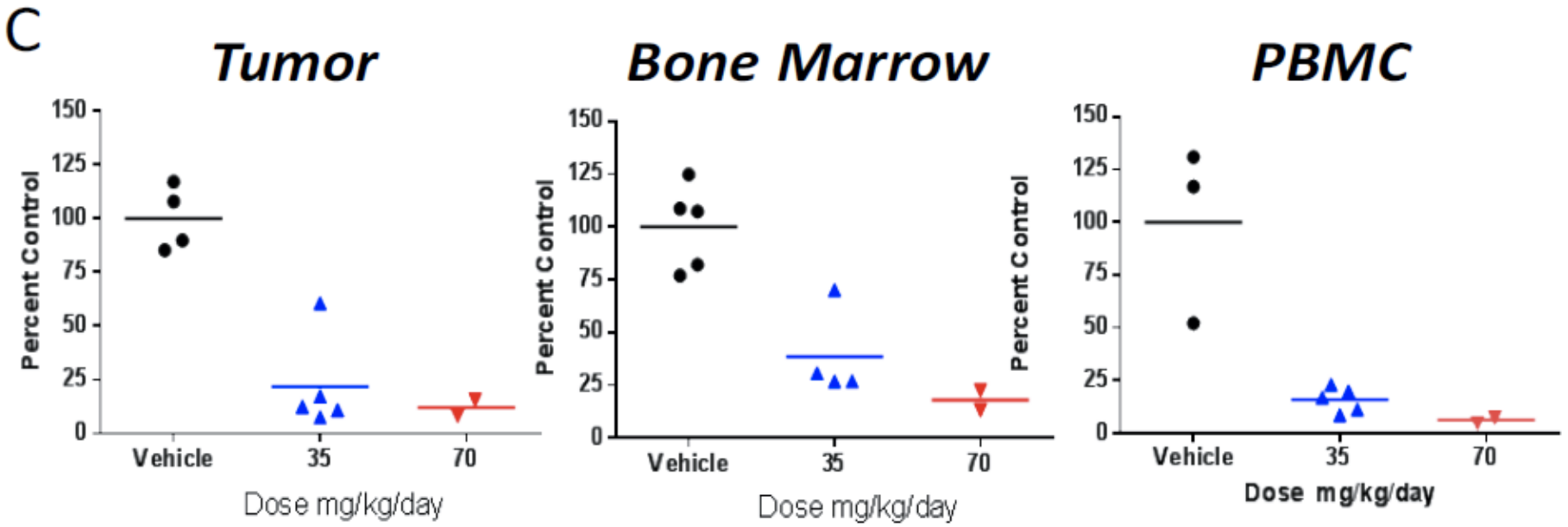
H3K79me2 Levels in Tumor, Bone Marrow and Peripheral Blood Mononuclear Cells (PBMC) from Rats Treated with EPZ-5676



- 70mg/k/day of EPZ-5676 resulted in very low levels of H3K79me2 in the tumor, bone marrow and PBMC. However, we only have two samples for this estimate; therefore it is difficult to discern the variability
- At 35mg/kg/day dosing, one of five tumor samples had a suboptimal response to EPZ-5676. We do not know the dosing schedule used in this data.

Source: Pollack, ASH 2012

EPZ-5676 Selectively Kills MLL-r Leukemic Cells *in vitro*

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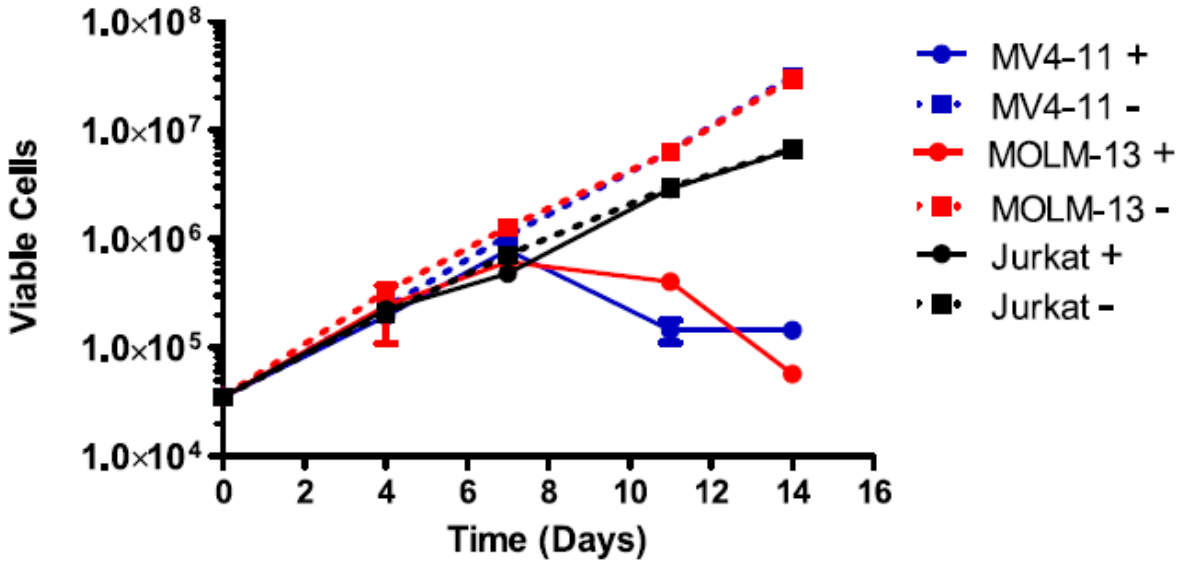
Growth of Cancer Cell Lines After Several Days Incubation with 3uM of EPZ004777



MLV4-11 cell lines simulate MLL-AF4, MOLM-13 simulates MLL-AF9 and Jurkat cell line is a non-MLL-r leukemic cell line

- There is a significant delay before the anti-proliferative effects of EPZ004777 became apparent; both MLL-rearranged cell lines continued to proliferate at a normal rate for several days after exposure to the inhibitor. This may reflect the time required to reverse fully the aberrant expression of MLL fusion target genes following DOT1L inhibition, a process that presumably involves depletion of methylated H3K79, followed by decreased mRNA expression and reduced levels of gene products critical for leukemogenic growth.

Source: Daigle, Cancer Cell 2011

EPZ-5676 Demonstrated Evidence of Biological Activity Consistent with the Mechanism of Action

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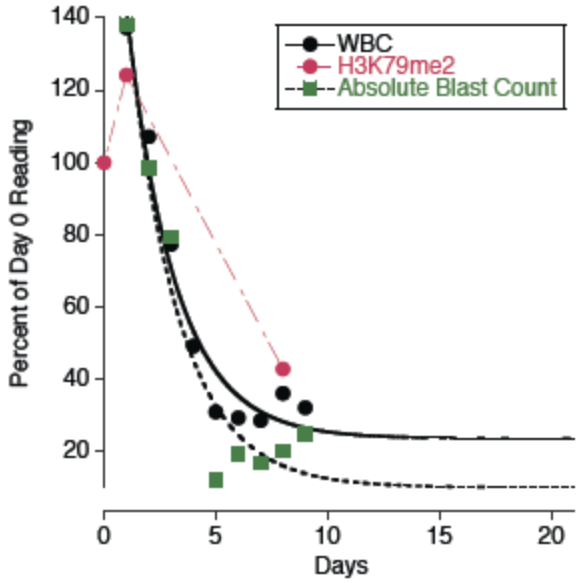
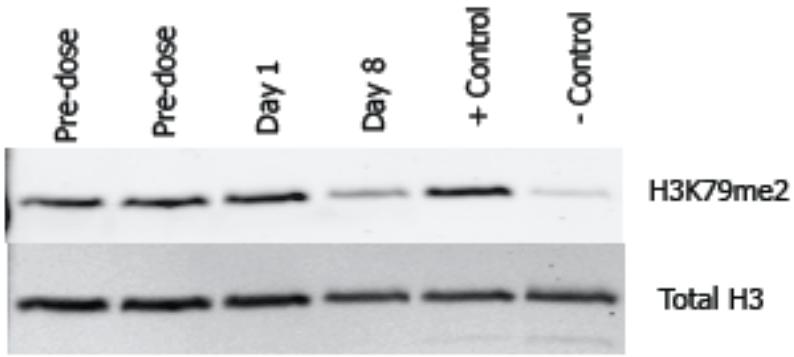
- The patient with evidence of drug effect, patient #2 was a 41-year old woman with mixed lineage leukemia t(4;11), which corresponds to MLL-AF4, who had relapsed post allogeneic transplant
  - Time course of response is reasonable given the mechanism of action of the drug, and similar to animal models where the drug requires a few days of dosing to see therapeutic effect
  - H3K79me2 levels in the PBMCs demonstrated that there was de-methylation occurring, consistent with the proposed mechanism of action of the drug

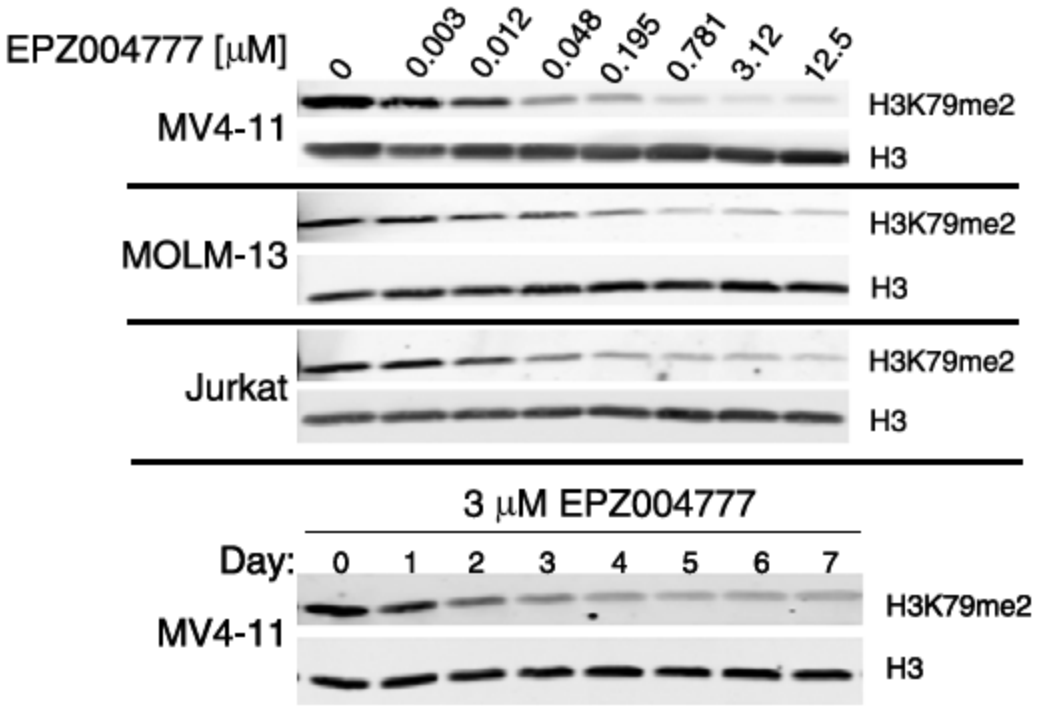




Source: Company Reports

PBMC = peripheral blood mononuclear cells

The Precursor Molecule to EPZ-5676 in Pre-clinical Models was Active Against the MLL-AF4 Fusion



- The MV4-11 cell line is designed to mimic the MLL-AF4 (the fusion protein seen with patient #2 in the Phase I)
- The time course of response (bottom panel) shows the time course of response with this agent. The drug does achieve full cellular depletion of H3K79me2 until days 4 or 5.

Source:Daigle, Cell 2011

PBMC = peripheral blood mononuclear cells

EPZ-5676 is Designed to Be More Potent than EPZ004777

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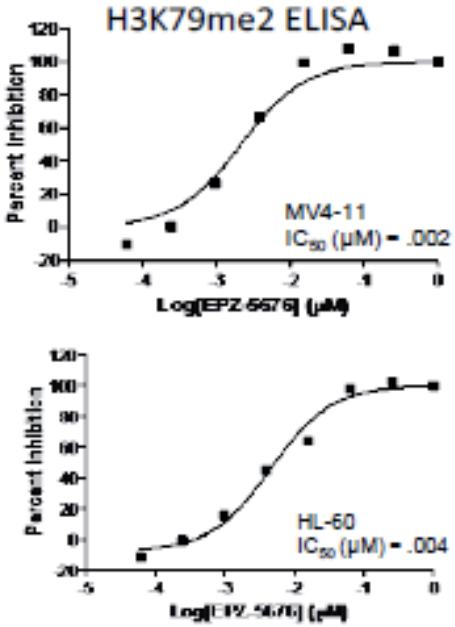
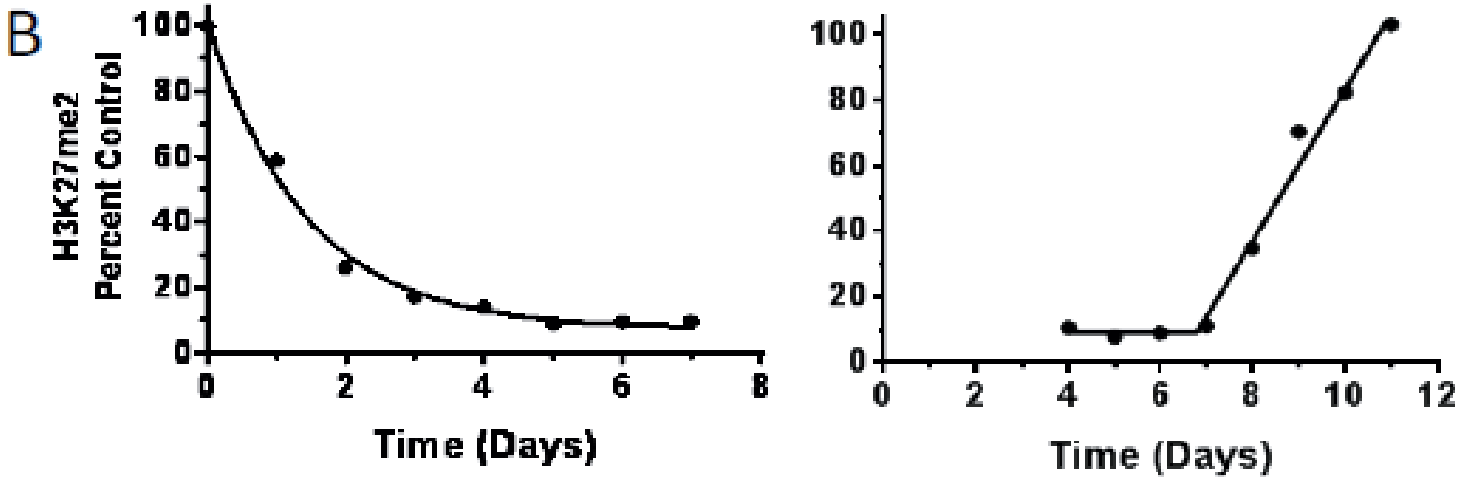
Property	EPZ-5676	EPZ004777
DOT1L inhibition K_i (nM)	0.08 ± 0.03	0.3 ± 0.02
Residence time (hr)	> 24	1
Fold selectivity	> 37,000	> 1,000
MV4-11 proliferation IC_{50} (nM)	3.5 ± 0.7	151 ± 42
H3K79me2 inhibition IC_{50} (nM)	2.7 ± 0.9	11 ± 4
HOXA9 inhibition IC_{50} (nM)	67 ± 27	691 ± 145
MEIS1 inhibition IC_{50} (nM)	53 ± 17	984 ± 234



- EPZ-5676 has improved efficacy and a wider therapeutic window than EPZ004777
- EPZ-5676 is selective for in reducing levels of methylated H3K79

Source: Daigle, Cell 2011; Polluck, ASH 2012

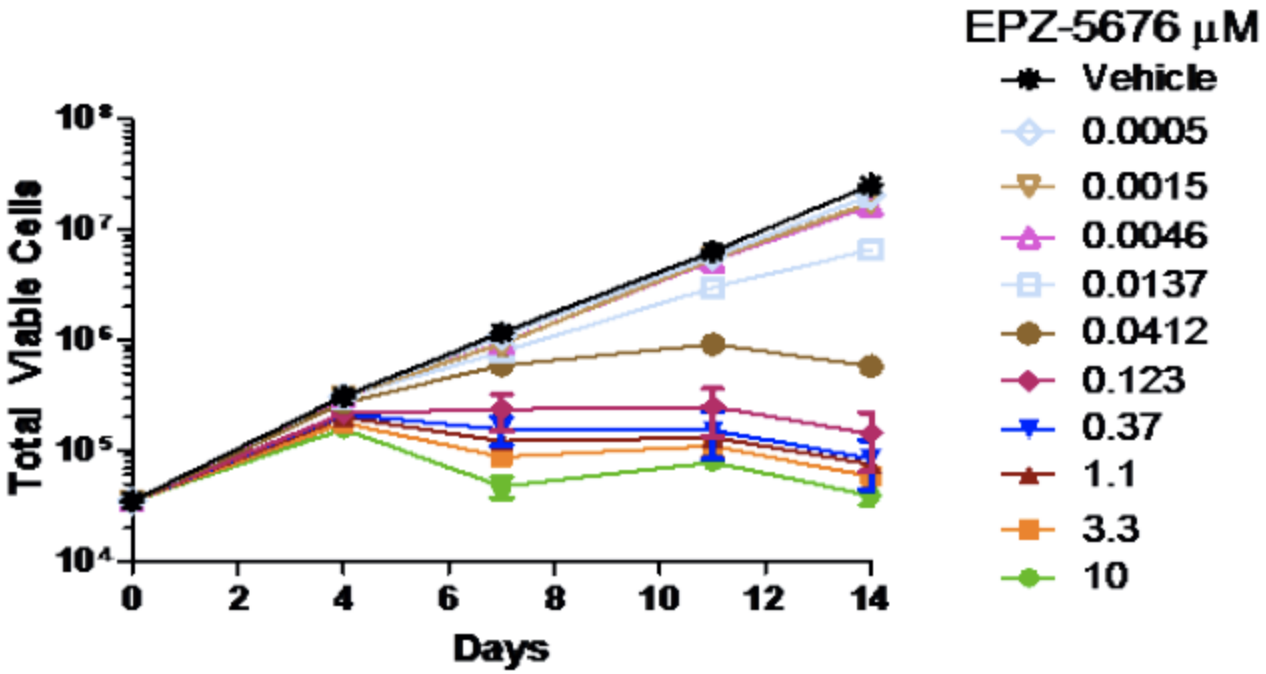
EPZ-5676 Depletes H3K79me2 in MV4-11 Cell Lines



- Depletion of H3K79me2 levels following administration of EPZ-5676 in MV4-11 cell lines (left panel)
- Recovery of H3K79me2 levels following wash out of EPZ-5676 (right panel)

Source: Polluck, ASH 2012

EPZ-5676 Is Effective in Inhibiting Tumor Cell Growth in MV4-11 Cell Lines



Inhibition of MV4-11 cell proliferation

- EPZ-5676 demonstrates dose dependent effects on tumor cell proliferation in MV4-11 cell lines
- Delayed effect of EPZ-5676, with continued cell growth for the first 4 days of dosing. This is consistent with the time course to achieve maximal reduction in H3K79me2 levels

Source: Polluck, ASH 2012

EPZ-5676 Demonstrates Activity Against a Number of MLL-r Cell Lines

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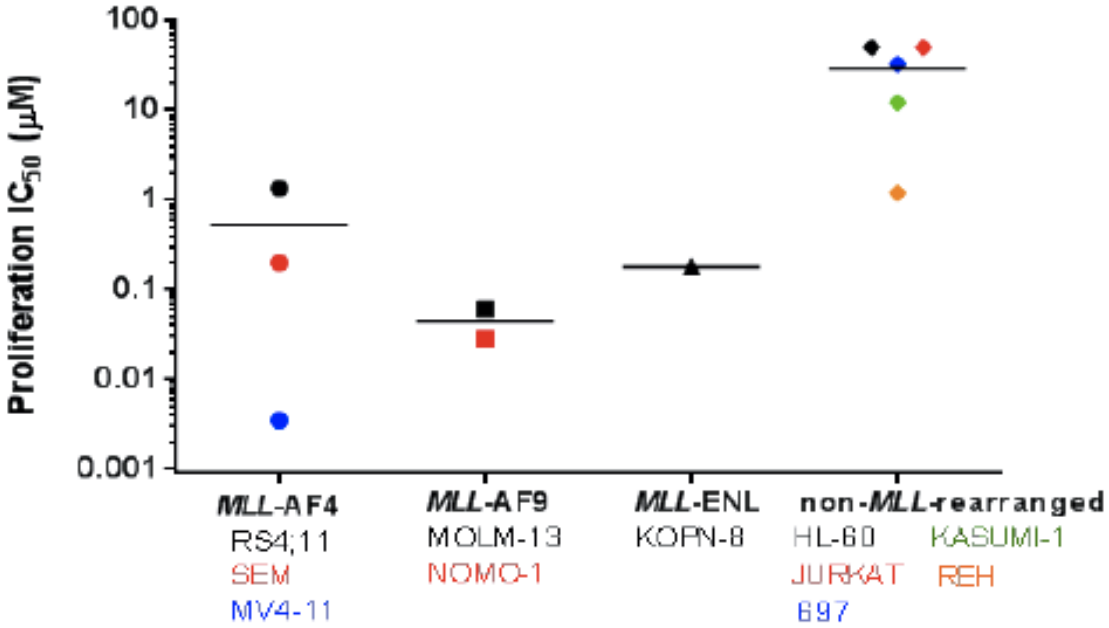
Proliferation IC50 for EPZ-5676 in Various Cell LInes



Proliferation IC50 and IC90 for EPZ-5676 in Various Cell Lines

MLL Fusion	Cell Type	IC_{50} (µM)	IC_{90} (µM)
MLL-AF4	RS4;11	1.3	49
MLL-AF4	MV4-11	0.003	0.037
MLL-AF4	SEM	0.2	2.2
MLL-AF9	MOLM-13	0.061	0.12
MLL-AF9	NOMO-1	0.028	0.094
MLL-ENL	KOPN-8	0.17	9
No	REH	1.2	>50
No	KASUMI-1	12.2	>50
No	697	32.7	>50
No	JURKAT	>50	>50
No	HL-60	>50	>50

- Sensitivity of MLL-AF4 to EPZ-5676 varies depending on the cell line utilized (with proliferation IC50s varying from .003 to 1.3uM). It appears that the MV4-11 cell line is the most sensitive to the drug. It is unclear which cell line is most predictive of the clinic
- The therapeutic window of EPZ-5676 may also vary depending on the specific MLL partner fusion gene

Source: Polluck, ASH 2012

Initial EPZ-5676 Phase I Results Expected in 2H 2013

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- Phase I (NCT01684150) initiated in September 2012
  - 2 phases for the Phase I
    - 1st phase is dose escalation phase that will include some MLL-r patients
    - 2nd phase is an expansion phase utilizing the dose selected in the 1st phase and will enroll only MLL-r patients
  - Administered as a continuous IV infusion to patients
  - Primary endpoint is safety and tolerability to determine the maximum tolerated dose
  - Secondary endpoints include Pharmacodynamics/ Pharmacokinetics (PK/PD) and clinical signs of efficacy
  - Estimated enrollment of 40 patients
  - 2 sites are currently enrolling patients (Memorial Sloan-Kettering and Sarah Cannon Research Institute)

Source: Company Reports

EPZ-5676 Demonstrated Early Signs of Clinical Activity

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- As of May 20, 2013:
  - 4 patients had been dosed in the dose escalation phase of the Phase I
  - 1 of the 3 patients in the second-dose cohort was diagnosed with MLL-r AML
    - Partial DOT1L target inhibition was observed
    - This patient experienced a 90% reduction in circulating leukemic blast count by the 5th day of EPZ-5676 treatment.
    - Patient also experienced resolution of fevers, believed by the investigator to be related to the leukemia
    - EPZ-5676 treatment was terminated on day 10 due to CNS disease progression (VI nerve palsy, MRI-documented leptomenigeal disease
    - Patient experienced a single episode of transient hypertension that was possibly related to EPZ-5676 treatment

Source: Company Reports

EPZ-5676 Phase I Expansion Initiation is Expected in the 2H 2013

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- Once the dose escalation is complete, EPZM will initiate the expansion phase of the trial based on the selected dose.
- This portion of the study will enroll only MLL-r patients

Source: Company Reports

KOL Feedback Suggests MLL-r is an Area of High Unmet Medical Need

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- KOLs note that MLL-r are a very difficult to treat patient population
- The pre-clinical data was characterized as encouraging, and KOLs were excited to test the drug in patients
- The continuous dosing was viewed as acceptable in this patient population without other treatment options
- The patient with the drop in blast counts was viewed as a sign of efficacy and very encouraging. The CNS relapse is uncommon in these patients, and lack of penetration into the brain for the drug is not important

Source: Leerink Swann analysis

Companion Diagnostic Being Developed with Abbott

LEERINK SWANN

- Entered into agreement with Abbott in February 2013 to develop a companion diagnostic to identify patients with the MLL-r genetic alteration targeted by EPZ-5676
- Paid ABT upfront of $0.9M
- Milestone based development payments of up to $6.0M and obligated to reimburse ABT for specified costs for clinical trials necessary to obtain regulatory approvals for the companion diagnostics. These reimbursable costs are not to exceed $0.9M unless agreed to in advance by both EPZM and ABT
- Expect to pay $1.5M in milestone based development payments in 2013 under this agreement

Source: Company Reports

Market Opportunity for EPZ-5676 in MLL

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MLL-r	US	EU	Japan
Population Growth (Source: CIA World Factbook)	0.90%	0.21%	-0.08%
Incidence of Leukemia 2012 (Source: Globocan 2008, factored by population growth)	45,884	59,880	9,608
% ALL and AML amongst leukemias (Source: Based on SEER incidence numbers for 2012)	13% ALL and 29% AML		
Incidence of ALL in 2012	5,965	7,784	1,249
Incidence of AML in 2012	13,306	17,364	2,786
ALL/AML Age Breakdown (Source: NCI; Felix CA & Lange BJ (1999) The Oncologist vol. 4 no. 3 225-240, SEER 2012)	60% Pediatric in ALL (4% of ped. is infant) 6% Pediatric in AML (10% of ped. is infant)		
% MLL-r in ALL and AML (Source: Muntean AG & Hess JL (2012) Annu Rev Pathol.; 7:))	8% ALL and 10% AML in adults & children 80% ALL and 50% AML in infants		
Incidence of ALL with MLL-r	580	757	121
Incidence of AML with MLL-r	1,363	1,778	285
First Line Treatment Rate for MLL-r Leukemias	85% in adults 95% in children & infants		
Total 1st Line Chemo Intolerant Patients	241	315	51
Relapse Rates (Sources: Pui CH et al (2003) Leukemia 17, 700–706., Marks DI (2013) Haematol online ahead of print, Byrd J C et al. Blood 2002;100:4325-4336, Balgobind BV et al. (2009) Blood vol. 114 no. 12; 2489)	66% ALL and 80% AML-MLL-r in adults 58% ALL and 56% AML-MLL-r in children 81% ALL and AML-MLL-r in infants		

Globally, estimated to be ~3,200 relapsed and ~4,000 1st line MLL-r patients

Source: Company Reports

DOT1Li Competitors

- No known direct epigenetic competitors for MLL-r leukemias
- Competitors in non-genetically defined acute leukemia include BRD inhibitors by OncoEthix (OTX015) and Constellation (unconfirmed)

Source: Company Reports and Presentations

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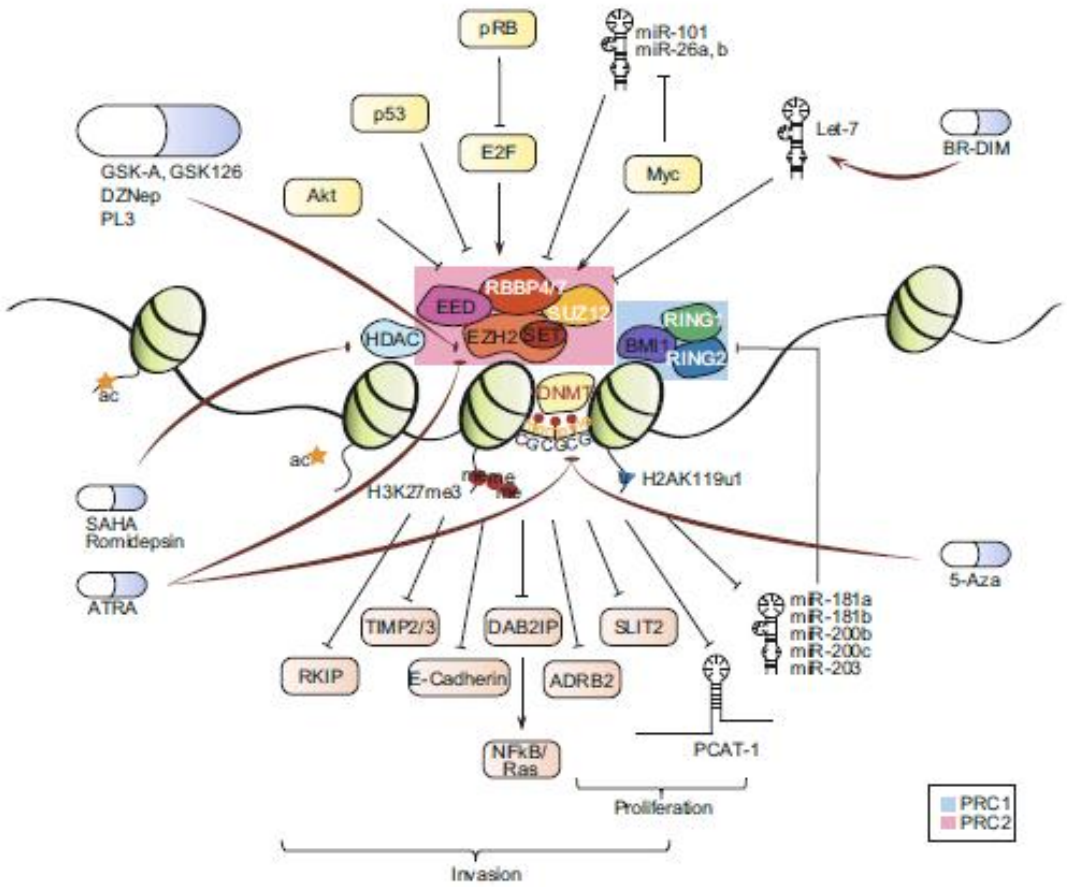
EPZ-6438 (EZH2 INHIBITOR)

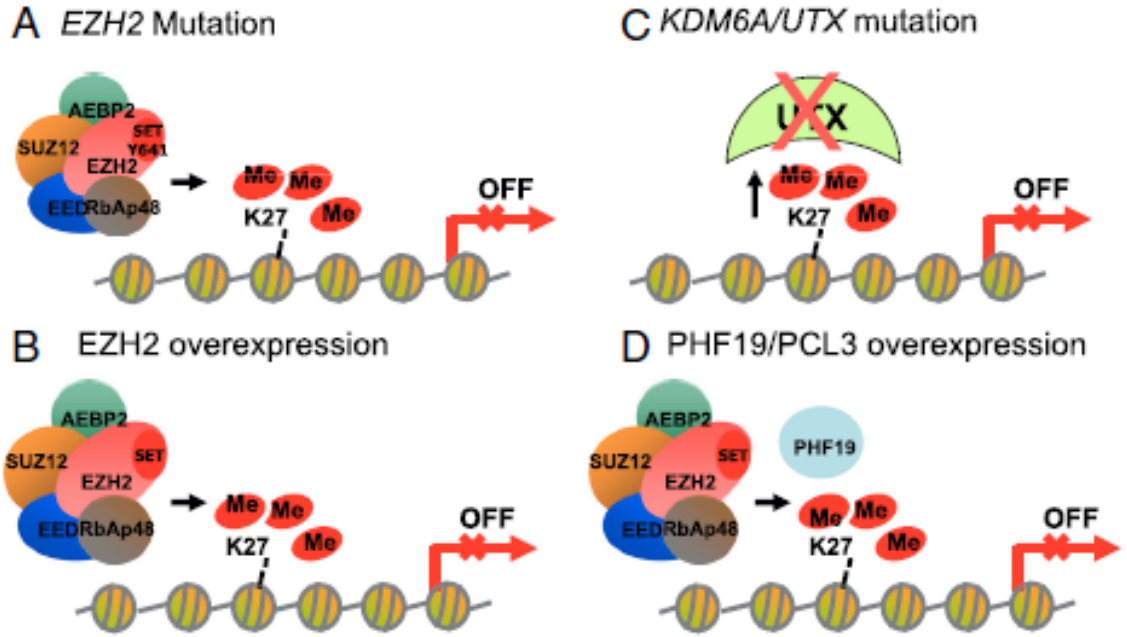
EZH2 Silences Tumor Suppressor Genes – Thus Over-expression or Mutation Can Result in Tumorigenesis



- EZH2 is the enzymatic member of the polycomb repressor complex (PRC2) which catalyzes trimethylation of the histone H3 at lysine 27.
- EZH2 induces chromatin compaction and epigenetic silencing of key tumor suppressor genes, which subsequently result in tumorigenesis and metastasis.
- EZH2 itself can be regulated through multiple pathways transcriptionally (by E2F, p53 and Myc), post-transcriptionally (by microRNAs), and post-translationally (by Akt-mediated phosphorylation).

Source: Yang, Protein and Cell 2013

Multiple Mechanisms Can Lead to Increases in Tri-Methylated H3K27 States and the Resultant Gene Repression



A. EZH2 mutations allow for more efficient methylation of the mono- or di-methylated to create the try-methylated form of H3K27
   - The normal form of EZH2 is most efficient at the mono-methylated step and less efficient at the di- or tri- methylated step
   - Histone mono-methylation is associated with active transcription of the genes, while the tri-methylated form is associated with repression

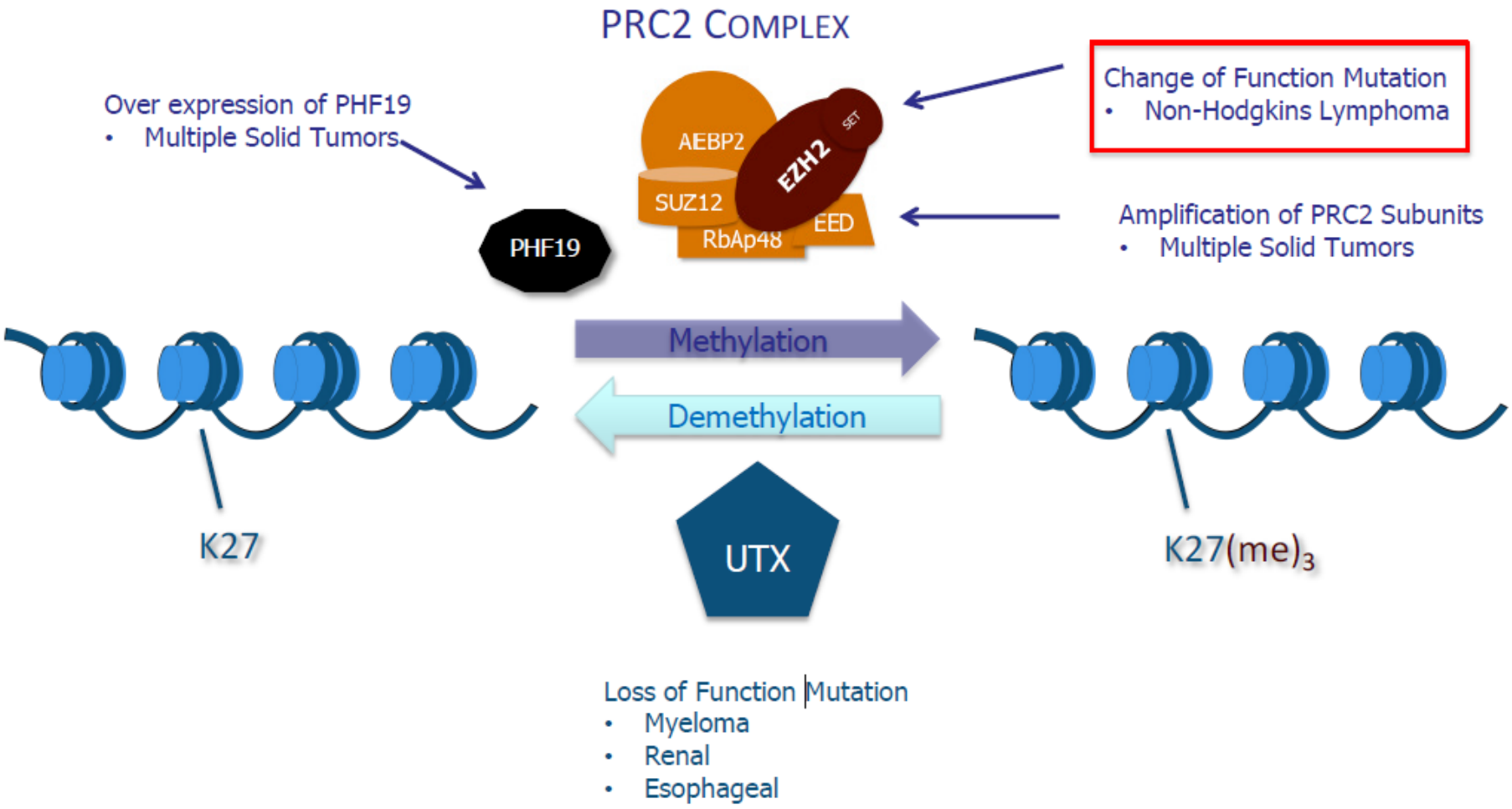
B. EZH2 over-expression can also result in a similar result as the mutant with increased tri-methylated forms of H3K27

C. UTX de-methylates H3K27, thus mutations that inactivate function result in increased tri-methylated states

D. over-expression of the PRC2 complex subunit of PHF19/PCL3 that leads to increased recruitment of the PRC2 complex to specific genes and an increase in histone H3K27 tri-methylation

Source: Sneeringer, PNAS 2010

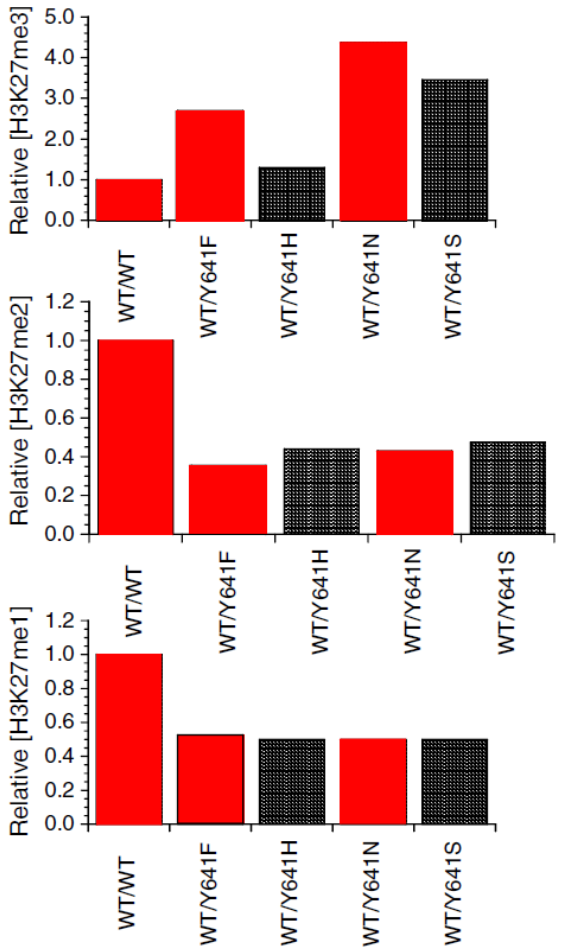
EZH2 is an Oncogenic Driver in Non-Hodgkin's Lymphoma (NHL)



Source: Keilhack, ASH 2012

Malignant Phenotypes of Disease Require Both Wild-Type and Mutant EZH2

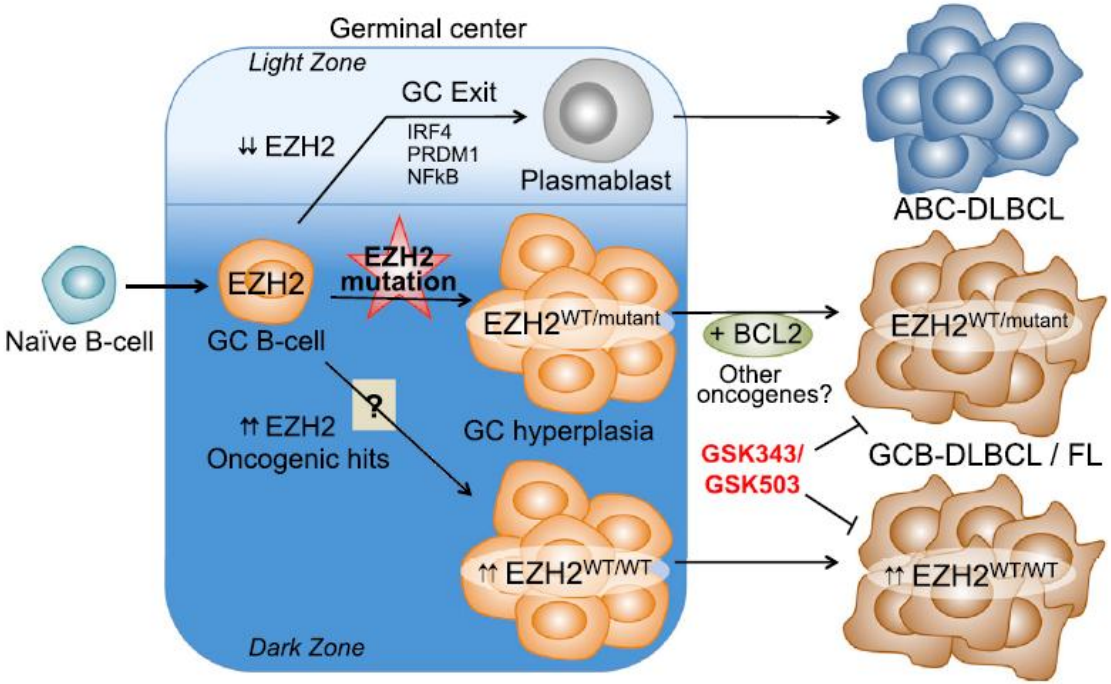
Predicted relative levels of H3K27me3, H3K27me2, H3K27me1 for cells containing different EZH2 mutants



- Histone H3K27 tri-methylation is a mechanism for suppressing transcription of specific genes.
- WT EZH2 is most efficient at the first methylation step for H3K27. It is less efficient at catalyzing the mono- to di- and di to tri-methylation reaction
- The mutant EZH2 is the inverse. Mutant EZH2 is more efficient at catalyzing the mono- to di- and the di- to tri- methylation step, but has very limited ability to perform the first methylation reaction
- Therefore the malignant phenotypes of B-cell lymphoma are dependent on the combined activity of both the wild-type and mutant EZH2 leading to increased tri-methylated H3K27

Source: Sneeringer, PNAS 2010

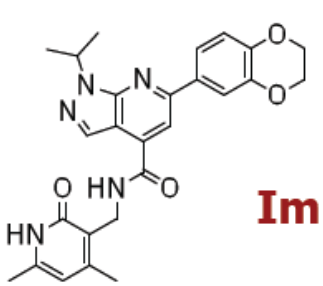
EZH2 in the Presence of Additional Oncogenic Hits Induces the Development of Diffused Large B-Cell Lymphoma (DLBCL)



- **EZH2 somatic mutations sustains repression of proliferation checkpoints resulting in germinal cell hyperplasia**
- **This, combined with the presence of other oncogenic hits, such as BCL2, enables transformation to GCB-type DLBCL or FL**
- **An alternative route that can result in GCB-DLBCL could involve over-expression of WT EZH2**
- **However, expression of mutant EZH2 alone is insufficient to induce development of DLBCL**
- **ABC-DLBCL do not require EZH2 to maintain their proliferation and survival and thus EZH2 inhibitors would have no effect**

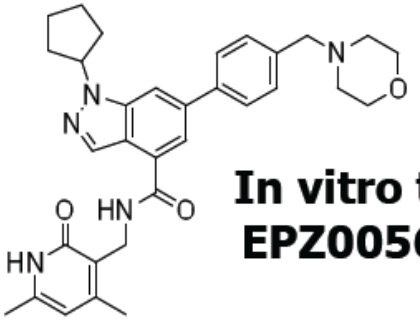
Source: Beguelin, Cancer Cell 2013

Discovery of EPZ-6438



HTS Hit

Improved solubility and potency

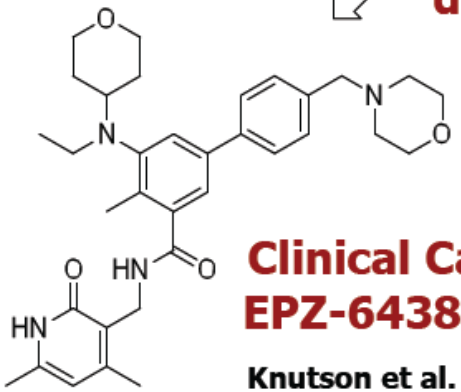


In vitro tool EPZ005687

Knutson et al. NatChemBio, 2012

Improved potency and drug-like characteristics

EZH2 K_i = 2.5 nM

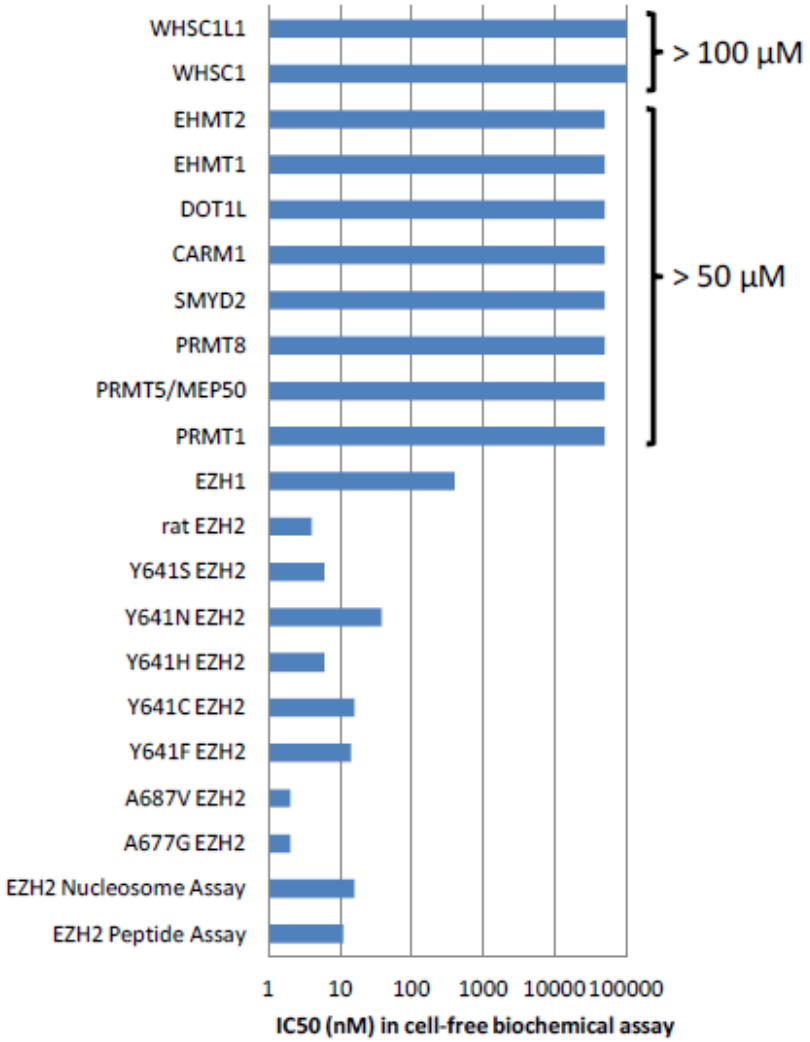


Clinical Candidate EPZ-6438 (E7438)

Knutson et al. PNAS, 2013

Source: Kuntz, ICML 2013

EPZ-6438 is a Selective Inhibitor of EZH2



Source: Keilhack, ASH 2012

EPZ-6438 Selectively Kills EZH2 Y641F Mutant Cells but Spares Wild Type (WT) Cells

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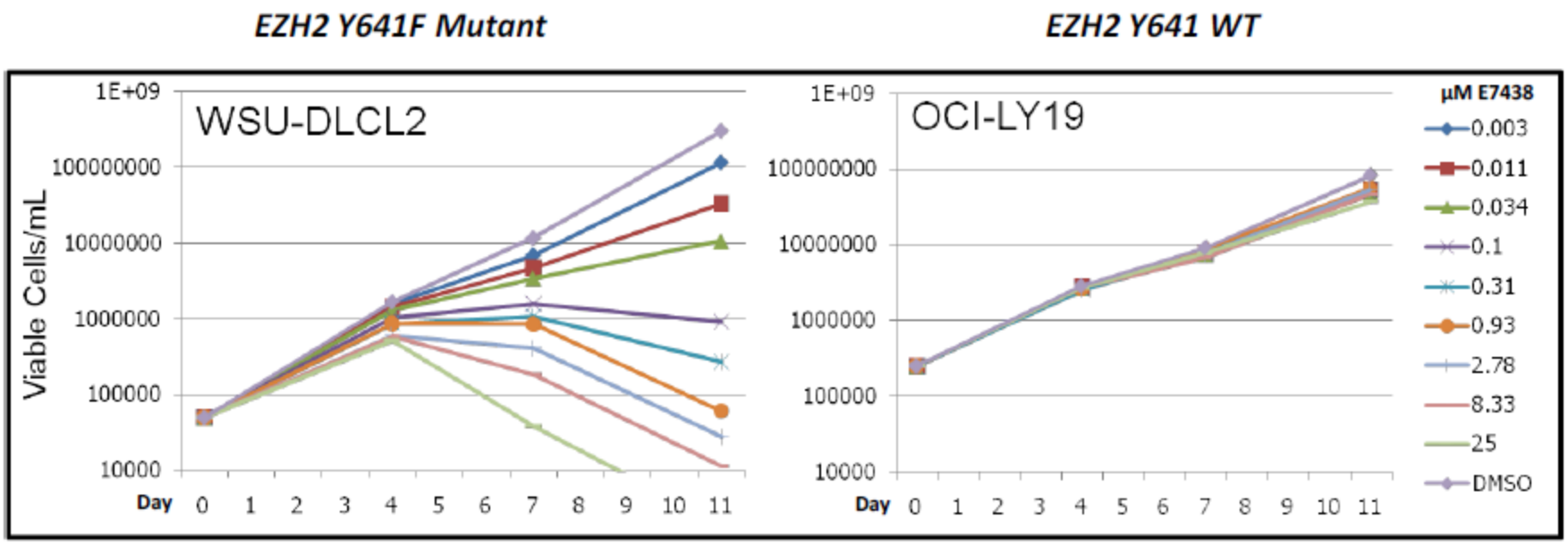

- **The effect of EPZ-6438 is not immediate. Cancer cells continue to grow through days 4 then from days 4-7 cell levels stabilize, before starting to decrease afterwards.**
- **WT cell line growth is not affected by EPZ-6438 (right panel)**

Source: Keilhack, ASH 2012

EPZ-6438 Demonstrated Anti-Tumor With No Tumor Re-growth After Cessation of Dosing in Mice Models

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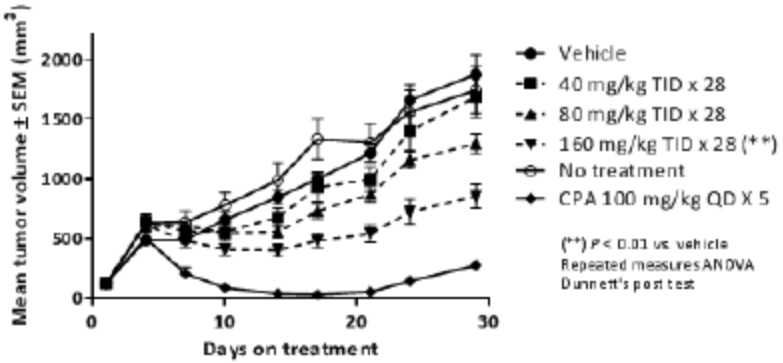
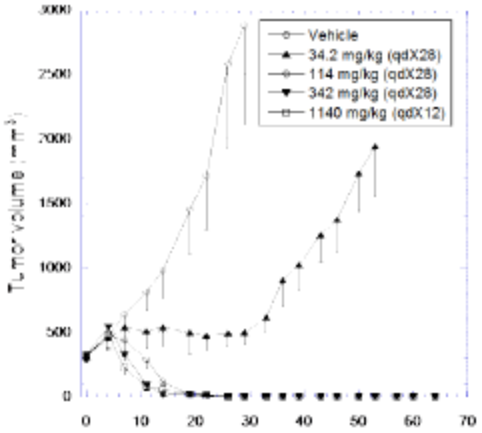
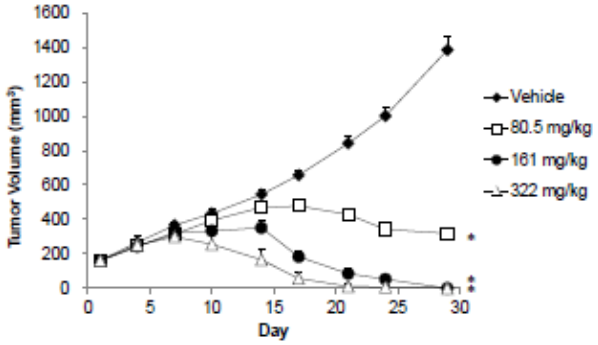
A *WSU-DLCL2 (Y641F)*

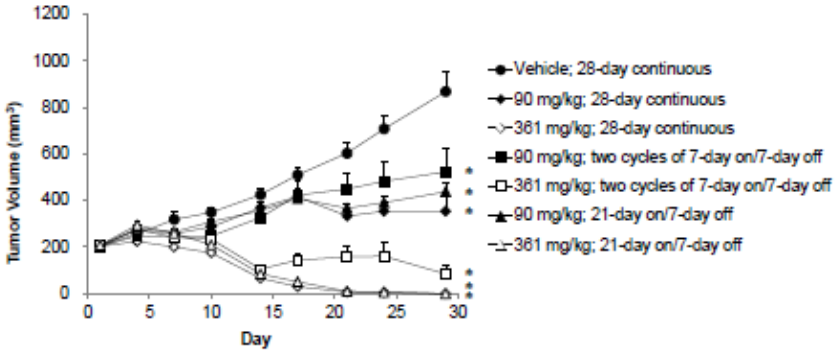


B *Pfeiffer (A677G)*



C *KARPAS-422 (Y641N) – BID schedule*





In a separate tumor growth delay study no tumor re-growth was detected through day 91 at 322 mg/kg (63 days after dosing stop on Day 28).

No tumor re-growth observed in the Pfeiffer and KARPAS-422 models after dosing was stopped

Source: Keilhack, ASH 2012

Pfeiffer Cells are Hypersensitive to EZH2 Inhibition

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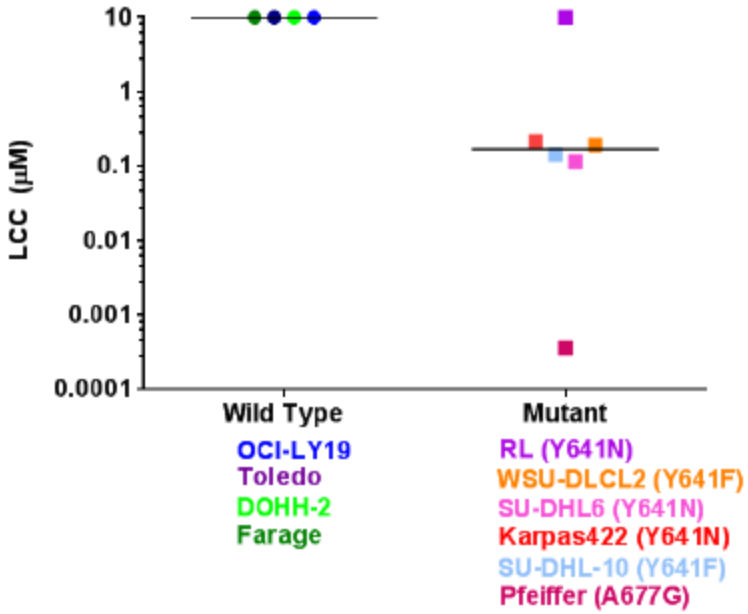
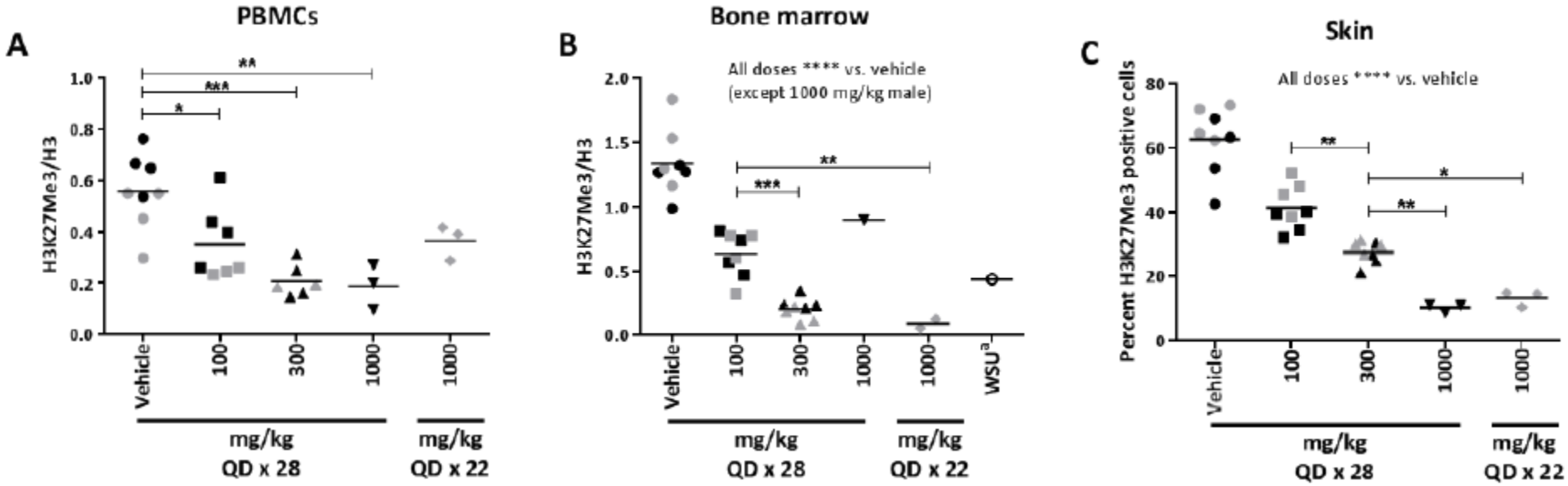
- LLC = lowest cytotoxic concentration (= levels of drug inducing stasis in 11-day growth assay)
  - Below LLC = cell death, above LLC = progressive growth
- The Pfieffer cell line is an outlier, in that it is hypersensitive to E7438
  - The Pfieffer cell line has a gain of function mutation with A682G, which makes it much more efficient than other mutants at attaching all 3 methyl marks. This may explain the exquisite sensitivity of E7438 in this cell line – the efficiency in attaching all 3 methyl marks may create an increased dependency on this pathway
- The RL cell line is also an outlier in that E7438 has virtually no effect on this mutant

In Vitro Sensitivity to E7438



Source: Keilhack, ASH 2012; Kuntz, ICLM 2013

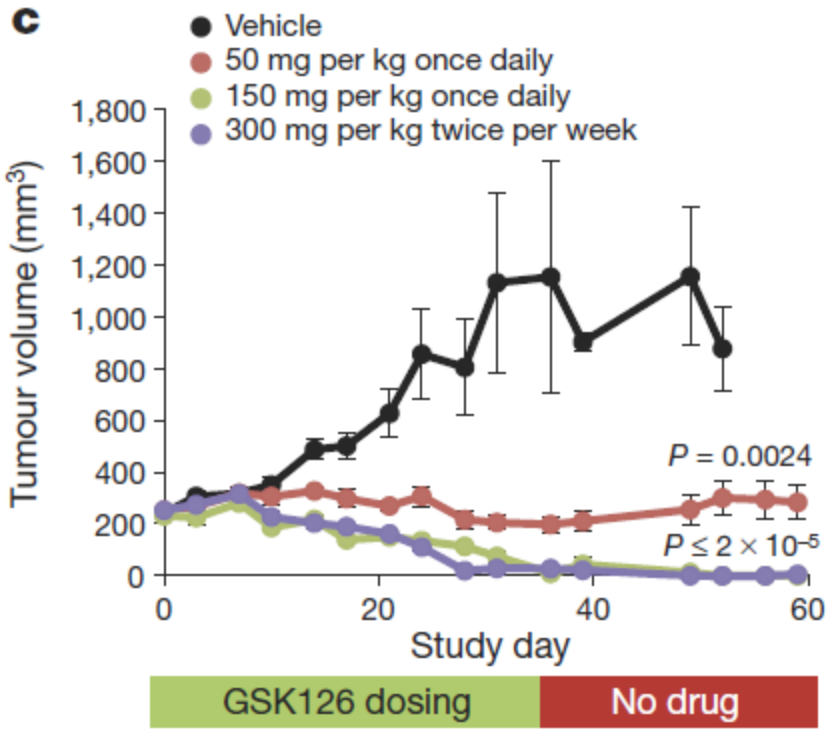
E7438 Inhibits H3K27 Methylation in Non-Tumor Tissues in Animal Models – If Replicated in Humans, Could Allow for Surrogate Measures of Efficacy and Drug Dose Levels

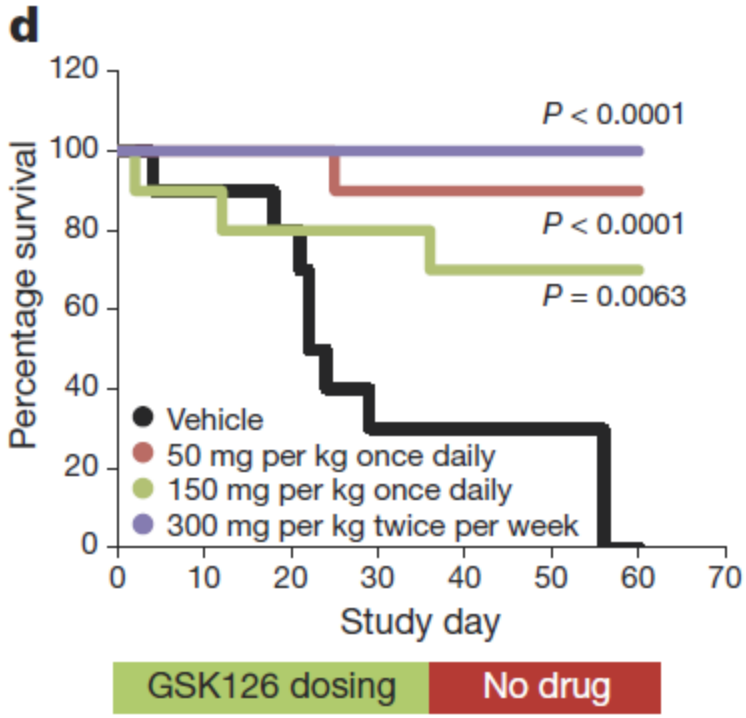


- Oral dosing of E7438 in rats lead to dose-dependent inhibition of H3k27Me3 in multiple tissue including A) PBMC, B) bone marrow and C) skin.

Source: Keilhack, ASH 2012; Kuntz, ICLM 2013

GSK's EZH2 Inhibitor Also Demonstrated Long Lasting Anti-Tumor Effects





The long lasting effects of EZH2 inhibitors even after cessation of dosing is due to the underlying differences between epigenetic malfunction and genetic mutations. Epigenetic malfunction can potentially be reversed, as the underlying DNA sequence is not damaged. In contrast, mutations in the genetic sequence can be difficult to correct.

Source: McCabe, Nature 2012; Yang, Protein and Cell 2013

EPZ-6438 Phase I/II Enrollment Began in June 2013

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- EPZ-6438 is an orally available small molecule inhibitor of EZH2 HMT being studied in non-Hodgkin's lymphoma (NHL) patients with a point mutation in EZH2
- Phase I portion will include a variety of patients (do not have to have the EZH2 point mutation).
- Phase II portion will only enroll EZH2 patients
- Early assessment of therapeutic effect in 1H 2014
- Agreement with Roche to develop a companion diagnostic for use with EPZ-6438

Source: Company Reports and Presentations

EPZ-6438 Could Have Efficacy in Prostate Cancer and Breast Cancer

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- EZH2 plays a role in prostate cancer
  - Analysis of patient samples significantly correlate abnormally elevated EZH2 levels with increased proliferation rates, invasiveness, and metastasis
  - Knockdown of endogenous EZH2 reduced proliferation and invasion in prostate cancer cells
  - In castrate resistant prostate cancer, EZH2 could be a transcriptional co-activator of androgen receptor instead of a transcriptional repressor of PCR2
- EZH2 is abundant in basal-like, triple negative and HER2-enriched breast cancer
  - EZH2 levels are higher in BRCA1-deficient cancer cells
  - Treatment with a EZH2 inhibitor was found to inhibit the growth of these BRCA1 deficient cancer cells

Source: Shen, Oncotargets and Therapy 2013

EZH2 Inhibition May have Potential in Ovarian and Non Small Cell Lung Cancer (NSCLC)

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- EZH2 in ovarian cancer
  - High EZH2 expression was found in 3% of cystadenomas, 23% of border-line tumors and in 50% of ovarian carcinomas
  - EZH2 may also play a key role in the maintenance of chemotherapy resistant tumor cells
- EZH2 in NSCLC
  - High EZH2 expression has been found to be correlated with non-adenocarcinoma histology, and larger tumor size
  - EZH2 expression may also be a negative prognostic factor for overall survival (OS)

Source: Shen, Oncotargets and Therapy 2013

EPZ-6438 Has Demonstrated Efficacy in Solid Tumor Animal Models

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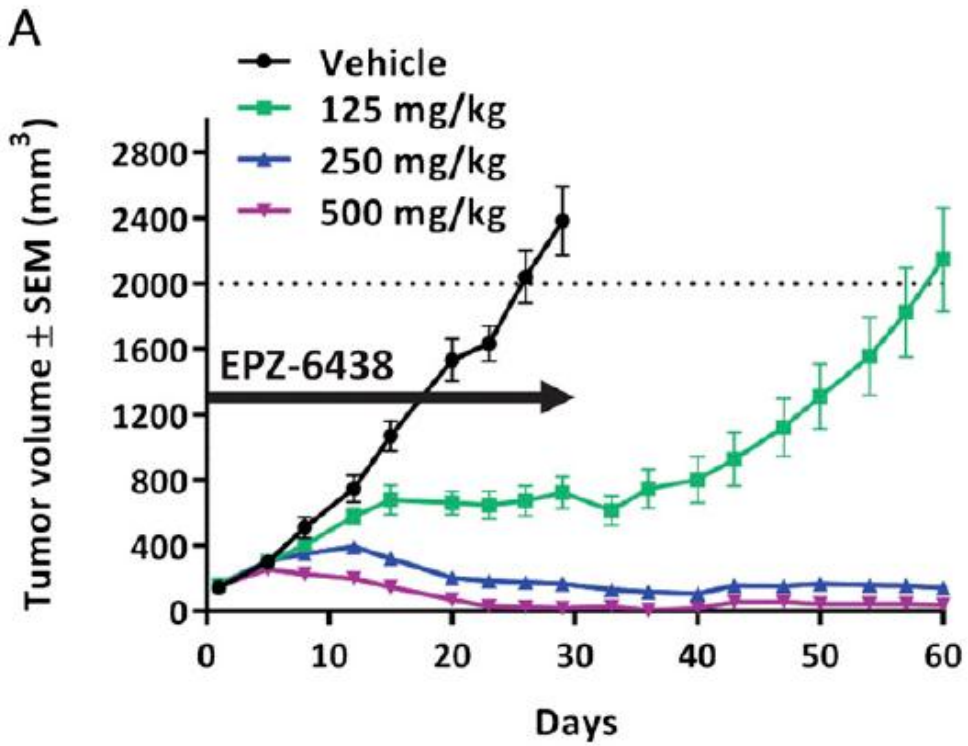
EPZ-6438 dosed BID for 28 days in SMARCB1-deleted MRT Xenograft Mice resulted in tumor eradication at doses of 250 and 500mg/kg



- Malignant rhabdoid tumor (MRT) is a very aggressive tumor that occurs mainly in children <2 years of age.
- The SMARCB1 subunit is inactivated via biallelic mutations in nearly all MRTs and atypical teratoid rhabddoid tumors (ATRTs). SMARCB1 loss leads to decreased expression of cell cycle inhibitors, tumor suppressors and genes of neuronal differentiation
- EZH2 expression is elevated in primary SMARCB1-deficient tumors, but EZH2 itself is not genetically altered in this context. This provides proof of concept that EZH2 inhibition may be effective in a variety of tumors which become dependent on EZH2 enzymatic activity

Source: Knutson, PNAS 2013

Market Opportunity for EPZ-6438 in DLBCL and FL

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DLBCL-GCB & FL	US	EU	Japan
Population Growth (Source: CIA World Factbook)	0.90%	0.21%	-0.08%
Incidence of Non-Hodgkins Lymphoma 2012 (Source: Globocan 2008, factored by population growth)	68,539	74,787	15,053
% NHL that is DLBCL (Sources: Morton LM et al. (2006) Blood; Leuk. & Lymph. Society (US); Sant M et al. (2010) Blood (EU); Lymphoma Study Group of Japanese Pathologists (2000) Pathol Int. (Japan)	35%	27%	33%
% DLBCL that is DLBCL-GCB (Source: Alizadeh AA et al. (2000) Nature 403, 503-511)	50%		
% NHL that is FL (Sources: Same as sources for '% NHL that is DLBCL)	25%	16%	7%
% DLBCL-GCB and FL with EZH2 Mutations (Source: Morin RD et al. (2010) Nat Genet. 42(2):181-5; Böodõor C et al (2012) Blood (ASH Annual Meeting Abstracts) 120: Abstract 54; Ryan RJH et al. (2011) PLoS One. 6(12))	22%		
Incidence of DLBCL-GCB with EZH2 Mutations	2,651	2,231	549
Incidence of FL with EZH2 Mutations	3,770	2,632	222
First Line Treatment Rate for DLBCL-GCB and FL	95%		
Relapse Rates (Sources: ASH Education Book (2011) vol. 2011 no. 1 498-505, Bello C et al (2012) Cancer Control.;19(3):187-95., Montoto S et al. (2002) Ann Oncol 13 (4): 523-530; U. MD Med. Ctr)	33% DLBCL-GCB and 100% FL		

Globally, estimated to be ~8,000 relapsed and ~12,000 1st line EZH2 patients

Source: Company Reports and Presentations

EZH2i Competitors

- GSK believed to be in Phase I development
  - GSK has published data on GSK126, a small molecule inhibitor of EZH2 in pre-clinical models (McCabe, Nature 2012)
- Constellation Pharma (private) has pre-clinical compounds in development targeting EZH2

Source: Company Reports and Presentations

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FOUR EPIGENETIC AGENTS HAVE BEEN APPROVED; SURVIVAL BENEFITS SUPPORT TARGETING EPIGENETICS IN CANCER

Two Classes of FDA-Approved Epigenetic Therapies

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EPIGENETIC-ACTING DRUG	CLINICAL INDICATION	MAJOR DATA	SUPPORTING LITERATURE
DNA methyltransferase inhibitors			
5-azacytidine (azacitidine)	Symptomatic MDS	16% overall response rate; 66% hematologic improvement/transfusion independence	Kaminskas 2005[137] Fenaux 2009[138]
5-aza-2′-deoxycytidine (decitabine)	Intermediate and High-risk MDS	73% objective response rate; 34% complete response rate	Kantarjian 2007[139]
Histone deacetylase inhibitors			
Suberoylanilide hydroxamic acid (vorinostat)	Progressive, persistent, or recurrent cutaneous T-cell lymphoma	30% objective response rate	Mann 2007[140]
Romidepsin (depsipeptide)	Progressive, persistent, or recurrent cutaneous T-cell lymphoma	34% overall response rate; 6% complete response rate	Piekarz 2009[141]

MDS indicates myelodysplastic syndrome.

Source: Taby, CA Cancer J Clin 2010

Vidaza – A Chemotherapy Leading to DNA Hypomethylation

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- Vidaza (5-azacytidine) is an analogue of cytidine
- Vidaza incorporates into DNA and RNA at high dose, leading to failure of DNA replication or RNA translation and the consequent death of rapidly dividing cells
- Vidaza also inhibits DNA methyltransferase at low dose, leading to hypomethylation and subsequent activation of tumor suppressor genes and apoptosis, as well as cell differentiation
- The drug was approved in 2004 for the treatment of myelodysplastic syndrome (MDS) with all five FAB subtypes (RA – refractory anemia, RARS – refractory anemia with ringed sideroblasts, RAEB – refractory anemia with excess blasts, RAEB-T – refractory anemia with excess blasts in transformation, CMMoL – chronic myelomonocytic leukemia), and all three IPSS classification (intermediate-1, -2, and high risk)

Source: Vidaza Label; FAB – French-American-British; IPSS – international Prognostic Scoring System

Vidaza – Achieved Significant Overall Response Rates (ORR) in MDS Patients with All Five FAB Subtypes

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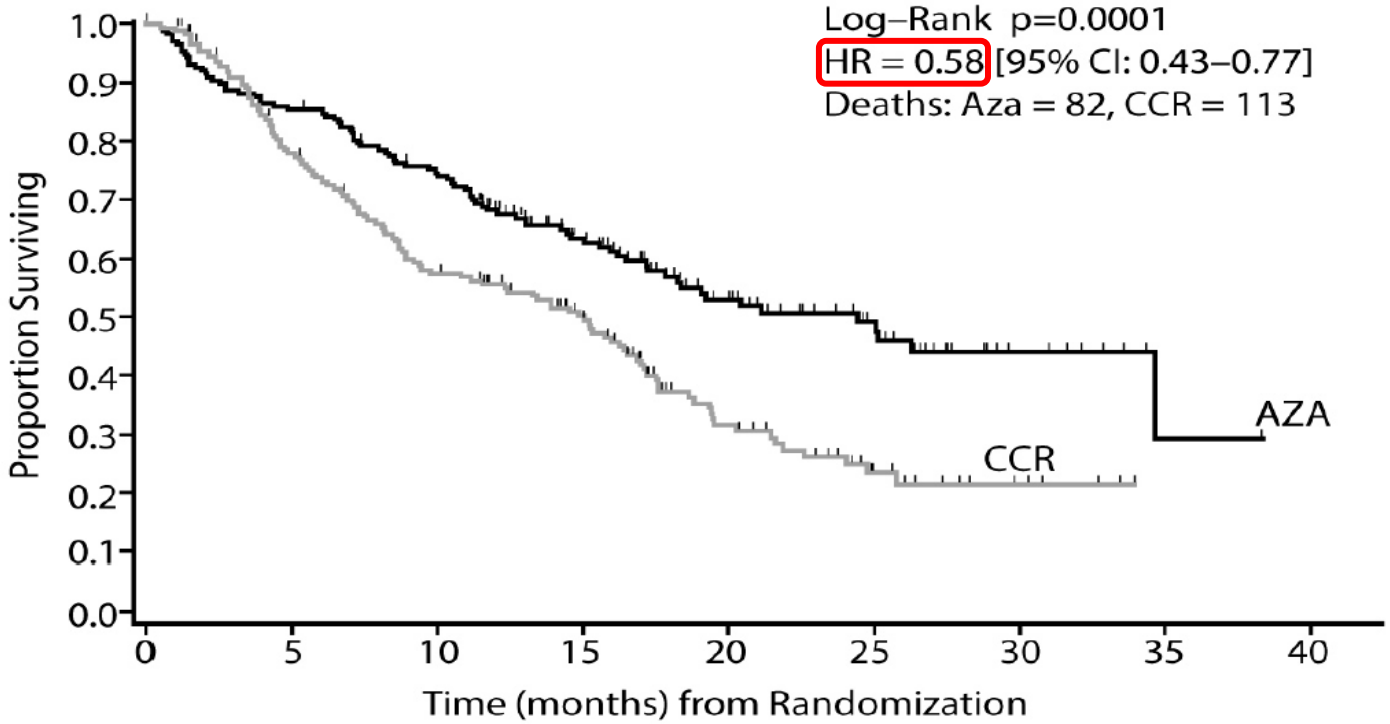
- Vidaza achieved ORR of 15.7% in MDS patients with all five FAB subtypes vs. 0% in the observation group with supportive care
- The observation group had ORR of 12.8% after crossover
- Mean and median duration of ORR was 512 days and 330 days, respectively

	VIDAZA (N=89)	Observation Before Crossover (N=83)	
Response	**n (%)**	**n (%)**	**P value**
Overall (CR+PR)	14 (15.7)	0 (0.0)	(<0.0001)
Complete (CR)	5 (5.6)	0 (0.0)	(0.06)
Partial (PR)	9 (10.1)	0 (0.0)	--

Source: Vidaza Label; ORR – overall response rate

Vidaza – Despite Modest Response Rate, Survival Benefit Was Impressive

- Vidaza achieved significant OS benefit (24.5 months for AZA vs. 15.0 months for CCR, p=0.0001) in MDS patients with RAEB, RAEB-T or modified CMMoL



# at risk									
AZA	179	152	130	85	52	30	10	1	0
CCR	179	132	95	69	32	14	5	0	0

Source: Vidaza Label; AZA – azacitidine, CCR – conventional care regimens; CI – confidence interval; HR – hazard ratio

Vidaza – Treatment Led to Reduced Need for Red Blood Cell Transfusions

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Efficacy Parameter	Azacitidine plus BSC (n= 179)	Conventional Care Regimens (n= 179)
Number and percent of patients who were transfusion dependent at baseline who became transfusion independent on treatment[1]	50/111 (45.0%) **Median duration – 13 months** (95% CI: 35.6%, 54.8%)	13/114 (11.4%) (95% CI: 6.2%, 18.7%)
Number and percent of patients who were transfusion-independent at baseline who became transfusion-dependent on treatment	10/68 (14.7%) (95% CI: 7.3%, 25.4%)	28/65 (43.1%) (95% CI: 30.9%, 56.0%)

[1]A patient was considered RBC transfusion independent during the treatment period if the patient had no RBC transfusions during any 56 consecutive days or more during the treatment period. Otherwise, the patient was considered transfusion dependent.

Source: Vidaza Label

Dacogen – A Second Example Of Approved Drug Targeting Hypomethylation

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- Dacogen (decitabine) is a cytidine analog
- Dacogen functions similarly to Vidaza; however, Dacogen can only be incorporated into DNA (vs. both DNA and RNA for Vidaza)
- Similar to Vidaza, Dacogen inhibits DNA methyltransferase, leading to hypomethylation, which awakes tumor suppressor genes and causes cellular differentiation and apoptosis
- Dacogen was approved in 2006 for the treatment of MDS of all FAB subtypes (RA, RARS, RAEB, RAEB-T, CMMoL) and IPSS subtypes (intermediate-1, -2, high risk)

Source: Dacogen Label; FAB – French-American-British; IPSS – international Prognostic Scoring System

Dacogen – Similar ORR, Slightly Short Duration vs. Vidaza in MDS Patients

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Parameter	Dacogen N=89	Supportive Care N=81
	Vs. 16% for Vidaza	
Overall Response Rate (CR+PR)†	15 (17%)**	0 (0%)
Complete Response (CR)	8 (9%)	0 (0%)
Partial Response (PR)	7 (8%)	0 (0%)
Duration of Response		
Median time to (CR+PR) response - Days (range)	93 (55-272)	NA
	Vs. 330 for Vidaza	
Median Duration of (CR+PR) response - Days (range)	288 (116-388)	NA

**p-value <0.001 from two-sided Fisher's Exact Test comparing Dacogen vs. Supportive Care.

†In the statistical analysis plan, a p-value of ≤ 0.024 was required to achieve statistical significance.

Source: Dacogen Label

Dacogen – Survival Benefit Suggested in Head-to-Head Trial Compared to Active Control

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- Dacogen was approved in Europe for the treatment of 1st and 2nd line AML in adults 65 years and older in 2012
- The approval was based on the open-label controlled study comparing Dacogen vs. physician's choice, including low-dose cytarabine
- Pre-specified OS was not significant (7.7 months vs. 5.0 months, HR=0.85, p=0.10)
- Updated analysis of mature survival data confirmed strong trend of OS benefit (HR=0.82, nominal p=0.03)
- However, the same indication was not approved by the FDA, citing risk/benefit profile was not favorable; the FDA AdCom voted 10 to 3 against the approval

Source: Company Report

Zolinza – Histone Deacetylase Inhibitor (HDACi) for a Difficult-to-Treat Cancer

LEERINK SWANN

- Zolinza (vorinostat) inhibits the active site of HDAC1, HDAC2, HDAC3 and HDAC6.
- Over-expression or aberrant recruitment of HDACs was observed in some cancer cells, causing hypoaceylation, condensed chromatin structure and repression of transcription
- Inhibition of HDAC results in the accumulation of acetylated histones and transcription factors, leading to cell differentiation and/or apoptosis
- Zolinza was approved in 2006 for the treatment of refractory cutaneous T-cell lymphoma (CTCL)

Source: Zolinza Label

Zolinza – Approval Based on Uncontrolled Studies

LEERINK SWANN

- Single arm study
  - Zolinza achieved ORR 29.7% (22/74) in all patients
  - Median time to response was 55 days
  - Median response duration was estimated to exceed 6 months
- Study assessing several dosing regimens
  - Zolinza achieved ORR of 24.2% (8/33) in all patients, 25% (7/28) in patients with stage IIB or higher, and 36.4% (4/11) in patients with Sezary syndrome
  - ORR is optimized dosing cohort (400mg QD) was 31%

Source: Zolinza Label

Istodax – 2nd HDACi for a Difficult-to-Treat Cancer

LEERINK SWANN

- Istodax (romidepsin) is a HDAC inhibitor
- HDACs deacetylate histones and non-histone proteins such as transcription factors. Hypoaceylation causes condensed chromatin structure and repression of transcription
- Istodax causes the accumulation of acetylated histones and transcription factors, inducing cell cycle arrest and apoptosis
- Istodax was approved in 2009 for the treatment of 2nd line cutaneous T-cell lymphoma (CTCL) and 2nd line peripheral T-cell lymphoma (PTCL)

Source: Istodax Label

Istodax – Approval in CTCL Based on Single Arm Studies

LEERINK SWANN

- ORR was 34-35% in both studies
- Median time to response was 2 months, median time to CR was 4 months in Study 1 and 6 months in Study 2

Response Rate	Study 1 (N=96)	Study 2 (N=71)
ORR (CR + PR), n (%)	33 (34)	25 (35)
[95% Confidence Interval]	[25, 45]	[25, 49]
CR, n (%)	6 (6)	4 (6)
[95% Confidence Interval]	[2, 13]	[2, 14]
PR, n (%)	27 (28)	21 (30)
[95% Confidence Interval]	[19, 38]	[20, 43]
Duration of Response (months)		
N	33	25
Median (range)	15 (1, 20*)	11 (1, 66*)
*denotes censored value		

Source: Istodax Label

Istodax – Approval in PTCL Based on Two Single Arm Studies

LEERINK SWANN

- ORR was 25% and CR was 15%
- Similar CR were observed across 3 major PTCL subtypes (NOS, AITL and ALK-1 negative ALCL

Response Rate	Study 3 (N=130)
CR+CRu, n (%)[1]	19 (14.6) [9.0, 21.9][3]
PR, n (%)[2]	14 (10.8) [6.0, 17.4][3]
ORR (CR+CRu+PR), n (%)[2]	33 (25.4) [18.2, 33.8][3]

[1] Primary Endpoint

[2] Secondary Endpoint

[3] 95% Confidence Interval

Source: Istodax Label

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IMPRESSIVE, INCREASINGLY FAVORABLE ECONOMICS ON PARTNERSHIPS PROVIDE VALIDATION OF THE PLATFORM

GSK Partnership

LEERINK SWANN

- In January 2011 EPZM entered into a collaboration and license agreement with GSK to discover, develop and commercialize novel small molecule HMT inhibitors (HMTi) directed up to 3 targets.
  - GSK has now selected and licensed 3 targets of HMTi (GSK1, 2, 3)
  - Received upfront payment of $20M. EPZM will receive royalties in mid-single digits to the low double-digits of sales on licensed products based on worldwide net product sales.
  - Through March 31, 2013 EPZM has received $4.5M of research funding and $8M of preclinical research and development milestone payments.
  - Eligible to receive up to $630M in additional milestone payments
    - Preclinical R&D, clinical development and regulatory milestones of $360M
    - Sales-based milestone payments of up to $270M

Source: Company Reports

Eisai Partnership Validates Platform Given Its Familiarity with Epigenetics (Dacogen)

LEERINK SWANN

- In April 2011 EPZM granted Eisai an exclusive worldwide license to the EZH2 program, including EPZ-6438
  - EPZM received $3M upfront. Eisai funds all R&D and commercialization costs for licensed compounds
  - EPZM receives royalties on net sales in mid-single digits on net sales OUS and from mid-single digits to low double-digits on net sales in the US. If exercises the opt-in right, EPZM will have 50/50 co-development, co-commercialization and profit share in the US. Eisai can recover a portion of past development costs as a partial reduction of future milestone payments and royalties, and the future milestone payments are reduced
  - Through March 31, 2013 EPZM had received $11.3M in research funding payments and $7M in preclinical R&D milestone payments
  - Eligible to receive up to $201M in additional milestone payments
    - Preclinical R&D, clinical development and regulatory milestones of $86M
    - Sales-based milestone payments of up to $115M

Source: Company Reports

CELG Partnership Validates Platform Given Its Familiarity with Epigenetics (Vidaza)

LEERINK SWANN

- In April 2012 Epizyme granted CELG an exclusive license to OUS rights to the DOT1L program (including EPZ-5676), and to two other HMT programs
  - EPZM received $65M upfront and $25M from the sale of $25M in series C preferred stock
  - Up to $160M in clinical and regulatory milestones for DOT1L
  - CELG has the option to license OUS rights for other HMT programs (excluding HMT targets covered by two other existing collaborations)
  - Up to $165M in option exercise fees, clinical and regulatory milestones for each additional a target as to which CELG exercises its option by July 2015
  - CELG can extend the option period until 2016 by making a significant option extension payment
  - EPZM retains full US rights and is eligible to receive royalties for each target from mid-single digits to the mid-teens on net product sales OUS

Source: Company Reports

Epizyme Has Raised >$144M From Partners On the Basis of Pre-Clinical Data

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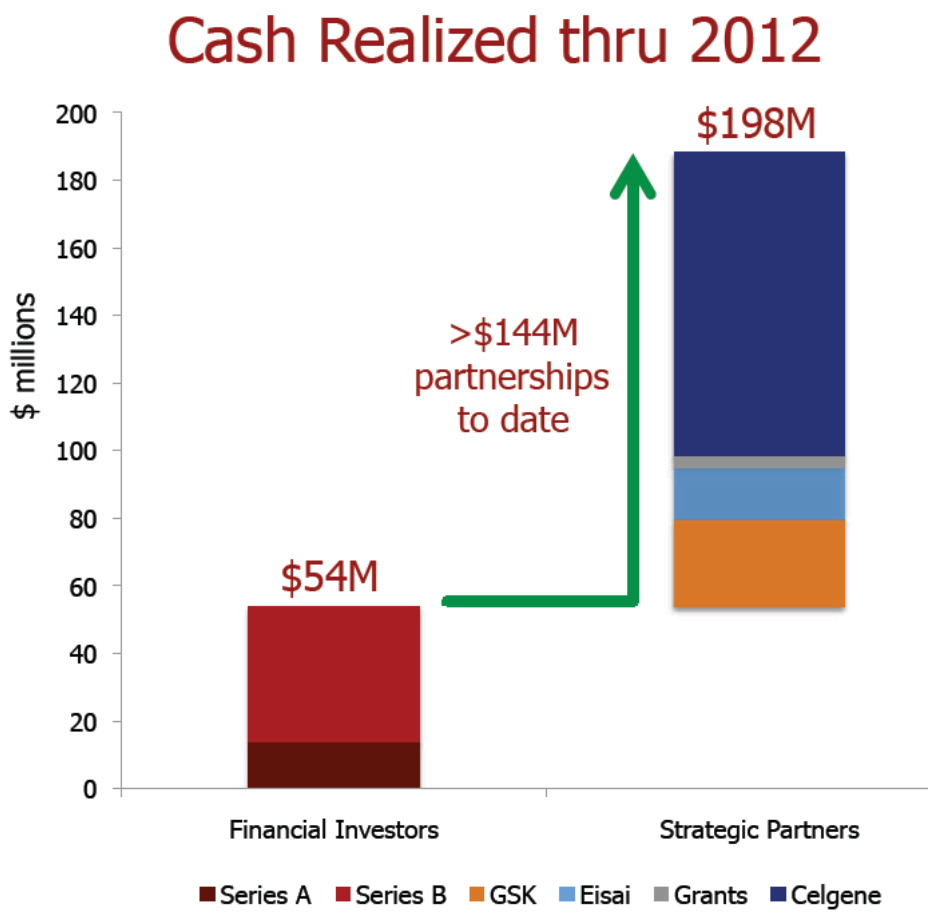

Series A: MPM, KPCB
Series B: MPM, KPCB, BCC, NEA, Amgen, Astellas

Source: Company Reports

LEERINK SWANN

INTELLECTUAL PROPERTY

Intellectual Property

- Exclusive worldwide license from the University of North Carolina
  - Fundamental biochemistry and diagnostic claims for the development of therapeutics directed to HMTs, including DOT1L and EZH2
  - 3 issued and 4 pending US patents and patent applications
  - 21 issued and 5 pending related patent cooperation treaty (PCT) applications and international patents and patent applications
  - Expire in 2027 and 2028

Source: Company Reports

DOT1L Patent Estate

LEERINK SWANN

- 1 US pending patent application for composition of Matter patent and Methods of Making EPZ-5676 – expires in 2031
  - Related PCT and international applications pending – expires in 2031
- Method-of-use patents, including composition of matter
  - 4 pending US provisional applications and 2 PCT applications – expire in 2031, 2032 and 2033
- Method of use for biomarkers
  - Clear freedom to operate with existing diagnostics as standard of care

Source: Company Reports

EZH2 Patent Estate

LEERINK SWANN

- Composition of Matter and Methods of Making on EPZ-6438
  - US Notice of Allowance for Patent Application 13/447,007 – expires in 2032 (Related PCT applications and international patent applications pending)
  - 3 pending US patent applications covering the composition of and method of making and using EPZ-6538 – expires in 2032
- Method of use and Composition of Matter on Additional New Chemical Entities
  - 11 pending US provisional applications (also eligible for worldwide filing) – expires in 2034
- Method of use for biomarkers
  - 2 pending US patent applications and 1 PCT application relating to method of using EZH2 modulators – expires in 2031

Source: Company Reports

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MANAGEMENT

Strong Management Team With History of Successful Drug Development

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Name	Title	Prior Experience
Robert Gould, PhD	President and CEO	Director of Novel Therapeutics at the Broad Institute of MIT and Harvard, VP Licensing and External Research at Merck
Robert Copeland, PhD	EVP of R&D and CSO	VP of Cancer Biology, Oncology Center of Excellence in Drug Development at GSK, scientific staff at Merck and BMS
Eric Hedrick, MD	CMO	VP Oncology Development at Pharmacyclics, Medical Director at Genentech
Jason Rhodes	EVP and CFO	VP Business Development at Alnylam, Founder and Partner at Fidelity Biosciences

Source: Company Reports

Impressive Scientific Advisory Board Lends Additional Credibility

LEERINK SWANN

Bob Horvitz, PhD (Chair)@*^	MIT	Cancer pathway genetics, epigenetics
Steve Henikoff, PhD*^	Fred Hutchinson Cancer Center	Epigenetics, chromatin
Yi Zhang, PhD^	Boston Children's	Epigenetic targets, biochemistry
Ron Evans, PhD*^	Salk Institute	Gene expression, cancer biology
Tyler Jacks, PhD*^	MIT	Cancer biology, cellular/animal models
George Daley, MD PhD^θ	Boston Children's Hospital	Epigenetic reprogramming, cancer biology
Chris Walsh, PhD*	Harvard Medical School	Biochemistry/enzymology, chemistry
Joel Huff, PhD	Merck retired	Medicinal chemistry
Bruce Chabner, MD	Mass General Hospital	Clinical oncology, drug development

Experienced and engaged

- Academic and industrial
- Epigenetics
- Cancer biology
- Drug discovery
- Animal models
- Medicinal chemistry
- Clinical oncology

@Nobel Laureate *Member, National Academy of Sciences θInstitute of Medicine ^Howard Hughes Medical Investigator

Source: Company Reports

Figures in $000, except EPS	2011A	2012A					2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
EPZ-5676																
US											6,753	62,552	123,760	170,843	230,779	338,118
EU											0	7,028	56,341	100,932	164,122	215,866
JP											0	0	1,114	8,908	18,153	25,842
Total											6,753	69,580	181,214	280,684	413,053	579,826
Probability of success											*50.0%*	*50.0%*	*50.0%*	*50.0%*	*50.0%*	*50.0%*
OUS Royalty Rate												*5.0%*	*5.0%*	*6.0%*	*7.0%*	*8.0%*
EPZ-6438																
US											0	23,725	219,752	431,736	587,653	846,568
EU											0	0	13,627	122,900	236,425	316,887
JP											0	0	0	1,644	14,800	29,569
Total											0	23,725	233,379	556,280	838,877	1,193,024
Probability of success											*40.0%*	*40.0%*	*40.0%*	*40.0%*	*40.0%*	*40.0%*
OUS Royalty Rate												*6.0%*	*6.0%*	*6.0%*	*6.0%*	*6.0%*
Booked by Epizyme																
EPZ-5676 US (POS adjusted)											3,377	31,276	61,880	85,422	115,389	169,059
EPZ-6438 US (POS adjusted) - 50% share											0	4,745	43,950	86,347	117,531	169,314
Sales booked by other companies																
EPZ-5676 (POS adjusted)											0	3,514	28,727	54,920	91,137	120,854
EPZ-6438 (POS adjusted)											0	0	5,451	49,818	100,490	138,583
Royalties																
EPZ-5676 (POS adjusted)											0	176	1,436	3,295	6,380	9,668
EPZ-6438 (POS adjusted)											0	0	327	2,989	6,029	8,315
Collaboration revenue	6,944	45,222	8,882	13,000	9,000	10,000	40,882	60,000	35,000	20,000	20,000	20,000	0	0	0	0
Total revenues			8,882	13,000	9,000	10,000	40,882	60,000	35,000	20,000	23,377	56,197	107,594	178,053	245,329	356,356
Operating expenses:																
Research and development	22,911	38,482	13,361	15,000	15,000	15,000	58,361	65,000	70,000	70,000	70,000	70,000	70,000	70,000	70,000	70,000
General and administrative	5,000	7,508	2,998	3,000	3,000	3,000	11,998	15,000	15,000	15,000	35,000	50,000	50,000	50,000	50,000	50,000
Total operating expenses	27,911	45,990	16,359	18,000	18,000	18,000	70,359	80,000	85,000	85,000	105,000	120,000	120,000	120,000	120,000	120,000
Loss from operations	(20,967)	(768)	(7,477)	(5,000)	(9,000)	(8,000)	(29,477)	(20,000)	(50,000)	(65,000)	(81,623)	(63,803)	(12,406)	58,053	125,329	236,356
Other income (expense):																
Interest income	33	145	19	20	20	20	79	79	79	79	79	79	79	79	79	79
Other expense	(23)	(78)	(39)	(40)	(40)	(40)	(159)	(159)	(159)	(159)	(159)	(159)	(159)	(159)	(159)	(159)
Other income (expense), net	10	67	(20)	(20)	(20)	(20)	(80)	(80)	(80)	(80)	(80)	(80)	(80)	(80)	(80)	(80)
Loss before income taxes	(20,957)	(701)	(7,497)	(5,020)	(9,020)	(8,020)	(29,557)	(20,080)	(50,080)	(65,080)	(81,703)	(63,883)	(12,486)	57,973	125,249	236,276
Income tax expense	—	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Net income	(20,957)	(702)	(7,497)	(5,020)	(9,020)	(8,020)	(29,557)	(20,080)	(50,080)	(65,080)	(81,703)	(63,883)	(12,486)	57,973	125,249	236,276
Less: accretion of redeemable convertible preferred stock to redemption value	45	486	157	0	0	0	157	0	0	0	0	0	0	0	0	0
Loss attributable to common stockholders	(21,002)	(1,188)	(7,654)	(5,020)	(9,020)	(8,020)	(29,714)	(20,080)	(50,080)	(65,080)	(81,703)	(63,883)	(12,486)	57,973	125,249	236,276
Loss per share attributable to common stockholders:																
Basic	($14.65)	($0.72)	($4.27)	($2.80)	($0.32)	($0.28)	($7.67)	($0.69)	($1.70)	($2.18)	($2.70)	($2.08)	($0.40)	$1.83	$3.89	$7.24
Diluted	($14.65)	($0.72)	($4.27)	($2.80)	($0.27)	($0.24)	($7.59)	($0.60)	($1.47)	($1.88)	($2.32)	($1.79)	($0.34)	$1.58	$3.35	$6.23
Weighted average shares outstanding:																
Basic	1,434	1,645	1,791	1,791	28,414	28,414	15,103	28,982	29,417	29,858	30,306	30,761	31,222	31,690	32,166	32,648
Diluted	1,434	1,645	1,791	1,791	32,985	32,985	17,388	33,645	34,149	34,662	35,182	35,709	36,245	36,789	37,340	37,901

Source: Company information and Leerink Swann estimates

Disclosures Appendix

Analyst Certification

I, Howard Liang, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

Distribution of Ratings/Investment Banking Services (IB) as of 03/31/13				
			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	107	61.14	32	29.91
HOLD [MP]	68	38.86	0	0.00
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): **We expect this stock to outperform its benchmark over the next 12 months.**

Market Perform (Hold/Neutral): **We expect this stock to perform in line with its benchmark over the next 12 months.**

Underperform (Sell): **We expect this stock to underperform its benchmark over the next 12 months.The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.**

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

Important Disclosures

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