INITIATING COVERAGE
Biotechnology
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EPIZYME INC (NASDAQ:EPZM)

Harnessing the power of epigenetics to address orphan cancers

We are initiating coverage on Epizyme with an Outperform rating. Epizyme is the first company to enter the clinic with highly selective inhibitors of histone methyltransferases, a novel class of epigenetic targets, which play a key role in fine-tuning the transcriptional regulation of gene expression.

Employing the Xalkori/Zelboraf model in hematology, harnessing the power of epigenetics.

Both of Epizyme's clinical programs are targeting high unmet medical need hematology/oncology indications (leukemia for EPZ-5676 and lymphoma for EPZ-6438), with genetically defined patient populations, and are being developed together with companion diagnostics. Epizyme is taking a page out of Pfizer's and Roche's playbooks, aiming to emulate the quick-to-market success of next-generation, truly-targeted cancer therapies plus companion diagnostics, Xalkori and Zelboraf, that at least partly due to appropriate patient screening of ALK and BRAF mutational status in lung cancer and melanoma, respectively, were able to make it from first patient treated to approval in about five years.

Multiple partnerships provide cash and validation, but without having given away the store.

Epizyme has formed three partnerships since 2011 (GSK, Eisai, Celgene), which have provided 1) big pharma validation for its R&D efforts and 2) $150M in cash as of today, with another $1B in possible milestones. Epizyme has managed to get this, while retaining US rights in one case (Celgene), and the option to co-promote in the US (Eisai) in another.

We expect investors to continue to assign a premium to Epizyme's valuation.

We believe Epizyme's market cap and EV are certainly outliers when looked at by standard valuation metrics for biotechs, given its early stage of development. However, we believe that this is a company that will continue to trade at a premium to what would have been considered its conventional peers, given among others, 1) the novelty of its targets and 2) the value that investors would assign to the company's "platform" of additional HMT targets, IP, and know-how.

Please see addendum of this report for important disclosures.

Recommendation

Rating:	Outperform
Price Target (in $):	NA
Dividend:	NA
Enterprise Value (MM):	$761.0

Revenue ($M)

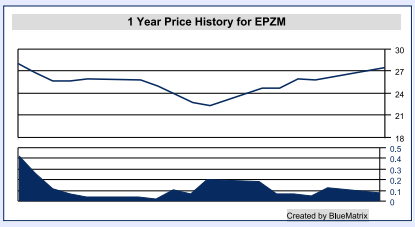
	2012A	2013E	2014E
Q1	5.7	8.9A	6.5
Q2	--	14.8	31.5
Q3	--	9.2	6.5
Q4	--	9.5	16.5
FY	45.2	42.4	60.8

Stock Statistics as of 06/24/2013 (in $)

Price:	$27.55
52W Range:	$30.86-$15.00
Shares Out (MM):	33.0
Market Cap (MM):	$782.8
Net Debt (MM):	$0.0
Net Cash Per Share:	$5.18

Fundamentals

Earnings Per Share ('12A)	*$(0.72)*
Earnings Per Share ('13E)	*$(1.11)*
Earnings Per Share ('14E)	*$(0.51)*
P/E ('12)	NM
P/E ('13)	NM
P/E ('14)	NM



Company Description

Epizyme is a biotechnology company focused on discovering, developing, and commercializing personalized therapeutics for patients with genetically defined cancers. Specifically, the company is focused on the field of epigenetics and on developing small molecule inhibitors against a class of enzyme targets called histone methyltransferases (HMTs) that play a key role in the regulation of gene expression. Epizyme's pipeline programs include: 1) EPZ-5676, an intravenously-administered small molecule inhibitor of DOT1L, a well-characterized HMT, which is partnered with Celgene ex-U.S., and is currently in a Phase I dose-escalation trial in MLL-rearranged leukemia, an aggressive subtype of acute leukemia (AML and ALL), with data expected in 2H13, and 2) EPZ-6438, an orally available, small molecule inhibitor of EZH2, another well-characterized HMT, which is partnered with Eisai WW and recently entered a Phase I/II trial for the treatment of genetically defined subtypes of non-Hodgkin lymphoma. In addition to the Celgene and Eisai partnerships, Epizyme also has a collaboration agreement with GlaxoSmithKline to develop and commercialize small molecule HMT inhibitors, directed against up to three undisclosed targets. These three collaborations have generated $150M in realized funding for the company. Epizyme was founded in November 2007, and went public in May 2013. The company is headquartered in Cambridge, MA and has 49 employees.

Epizyme: R&D pipeline

Candidate name	Indication	P-C	I	II	III	FILING	MKT	Comments
EPZ-5676 (DOT1L inhibitor)	MLL-r subtype of AML and ALL		•					Partnered with Celgene ex-US; Dose-escalation data expected 2H13
EPZ-6438 (EZH2 inhibitor)	DLBCL/FL with EZH2 mutation		•					Partnered with Eisai; Phase I/II trial initiated June 2013
Total Drugs in Development		**0**	**2**	**0**	**0**	**0**	**0**	
Cambridge, MA	**Investor Relations Contact: Stephanie Ascher - 212.362.1200**							

Source: Cowen and Company, Epizyme

Epizyme: Upcoming Milestones

Milestones	Timing
EPZ-5676 (DOT1L)	
Initiate expansion cohort of Phase I trial of EPZ-5676 in MLL-r subtype of AML and ALL	2H13
Data from the dose-escalation portion of the Phase I trial of EPZ-5676 in MLL-r subtype of AML and ALL	2H13
Initiate pivotal trial of EPZ-5676 in MLL-r subtype of AML and ALL	2015
EPZ-6438 (EZH2)	
Initiate Phase II portion of the Phase I/II trial of EPZ-6438 in NHL (DLBCL/FL) subtypes	1H14
Data from a Phase I/II trial of EPZ-6438 for the treatment of genetically defined NHL (DLBCL/FL) subtypes	1H14
Other	
Submit IND application for GSK's 1st undisclosed HMT target	4Q14
Submit IND application for GSK's 2nd undisclosed HMT target	2015
Submit IND application for GSK's 3rd undisclosed HMT target	2015

Source: Cowen and Company, Epizyme

Investment Thesis

We are initiating coverage on Epizyme with an Outperform rating. Epizyme is the first company to enter the clinic with highly selective inhibitors of histone methyltransferases, a novel class of epigenetic targets, which play a key role in fine-tuning the transcriptional regulation of gene expression.

Employing the Xalkori/Zelboraf model in hematology, harnessing the power of epigenetics: Both of Epizyme's clinical programs are targeting high unmet medical need hematology/oncology indications (leukemia for EPZ-5676 and lymphoma for EPZ-6438), with genetically defined patient populations, and are being developed together with companion diagnostics. Epizyme is taking a page out of Pfizer's and Roche's playbooks, aiming to emulate the quick-to-market success of next-generation, truly-targeted cancer therapies plus companion diagnostics, Xalkori and Zelboraf, that at least partly due to appropriate patient screening of ALK and BRAF mutational status in lung cancer and melanoma, respectively, were able to make it from first patient treated to approval in about five years.

This development strategy aims for the most appropriate patient selection that, in addition to requiring smaller trials, could result in maximizing the drug's efficacy while minimizing safety and tolerability issues. Taking this approach a step further, when dealing with an orphan disease with a significant unmet medical need, a drug with these characteristics could command premium pricing and could be commercialized by a small specialty salesforce in the U.S.

First clinical data provide MOA validation and investor excitement: more to come in next 12-18 months: Epizyme initiated its first clinical trial with EPZ-5676, its first ever clinical program, in September 2012. EPZ-5676 targets DOT1L, a histone methyltransferase (HMT) that is recruited to the "wrong" transcriptional complexes in patients with MLL-rearranged leukemia, leading to inappropriate gene expression. This program is developed in collaboration with Celgene, with Epizyme owning US rights. Data from the first handful of patients treated with EPZ-5676 were consistent with the drug's mechanism of action, as seen in tissue culture and animals, and generated significant interest among investors. The hematologists we consulted with confirmed both the "*significant unmet need*" and "*very poor prognosis*" of MLL-r patients and were encouraged by the preclinical data, and especially the response seen by the first MLL-r patient treated in the Phase I trial of EPZ-5676. The company is expecting additional data from the dose escalation portion of the Phase I study in 2H13.

Second program in the clinic just initiated; first data expected 1H14: Epizyme initiated the Phase I/II study of EPZ-6438, its second clinical program, an EZH2 inhibitor, in June 2013, in patients with advanced solid tumors and hematologic malignancies, including Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL). We consulted with a number of hematologists that treat both diseases and familiar with the epigenetic space and the EZH2 mutation population in particular. Similar to the situation in MLL-r, our consultants believe that there's a real need for targeted agents in the space and were encouraged by the preclinical data Epizyme has produced thus far. This program is developed in collaboration with Eisai,

with Epizyme having the option to co-promote in the US. Data from the Phase I portion of the study are expected to be announced in 1H14.

Multiple partnerships provide cash and validation, but without having given away the store: Epizyme has formed three partnerships since 2011 (GSK, Eisai, Celgene), which have provided 1) big pharma validation for its R&D efforts and 2) $150M in cash as of today, with another $1B in possible milestones. Epizyme has managed to get this, while retaining US rights in one case (Celgene), and the option to co-promote in the US (Eisai) in another.

We expect investors to continue to assign a premium to Epizyme's valuation. We believe Epizyme's market cap and EV are certainly outliers when looked at by standard valuation metrics for biotechs, given its early stage of development. However, we believe that this is a company that will continue to trade at a premium to what would have been considered its conventional peers, given among others, 1) the novelty of its targets and 2) the value that investors would assign to the company's "platform" of additional HMT targets, IP, and know-how

It's still very early, and there's obviously significant clinical and downside risk… It is obvious to investors that given Epizyme's early stage of development, there are both significant clinical risk (both of the company's clinical programs are in Phase I trials, with data reported from only one MLL-r patient reported at the time of our report), and a lot of potential downside to an investment in EPZM, given the company's $900M valuation.

…but we believe that *if* one of the first two indications works, Epizyme, with its leading IP and know-how position in HMT biology, becomes an acquisition target. With that in mind, we also believe that even though Epizyme is built and operated to function as a stand-alone, fully-integrated biotech, with R&D, sales, and marketing in the US, *should* one of its first two clinical programs result in a clinical, regulatory, or commercial success, given its leading position in the HMT space, the company would become a very attractive acquisition target by a larger biopharma interested in owning all its clinical and preclinical assets, IP, and know-how.

Valuation

To value Epizyme shares, we use a sum-of-the-parts methodology, and estimate the probability-adjusted NPV of: **1)** EPZ-5676 sales, royalties, and milestone payments, **2)** EPZ-6438 sales, royalties, and milestone payments, **3)** Epizyme's platform technology, and **4)** the company's current net cash position.

1) EPZ-5676 sales, royalties, and milestone payments ($10.34/share)

Epizyme is developing EPZ-5676 in partnership with Celgene. Under the partnership agreement, Epizyme retains full U.S. rights, and Celgene has ex-U.S. rights. Epizyme is eligible to receive royalties at percentages ranging from the *mid-single digits to the mid-teens* on net sales outside of the U.S., which we have assumed to be starting at 5% and reaching as high as 15%. For modeling purposes and in our NPV calculations, we have assumed that Epizyme will receive milestone payments of $25M in 2014 from Celgene for achieving proof-of-concept (POC) for EPZ-5676, $35M in 2016 for BLA/MAA submissions, and $50M for U.S./E.U. approvals in 2017.

U.S./E.U. EPZ-5676 sales in MLL-rearranged leukemia: We have modeled that EPZ-5676 could reach peak sales of approximately $230M and $190M in the U.S. and E.U., respectively, for total peak sales of $420M in 2032. Based on these assumptions, and assuming success in both the Phase I/II and pivotal trials, Epizyme could start recording sales and receiving royalties on EPZ-5676 sales in 2017, which could reach a peak of around $258M by 2032.

Discount Rate and Probability of Success (POS): In calculating the net present value of EPZM-5676's free cash flows, we use a 10% discount rate and probability-adjust the revenues to Epizyme by assigning a 40% overall probability of success (POS) that the compound is fully developed, approved, and reaches the market in the U.S. and the E.U.

EPZ-5676: NPV analysis

($MM)	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E
EPZ-5676 Revenue																				
Total US Sales ($MM)	-	-	-	-	30.0	92.5	137.4	163.2	167.9	172.8	177.8	182.9	188.2	193.7	199.3	205.0	211.0	217.1	223.4	229.9
Total EU royalties ($MM)	-	-	-	-	-	1.4	6.1	11.6	16.7	20.1	23.7	24.2	24.7	25.2	25.8	26.3	26.9	27.4	28.0	28.6
Total Revenue to EPZM ($MM)	**0.0**	**0.0**	**0.0**	**0.0**	**30.0**	**93.9**	**143.5**	**174.7**	**184.6**	**192.9**	**201.5**	**207.1**	**212.9**	**218.9**	**225.0**	**231.4**	**237.8**	**244.5**	**251.4**	**258.5**
Milestone payments received from partner		25.0	-	35.0	50.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
COGS	-	-	-	-	3.0	9.2	12.4	13.1	13.4	13.8	14.2	14.6	15.1	15.5	15.9	16.4	16.9	17.4	17.9	18.4
R&D	13.4	13.9	9.0	9.0	7.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SG&A	-	-	-	1.5	18.0	18.3	17.7	18.0	18.3	18.6	18.9	19.3	19.6	19.9	20.3	20.6	21.0	21.3	21.7	22.1
Tax adjusted EBIT	(13.4)	11.1	(9.0)	24.5	51.9	61.0	102.1	102.0	99.4	104.3	109.4	112.6	115.9	119.3	122.7	126.3	130.0	133.8	137.7	141.7
Tax rate		*0%*	*0%*	*0%*	*0%*	*8%*	*10%*	*29%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
EPZ-5676 free cash flow	**(13.4)**	**11.1**	**(9.0)**	**24.5**	**51.9**	**61.0**	**102.1**	**102.0**	**99.4**	**104.3**	**109.4**	**112.6**	**115.9**	**119.3**	**122.7**	**126.3**	**130.0**	**133.8**	**137.7**	**141.7**
% y/y growth							*67%*	*0%*	*-3%*	*5%*	*5%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
Discount Period	*0.52*	*1.52*	*2.52*	*3.52*	*4.52*	*5.52*	*6.52*	*7.52*	*8.52*	*9.52*	*10.52*	*11.52*	*12.52*	*13.52*	*14.52*	*15.52*	*16.52*	*17.52*	*18.52*	*19.52*
Discount Factor	*0.95*	*0.87*	*0.79*	*0.72*	*0.65*	*0.59*	*0.54*	*0.49*	*0.44*	*0.40*	*0.37*	*0.33*	*0.30*	*0.28*	*0.25*	*0.23*	*0.21*	*0.19*	*0.17*	*0.16*
PV of EPZ-5676 FCF	**(12.8)**	**9.6**	**(7.1)**	**17.6**	**33.8**	**36.1**	**54.9**	**49.8**	**44.1**	**42.1**	**40.2**	**37.6**	**35.1**	**32.9**	**30.8**	**28.8**	**26.9**	**25.2**	**23.6**	**22.1**

Discount Rate	10%
Perpetual Growth Rate	2%
Final year FCF	$142
Terminal Value	$1,807
Discount Factor	0.16
Present Value of Terminal Value	**$281**
Present Value of Cash Flows	**$571**
Present Value of Total Cash Flows	**$852**
Fully Diluted Shares Outstanding	33
NPV of EPZ-5676	**$25.85**
Probability of Success	***40%***
NPV of EPZ-5676 (probability-adjusted)	**$10.34**

Source: Cowen and Company

2) EPZ-6438 sales, royalties, and milestone payments ($9.63/share)

Epizyme is developing EPZ-6438 in a worldwide partnership with Eisai, under which Epizyme is eligible to receive *mid-single digits to low double-digits royalties on U.S. sales and flat mid-single digit royalties on ex-U.S. sales*. Epizyme also has an opt-in right to co-develop, co-commercialize, and share profits with Eisai in the U.S. For modeling purposes and in our NPV calculations, we have assumed that Epizyme will exercise its option and will co-promote EPZ-6438 in the U.S. by building its own salesforce organization. We have assumed that both Epizyme and Eisai will book revenue. In our model, we assume that Epizyme will book its portion of U.S. sales and associated costs, and that Eisai will book full ex-U.S. sales and its half of U.S. sales. We are assuming that Epizyme will receive a milestone payment of $10M in 2014 from Eisai for achieving POC for EPZ-6438, $10M in 2015 for initiation of a pivotal trial, $20M in 2017 for BLA/MAA submissions, $25M in 2018 for U.S/E.U. approvals, and $25M in sales-based milestones in 2019, 2021, and 2023, respectively.

U.S./E.U. EPZ-6438 sales in NHL: We have modeled that EPZ-6438 could reach peak sales of approximately $540M and $400M in the U.S. and E.U., respectively, for total peak sales of $940M in 2032. Based on these assumptions, and assuming success in both the Phase I/II

and pivotal trials, Epizyme could start recording sales and receiving royalties on EPZ-6438 sales in 2018, which could reach a peak of $291M by 2032.

Discount Rate and Probability of Success (POS): In calculating the net present value of EPZ-6438's free cash flows, we use a 10% discount rate and probability-adjust the revenues to Epizyme by assigning a 33% overall probability of success (POS) that the compound is fully developed, approved, and reaches the market in the U.S. and the E.U.

EPZ-6438: NPV analysis

($MM)	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E
EPZ-6438 Revenues to EPZM																				
Total US Sales (50% of total US sales) ($MM)	-	-	-	-	-	39.0	120.4	178.9	198.2	204.0	209.9	216.0	222.2	228.7	235.3	242.1	249.1	256.4	263.8	271.4
Total EU royalties ($MM)	-	-	-	-	-	-	3.2	9.9	14.7	16.1	16.5	16.8	17.2	17.5	17.9	18.3	18.7	19.1	19.5	19.9
Total Revenue to EPZM ($MM)	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**39.0**	**123.6**	**188.8**	**212.9**	**220.1**	**226.4**	**232.8**	**239.4**	**246.2**	**253.2**	**260.4**	**267.8**	**275.4**	**283.2**	**291.3**
Milestone payments received from partner		10.0	10.0	-	20.0	25.0	25.0	-	25.0	-	25.0	-	-	-	-	-	-	-	-	-
COGS		-	-	-	-	3.9	10.8	14.3	15.9	16.3	16.8	17.3	17.8	18.3	18.8	19.4	19.9	20.5	21.1	21.7
R&D	2.1	3.4	10.0	10.0	7.5	2.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SG&A	-	-	-	-	1.5	8.6	8.8	8.9	9.0	9.2	9.4	9.5	9.7	9.9	10.0	10.2	10.3	10.5	10.7	10.8
Tax adjusted EBIT	(2.1)	6.6	-	(10.0)	11.0	45.1	116.1	117.6	138.5	126.5	146.4	133.9	137.8	141.7	145.8	150.1	154.4	158.9	163.4	168.2
Tax rate		*0%*	*0%*	*0%*	*0%*	*8%*	*10%*	*29%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
EPZ-6438 free cash flow	**(2.1)**	**6.6**	**0.0**	**(10.0)**	**11.0**	**45.1**	**116.1**	**117.6**	**138.5**	**126.5**	**146.4**	**133.9**	**137.8**	**141.7**	**145.8**	**150.1**	**154.4**	**158.9**	**163.4**	**168.2**
% y/y growth							*157%*	*1%*	*18%*	*-9%*	*16%*	*-9%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
Discount Period	*0.52*	*1.52*	*2.52*	*3.52*	*4.52*	*5.52*	*6.52*	*7.52*	*8.52*	*9.52*	*10.52*	*11.52*	*12.52*	*13.52*	*14.52*	*15.52*	*16.52*	*17.52*	*18.52*	*19.52*
Discount Factor	*0.95*	*0.87*	*0.79*	*0.72*	*0.65*	*0.59*	*0.54*	*0.49*	*0.44*	*0.40*	*0.37*	*0.33*	*0.30*	*0.28*	*0.25*	*0.23*	*0.21*	*0.19*	*0.17*	*0.16*
PV of EPZ-6438 FCF	**(2.0)**	**5.7**	**0.0**	**(7.2)**	**7.1**	**26.7**	**62.4**	**57.4**	**61.5**	**51.1**	**53.7**	**44.7**	**41.8**	**39.1**	**36.6**	**34.2**	**32.0**	**29.9**	**28.0**	**26.2**

Discount Rate	10%
Perpetual Growth Rate	2%
Final year FCF	$168
Terminal Value	$2,144
Discount Factor	0.16
Present Value of Terminal Value	**$334**
Present Value of Cash Flows	**$629**
Present Value of Total Cash Flows	**$962**
Fully Diluted Shares Outstanding	33
NPV of EPZ-6438	**$29.19**
Probability of Success	***33%***
NPV of EPZ-6438 (probability-adjusted)	**$9.63**

Source: Cowen and Company

3) Platform technology value ($6.07/share): We believe that the market assigns a certain value to the company's technology, know-how, IP, and additional preclinical targets. We also believe that this value A) is very difficult to accurately quantify, and B) could increase or decrease significantly, based on the outcome of the first two clinical programs. For the purpose of valuing the company at this point, we have decided to assign $200M in value to its epigenetics technology platform.

4) Net Cash ($5.18/share): Epizyme ended 1Q13 with $85M in cash. In May 2013, Epizyme raised $79.8M in net proceeds in its IPO by issuing 5.9M shares at $15/share. In June 2013, Epizyme received a $6M milestone payment from Eisai for the initiation of the Phase I/II trial of

EPZ-6438 in NHL. Epizyme's current proforma net cash position is approximately $171M or $5.18 per fully diluted share.

Epizyme: Company sum-of-the-parts valuation

EPZ-5676 (DOT1L)	$10.34
EPZ-6438 (EZH2)	$9.63
Platform value	$6.07
Net Cash	$5.18
Sum-of-the-parts total value for EPZM	**$31.22**

Source: Cowen and Company

EPZ-5676 Revenue Model

Epizyme is developing EPZ-5676 in partnership with Celgene. Under the partnership agreement, Epizyme retains full U.S. rights, and Celgene has ex-U.S. rights. Epizyme is eligible to receive royalties at percentages ranging from the *mid-single digits to the mid-teens* on net sales outside of the U.S., and is also entitled to receive up to $160M in milestones ($60M in development and $100M in regulatory milestones) related to EPZ-5676. There are no commercial milestones under the agreement. For modeling purposes and in our NPV calculations, we have assumed that Epizyme will receive milestone payments of $25M in 2014 for achieving proof-of-concept (POC) for EPZ-5676, $35M in 2016 for BLA/MAA submissions, and $50M for U.S./E.U. approvals in 2017.

MLL-rearranged (MLL-r) acute lymphoblastic leukemia (ALL) patients eligible for treatment with EPZ-5676: According to the latest NCI estimates, in 2013, approximately 48,610 patients will be diagnosed with acute and chronic leukemia, and approximately 6,070 patients will be diagnosed with ALL, which is the most common form of leukemia in children. According to a number of sources in published literature, MLL-r leukemia accounts for about 10% of all acute leukemias, corresponding to an incidence of approximately 610 MLL-r ALL patients in the U.S. According to our consultants, nearly all patients with MLL-r ALL are treated in the first line setting, with an approximately 70%-80% relapse rate. We have assumed that 95% of patients are treated in the first-line setting, and that 70% are refractory to or relapse after treatment. This corresponds to approximately 400 MLL-r ALL patients in the U.S. and 520 patients in the E.U. who would be eligible for treatment with EPZ-5676.

MLL-r acute myeloid leukemia (AML) patients eligible for treatment with EPZ-5676: AML represents the most common form of acute leukemia in adults. In the U.S., approximately 14,590 patients will be diagnosed with AML in 2013. According to a number of sources in published literature, MLL-r leukemia accounts for about 10% of all acute leukemias. For MLL-r AML, this would correspond with an incidence of approximately 1,460 patients in the U.S. According to our consultants, nearly all patients with MLL-r AML are treated in the first line setting, with an approximately 70%-90% relapse rate. We have assumed that 95% of patients are treated in the first-line setting, and that 70% are refractory to or relapse after treatment.

This corresponds to 1,021 MLL-r AML patients in the U.S. and 1,309 patients in the E.U. who would be eligible for treatment with EPZ-5676.

Total eligible U.S. and E.U. population: In calculating the total eligible population of MLL-r leukemia patients, we have added the EPZ-5676-eligible numbers we derived for the MLL-r subpopulations in ALL (404 in U.S. and 517 in E.U.) and AML (1,021 in U.S. and 1,309 in E.U.). The total numbers of patients eligible for EPZ-5676 treatment are therefore 1,425 and 1,826 in the U.S. and E.U., respectively.

Pricing and penetration rates: In terms of pricing, we estimate that EPZ-5676 will be launched in 2017, at an average yearly cost of $135,300 in the U.S. We arrive at that price by using a 2013 launch price of $125,000 and applying a 2% annual increase through 2017. Adcetris, which is approved for Hodgkin's Lymphoma, has an average annual treatment cost of $116,000. For the E.U., we have assumed a 25% discount to the U.S. pricing, with launch in 2018.

Peak penetration in the relapsed/refractory setting: We expect the pivotal registration trial evaluating EPZ-5676 in the relapsed/refractory setting to read out in 2016. We estimate that U.S./E.U. EPZ-5676 sales for relapsed/refractory MLL-r leukemia will reach $292M in 2020, and that at 75% penetration in the U.S. and E.U., EPZ-5676 could reach peak U.S./E.U. sales of $420M in 2032.

EPZ-5676 Revenue Model ($MM)

US EPZ-5676 MLL-r Revenue Model	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E
US population	319,455,250	322,266,457	325,102,401	327,963,303	330,849,380	333,760,854	336,697,950	339,660,892	342,649,907	345,665,227	348,707,081	351,775,703	354,871,329	357,994,197	361,144,546	364,322,618	367,528,657	370,762,909	374,025,623	377,317,048
Population growth	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*
# of new leukemia cases	48,610	49,038	49,469	49,905	50,344	50,787	51,234	51,685	52,139	52,598	53,061	53,528	53,999	54,474	54,954	55,437	55,925	56,417	56,914	57,415
# of leukemia patients with ALL	6,070	6,123	6,177	6,232	6,287	6,342	6,398	6,454	6,511	6,568	6,626	6,684	6,743	6,802	6,862	6,923	6,983	7,045	7,107	7,169
% of leukemia patients with ALL	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*
% of ALL patients with MLL-r	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
# of ALL patients with MLL-r	607	612	618	623	629	634	640	645	651	657	663	668	674	680	686	692	698	704	711	717
% of patients treated in the 1st-line setting	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients treated in the 1st-line setting	577	582	587	592	597	602	608	613	619	624	629	635	641	646	652	658	663	669	675	681
% relapse rate	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# of ALL patients with MLL-r eligible for treatment	**404**	**407**	**411**	**414**	**418**	**422**	**425**	**429**	**433**	**437**	**441**	**444**	**448**	**452**	**456**	**460**	**464**	**468**	**473**	**477**
# of leukemia patients with AML	14,590	14,718	14,848	14,979	15,110	15,243	15,377	15,513	15,649	15,787	15,926	16,066	16,208	16,350	16,494	16,639	16,786	16,933	17,082	17,233
% of leukemia patients with AML	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
% of AML patients with MLL-r	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
# of AML patients with MLL-r	1,459	1,472	1,485	1,498	1,511	1,524	1,538	1,551	1,565	1,579	1,593	1,607	1,621	1,635	1,649	1,664	1,679	1,693	1,708	1,723
% of patients treated in the 1st-line setting	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients treated in the 1st-line setting	1,386	1,398	1,411	1,423	1,435	1,448	1,461	1,474	1,487	1,500	1,513	1,526	1,540	1,553	1,567	1,581	1,595	1,609	1,623	1,637
% relapse rate	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# of AML patients with MLL-r eligible for treatment	**1,021**	**1,030**	**1,039**	**1,049**	**1,058**	**1,067**	**1,076**	**1,086**	**1,095**	**1,105**	**1,115**	**1,125**	**1,135**	**1,145**	**1,155**	**1,165**	**1,175**	**1,185**	**1,196**	**1,206**
Total # of ALL+AML MLL-r patients eligible for treatment	**1,425**	**1,437**	**1,450**	**1,463**	**1,476**	**1,489**	**1,502**	**1,515**	**1,528**	**1,542**	**1,555**	**1,569**	**1,583**	**1,597**	**1,611**	**1,625**	**1,639**	**1,654**	**1,668**	**1,683**
% EPZ-5676 penetration					*15%*	*45%*	*65%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
# of patients treated with EPZ-5676	-	-	-	-	221	670	976	1,136	1,146	1,156	1,167	1,177	1,187	1,198	1,208	1,219	1,230	1,240	1,251	1,262
Annual treatment cost	$125,000	$127,500	$130,050	$132,651	$135,304	$138,010	$140,770	$143,586	$146,457	$149,387	$152,374	$155,422	$158,530	$161,701	$164,935	$168,234	$171,598	$175,030	$178,531	$182,101
% price increase	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*
Total US Sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$30**	**$92**	**$137**	**$163**	**$168**	**$173**	**$178**	**$183**	**$188**	**$194**	**$199**	**$205**	**$211**	**$217**	**$223**	**$230**

EU EPZ-5676 MLL-r Revenue Model	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E
EU population	504,393,906	504,898,300	505,403,198	505,908,601	506,414,510	506,920,925	507,427,845	507,935,273	508,443,209	508,951,652	509,460,603	509,970,064	510,480,034	510,990,514	511,501,505	512,013,006	512,525,019	513,037,544	513,550,582	514,064,132
Population growth	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*
# of new leukemia cases	62,284	62,347	62,409	62,471	62,534	62,596	62,659	62,722	62,784	62,847	62,910	62,973	63,036	63,099	63,162	63,225	63,288	63,352	63,415	63,478
% of leukemia patients with ALL	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*
# of leukemia patients with ALL	7,778	7,785	7,793	7,801	7,809	7,816	7,824	7,832	7,840	7,848	7,856	7,864	7,871	7,879	7,887	7,895	7,903	7,911	7,919	7,927
% of ALL patients with MLL-r	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
# of ALL patients with MLL-r	778	779	779	780	781	782	782	783	784	785	786	786	787	788	789	790	790	791	792	793
% of patients treated in the 1st-line setting	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients treated in the 1st-line setting	739	740	740	741	742	743	743	744	745	746	746	747	748	749	749	750	751	752	752	753
% relapse rate	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# of ALL patients with MLL-r eligible for treatment	**517**	**518**	**518**	**519**	**519**	**520**	**520**	**521**	**521**	**522**	**522**	**523**	**523**	**524**	**524**	**525**	**526**	**526**	**527**	**527**
% of leukemia patients with AML	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
# of leukemia patients with AML	18,694	18,713	18,732	18,750	18,769	18,788	18,807	18,825	18,844	18,863	18,882	18,901	18,920	18,939	18,958	18,977	18,996	19,015	19,034	19,053
% of AML patients with MLL-r	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
# of AML patients with MLL-r	1,869	1,871	1,873	1,875	1,877	1,879	1,881	1,883	1,884	1,886	1,888	1,890	1,892	1,894	1,896	1,898	1,900	1,901	1,903	1,905
% of patients treated in the 1st-line setting	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients treated in the 1st-line setting	1,776	1,778	1,780	1,781	1,783	1,785	1,787	1,788	1,790	1,792	1,794	1,796	1,797	1,799	1,801	1,803	1,805	1,806	1,808	1,810
% relapse rate	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# of AML patients with MLL-r eligible for treatment	**1,309**	**1,310**	**1,311**	**1,313**	**1,314**	**1,315**	**1,316**	**1,318**	**1,319**	**1,320**	**1,322**	**1,323**	**1,324**	**1,326**	**1,327**	**1,328**	**1,330**	**1,331**	**1,332**	**1,334**
Total # of ALL+AML MLL-r patients eligible for treatment	**1,826**	**1,828**	**1,829**	**1,831**	**1,833**	**1,835**	**1,837**	**1,839**	**1,840**	**1,842**	**1,844**	**1,846**	**1,848**	**1,850**	**1,852**	**1,853**	**1,855**	**1,857**	**1,859**	**1,861**
% EPZ-5676 penetration				*0%*	*0%*	*15%*	*45%*	*65%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
# of patients treated with EPZ-5676	-	-	-	-	-	275	827	1,195	1,380	1,382	1,383	1,384	1,386	1,387	1,389	1,390	1,391	1,393	1,394	1,396
Annual treatment cost	$93,750	$95,625	$97,538	$99,488	$101,478	$103,508	$105,578	$107,689	$109,843	$112,040	$114,281	$116,566	$118,898	$121,276	$123,701	$126,175	$128,699	$131,273	$133,898	$136,576
% price increase	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*
Total EU Sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$0**	**$28**	**$87**	**$129**	**$152**	**$155**	**$158**	**$161**	**$165**	**$168**	**$172**	**$175**	**$179**	**$183**	**$187**	**$191**
Total US/EU sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$30**	**$121**	**$225**	**$292**	**$320**	**$328**	**$336**	**$344**	**$353**	**$362**	**$371**	**$380**	**$390**	**$400**	**$410**	**$420**

Source: Cowen and Company

EPZ-6438 Revenue Model

Epizyme is developing EPZ-6438 in a worldwide partnership with Eisai, under which Epizyme is eligible to receive *mid-single digits to low double-digit royalties on U.S. sales and flat mid-single digit royalties on ex-U.S. sales*. Epizyme also has an opt-in right to co-develop, co-commercialize, and share profits with Eisai in the U.S. Epizyme is entitled to receive up to $201M in milestone payments ($31M in development and $55M in regulatory milestones related to EPZ-6438, and up to $115M in commercial milestones) under this agreement. For modeling purposes and in our NPV calculations, we have assumed that Epizyme will exercise its option and will co-promote EPZ-6438 in the U.S. by building its own salesforce organization. Both Epizyme and Eisai will book revenue. In our model, we have assumed that Epizyme will book its portion of U.S. sales and associated costs, and that Eisai will book full ex-U.S. sales and its half of U.S. sales. We are assuming that Epizyme will receive a milestone payment of $10M in 2014 from Eisai for achieving POC for EPZ-6438, $10M in 2015 for initiation of a pivotal trial, $20M in 2017 for BLA/MAA submissions, $25M in 2018 for U.S/E.U. approvals, and $25M in sales-based milestones in 2019, 2021, and 2023, respectively.

DLBCL patients eligible for EPZ-6438 treatment: According to the latest NCI estimates, approximately 69,740 patients will be diagnosed with non-Hodgkin lymphoma (NHL) in 2013. Diffuse large B-cell lymphoma (DLBCL) accounts for approximately one third of all NHL cases. DLBCL is broadly divided into two subtypes, termed germinal center B-cell-like (GCB) and activated B-cell-like (ABC), each accounting for approximately 50% of DLBCL cases. According to sources in published literature, EZH2 mutations are found in the GCB subtype of DLBCL, with an incidence of about 20%. This corresponds to 2,092 GCB-DLBCL patients with EZH2 mutations in the U.S. Epizyme is initially developing EPZ-6438 for the treatment of relapsed/refractory patients in this population. According to literature sources and our consultants, approximately one third of all DLBCL patients treated in the front-line setting are refractory to or relapse after treatment. In our revenue model, we assume that approximately 33% of patients with newly diagnosed DLBCL are eventually treated in the relapsed/refractory setting. For our model, in the U.S. and E.U., this then corresponds to 690 and 781 relapsed/refractory GCB-DLBCL patients with EZH2 mutations, who would be eligible for EPZ-6438 treatment.

FL patients eligible for EPZ-6438 treatment: According to the latest NCI estimates, approximately 69,740 patients will be diagnosed with NHL in 2013. According to different literature sources, follicular lymphoma (FL) represents between 20% and 33% of all NHL cases. In our model, being conservative, we have assumed 22%. EZH2 mutations are found in FL with an incidence of about 20%. We estimate this corresponds to 3,069 FL patients with EZH2 mutations. Epizyme is initially developing EPZ-6438 for the treatment of relapsed/refractory patients in this population. According to literature sources and our consultants, nearly all FL patients who receive first-line treatment eventually relapse and are further treated with second-line therapies. In our revenue model, we have assumed that approximately 95% of patients with newly diagnosed FL are treated in the relapsed/refractory setting. In the U.S. and E.U., this then corresponds to 2,915 and 4,076 relapsed/refractory FL patients with EZH2 mutations, who would be eligible for EPZ-6438 treatment.

Total eligible U.S. and E.U. population: In calculating the total eligible population of DLBCL and FL patients in the U.S. and the E.U., we have added the EPZ-6438-eligible numbers we derived for the DLBCL population (690 in U.S. and 781 in E.U.) and the FL population (2,915 in U.S. and 3,296 in E.U.). The total numbers of patients eligible for EPZ-6438 treatment are therefore 3,606 and 4,076 in the U.S. and E.U., respectively.

Pricing and penetration rates: In terms of pricing, we estimate that EPZ-6438 will be launched in 2018 at an average yearly cost of $138,010 in the U.S. We arrive at that price by using a 2013 launch price of $125,000 and applying a 2% annual increase through 2018. Adcetris, which is approved for Hodgkin's Lymphoma, has an average annual treatment cost of $116,000. For the E.U., we have assumed a 25% discount to the U.S. pricing, with launch in 2019.

Peak penetration in the relapsed/refractory setting: We expect the pivotal registration trial evaluating EPZ-6438 in the relapsed/refractory setting will read out in 2017. We estimate that WW EPZ-6438 sales for relapsed/refractory DLBCL and FL will reach $560M in 2020, and that at 70% penetration in the U.S. and E.U., EPZ-6438 could reach peak U.S./E.U. sales of $940M in 2032.

EPZ-6438 Revenue Model ($MM)

US EPZ-6438 Revenue Model	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E
US population	319,455,250	322,266,457	325,102,401	327,963,303	330,849,380	333,760,854	336,697,950	339,660,892	342,649,907	345,665,227	348,707,081	351,775,703	354,871,329	357,994,197	361,144,546	364,322,618	367,528,657	370,762,909	374,025,623	377,317,048
Population growth	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*
# of new non-Hodgkin lymphoma (NHL) cases	69,740	70,354	70,973	71,597	72,227	72,863	73,504	74,151	74,804	75,462	76,126	76,796	77,472	78,153	78,841	79,535	80,235	80,941	81,653	82,372
% of NHL patients with Diffuse large B-cell lymphoma (DLBCL)	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
# of NHL patients with DLBCL	20,922	21,106	21,292	21,479	21,668	21,859	22,051	22,245	22,441	22,639	22,838	23,039	23,241	23,446	23,652	23,860	24,070	24,282	24,496	24,712
% of patients with DLBCL that is of the GCB-DLBCL subtype	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
# of patients with DLBCL that is of the GCB-DLBCL subtype	10,461	10,553	10,646	10,740	10,834	10,929	11,026	11,123	11,221	11,319	11,419	11,519	11,621	11,723	11,826	11,930	12,035	12,141	12,248	12,356
% of GCB-DLBCL patients with EZH2 mutation	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
# of GCB-DLBCL patients with EZH2 mutation	2,092	2,111	2,129	2,148	2,167	2,186	2,205	2,225	2,244	2,264	2,284	2,304	2,324	2,345	2,365	2,386	2,407	2,428	2,450	2,471
% relapse rate	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*
# of patients with DLBCL eligible for treatment	**690**	**697**	**703**	**709**	**715**	**721**	**728**	**734**	**741**	**747**	**754**	**760**	**767**	**774**	**781**	**787**	**794**	**801**	**808**	**815**
% of NHL patients with Follicular lymphoma (FL)	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*
# of NHL patients with Follicular lymphoma (FL)	15,343	15,478	15,614	15,751	15,890	16,030	16,171	16,313	16,457	16,602	16,748	16,895	17,044	17,194	17,345	17,498	17,652	17,807	17,964	18,122
% of patients with FL with EZH2 mutation	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
# of patients with FL with EZH2 mutation	3,069	3,096	3,123	3,150	3,178	3,206	3,234	3,263	3,291	3,320	3,350	3,379	3,409	3,439	3,469	3,500	3,530	3,561	3,593	3,624
% relapse rate	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients with FL eligible for treatment	**2,915**	**2,941**	**2,967**	**2,993**	**3,019**	**3,046**	**3,072**	**3,100**	**3,127**	**3,154**	**3,182**	**3,210**	**3,238**	**3,267**	**3,296**	**3,325**	**3,354**	**3,383**	**3,413**	**3,443**
Total # of eligible patients	**3,606**	**3,637**	**3,669**	**3,702**	**3,734**	**3,767**	**3,800**	**3,834**	**3,867**	**3,901**	**3,936**	**3,970**	**4,005**	**4,041**	**4,076**	**4,112**	**4,148**	**4,185**	**4,221**	**4,259**
% EPZ-6438 penetration						*15%*	*45%*	*65%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# of patients treated with EPZ-6438	-	-	-	-	-	565	1,710	2,492	2,707	2,731	2,755	2,779	2,804	2,828	2,853	2,878	2,904	2,929	2,955	2,981
Annual treatment cost	$125,000	$127,500	$130,050	$132,651	$135,304	$138,010	$140,770	$143,586	$146,457	$149,387	$152,374	$155,422	$158,530	$161,701	$164,935	$168,234	$171,598	$175,030	$178,531	$182,101
% price increase	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*
Total US Sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$0**	**$78**	**$241**	**$358**	**$396**	**$408**	**$420**	**$432**	**$444**	**$457**	**$471**	**$484**	**$498**	**$513**	**$528**	**$543**

EU EPZ-6438 Revenue Model	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E
EU population	504,393,906	504,898,300	505,403,198	505,908,601	506,414,510	506,920,925	507,427,845	507,935,273	508,443,209	508,951,652	509,460,603	509,970,064	510,480,034	510,990,514	511,501,505	512,013,006	512,525,019	513,037,544	513,550,582	514,064,132
Population growth	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*	*0.10%*
# of new non-Hodgkin lymphoma (NHL) cases	78,847	78,926	79,005	79,084	79,163	79,242	79,321	79,400	79,480	79,559	79,639	79,718	79,798	79,878	79,958	80,038	80,118	80,198	80,278	80,358
% of NHL patients with Diffuse large B-cell lymphoma (DLBCL)	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
# of NHL patients with DLBCL	23,654	23,678	23,701	23,725	23,749	23,773	23,796	23,820	23,844	23,868	23,892	23,916	23,939	23,963	23,987	24,011	24,035	24,059	24,083	24,108
% of patients with DLBCL that is of the GCB-DLBCL subtype	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
# of patients with DLBCL that is of the GCB-DLBCL subtype	11,827	11,839	11,851	11,863	11,874	11,886	11,898	11,910	11,922	11,934	11,946	11,958	11,970	11,982	11,994	12,006	12,018	12,030	12,042	12,054
% of GCB-DLBCL patients with EZH2 mutation	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
# of GCB-DLBCL patients with EZH2 mutation	2,365	2,368	2,370	2,373	2,375	2,377	2,380	2,382	2,384	2,387	2,389	2,392	2,394	2,396	2,399	2,401	2,404	2,406	2,408	2,411
% relapse rate	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*
# of patients with DLBCL eligible for treatment	**781**	**781**	**782**	**783**	**784**	**784**	**785**	**786**	**787**	**788**	**788**	**789**	**790**	**791**	**792**	**792**	**793**	**794**	**795**	**796**
% of NHL patients with Follicular lymphoma (FL)	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*
# of NHL patients with Follicular lymphoma (FL)	17,346	17,364	17,381	17,398	17,416	17,433	17,451	17,468	17,486	17,503	17,521	17,538	17,556	17,573	17,591	17,608	17,626	17,644	17,661	17,679
% of patients with FL with EZH2 mutation	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
# of patients with FL with EZH2 mutation	3,469	3,473	3,476	3,480	3,483	3,487	3,490	3,494	3,497	3,501	3,504	3,508	3,511	3,515	3,518	3,522	3,525	3,529	3,532	3,536
% relapse rate	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients with FL eligible for treatment	**3,296**	**3,299**	**3,302**	**3,306**	**3,309**	**3,312**	**3,316**	**3,319**	**3,322**	**3,326**	**3,329**	**3,332**	**3,336**	**3,339**	**3,342**	**3,346**	**3,349**	**3,352**	**3,356**	**3,359**
Total # of eligible patients	**4,076**	**4,080**	**4,085**	**4,089**	**4,093**	**4,097**	**4,101**	**4,105**	**4,109**	**4,113**	**4,117**	**4,121**	**4,126**	**4,130**	**4,134**	**4,138**	**4,142**	**4,146**	**4,150**	**4,155**
% EPZ-6438 penetration					*0%*	*0%*	*15%*	*45%*	*65%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# of patients treated with EPZ-6438	-	-	-	-	-	-	615	1,847	2,671	2,879	2,882	2,885	2,888	2,891	2,894	2,897	2,899	2,902	2,905	2,908
Cost per month	$93,750	$95,625	$97,538	$99,488	$101,478	$103,508	$105,578	$107,689	$109,843	$112,040	$114,281	$116,566	$118,898	$121,276	$123,701	$126,175	$128,699	$131,273	$133,898	$136,576
% price increase	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*
Total EU Sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$65**	**$199**	**$293**	**$323**	**$329**	**$336**	**$343**	**$351**	**$358**	**$365**	**$373**	**$381**	**$389**	**$397**
Total US/EU sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$0**	**$78**	**$306**	**$557**	**$690**	**$731**	**$749**	**$768**	**$788**	**$808**	**$829**	**$850**	**$871**	**$894**	**$917**	**$940**

Source: Cowen and Company

Epizyme: Income Statement and Balance Sheet

Income statement: Epizyme went public through an IPO on May 31, 2013. For the FY ending December 31, 2012, Epizyme reported a net loss of $1.2M, or ($0.72) per share, compared to a loss of $21M, or ($14.65) in 2011. For 1Q13, Epizyme reported a net loss of $7.7M, compared to a net loss of $5.5M in 1Q12.

Total operating expenses in 2012 were $46M, compared to $27.9M in 2011, while total operating expenses for 1Q13 were $16.4M, compared to $11.1M spent in 1Q12. R&D expenses in 2012 were $38.5M, compared to $22.9M in 2011, and in 1Q13 were $13.4M, compared to $9.2M spent in 1Q12. G&A expenses in 2012 were $7.5M, compared to $5M in 2011 and in 1Q13 were $3M, compared to $1.9M spent in 1Q12.

Balance sheet: Epizyme ended 1Q13 with $85M in cash. In May 2013, Epizyme raised $79.8M in net proceeds in its IPO by issuing 5.9M shares at $15/share. In June 2013, Epizyme received a $6M milestone payment from Eisai for the initiation of the Phase I/II trial of EPZ-6438 in NHL. Epizyme's current proforma net cash position is approximately $171M or $5.18 per fully diluted share.

Post-IPO share count: As of May 31, 2013, the company had 28.4 common shares and 4.5M options outstanding, bringing the fully diluted number of shares to approximately 33M.

EPZM: Shares and Options outstanding

Common Shares	22,501,764
IPO shares	5,142,000
Over-allotment	771,300
Stock options (exercise price $1.62)	4,553,654
Total Shares outstanding	**32,968,718**

Source: Cowen and Company, SEC Filings

EPZM: Quarterly P&L ($MM)

($MM)	2011A	2012A	Q1:13A	Q2:13E	Q3:13E	Q4:13E	2013E	Q1:14E	Q2:14E	Q3:14E	Q4:14E	2014E	2015E
Revenues to EPZM													
EPZ-5676 US sales	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EPZ-5676 EU royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EPZ-6438 US sales (50% of total)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EPZ-6438 EU royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Collaboration revenue	6.9	45.2	8.9	14.8	9.2	9.5	42.4	6.5	31.5	6.5	16.5	60.8	26.1
Total revenue	**6.9**	**45.2**	**8.9**	**14.8**	**9.2**	**9.5**	**42.4**	**6.5**	**31.5**	**6.5**	**16.5**	**60.8**	**26.1**
COGS	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
R&D	**22.9**	**38.5**	**13.4**	**14.2**	**15.1**	**16.3**	**59.0**	**15.7**	**15.9**	**15.9**	**16.1**	**63.6**	**63.5**
SG&A	**5.0**	**7.5**	**3.0**	**3.5**	**3.6**	**3.4**	**13.5**	**3.5**	**3.4**	**3.6**	**3.5**	**14.0**	**14.3**
Total Operating expenses	**27.9**	**46.0**	**16.4**	**17.7**	**18.7**	**19.7**	**72.5**	**19.2**	**19.3**	**19.5**	**19.6**	**77.6**	**77.8**
Operating Income/Loss	**(21.0)**	**(0.8)**	**(7.5)**	**(2.9)**	**(9.5)**	**(10.2)**	**(30.1)**	**(12.8)**	**12.2**	**(13.1)**	**(3.2)**	**(16.8)**	**(51.7)**
Interest income	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Interest expense	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other income (expense)	(0.0)	(0.1)	(0.0)	0.0	0.0	0.0	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0
Pretax income	(21.0)	(0.7)	(7.5)	(2.9)	(9.5)	(10.2)	(30.1)	(12.8)	12.2	(13.1)	(3.2)	(16.8)	(51.7)
Income tax expense	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net loss attributable to common stock	**(21.0)**	**(1.2)**	**(7.7)**	**(2.9)**	**(9.5)**	**(10.2)**	**(30.3)**	**(12.8)**	**12.2**	**(13.1)**	**(3.2)**	**(16.8)**	**(51.7)**
EPS (basic)	**($14.65)**	**($0.72)**	**($0.34)**	**($0.10)**	**($0.33)**	**($0.35)**	**($1.11)**	**($0.43)**	**$0.41**	**($0.37)**	**($0.09)**	**($0.51)**	**($1.38)**
EPS (diluted)	**($14.65)**	**($0.72)**	**($0.34)**	**($0.10)**	**($0.33)**	**($0.35)**	**($1.11)**	**($0.43)**	**$0.35**	**($0.37)**	**($0.09)**	**($0.51)**	**($1.38)**
Basic shares	1.4	1.6	22.4	28.6	28.8	29.1	27.2	29.4	29.7	35.7	36.1	32.7	37.5
Diluted shares	1.4	1.6	22.4	33.0	33.3	33.6	30.6	34.0	34.3	40.4	40.8	37.4	42.4

Source: Cowen and Company

EPZM: Annual P&L ($MM)

($MM)	2011A	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E
Revenues to EPZM																						
EPZ-5676 US sales	0.0	0.0	0.0	0.0	0.0	0.0	30.0	92.5	137.4	163.2	167.9	172.8	177.8	182.9	188.2	193.7	199.3	205.0	211.0	217.1	223.4	229.9
EPZ-5676 EU royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.4	6.1	11.6	16.7	20.1	23.7	24.2	24.7	25.2	25.8	26.3	26.9	27.4	28.0	28.6
EPZ-6438 US sales (50% of total)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	39.0	120.4	178.9	198.2	204.0	209.9	216.0	222.2	228.7	235.3	242.1	249.1	256.4	263.8	271.4
EPZ-6438 EU royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.2	9.9	14.7	16.1	16.5	16.8	17.2	17.5	17.9	18.3	18.7	19.1	19.5	19.9
Collaboration revenue	6.9	45.2	42.4	60.8	26.1	35.0	70.0	25.0	25.0	0.0	25.0	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total revenue	**6.9**	**45.2**	**42.4**	**60.8**	**26.1**	**35.0**	**100.0**	**157.9**	**292.1**	**363.6**	**422.5**	**413.0**	**452.8**	**439.9**	**452.3**	**465.1**	**478.2**	**491.7**	**505.6**	**519.9**	**534.6**	**549.7**
COGS	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**3.0**	**13.1**	**23.2**	**27.4**	**29.3**	**30.1**	**31.0**	**31.9**	**32.8**	**33.8**	**34.8**	**35.8**	**36.8**	**37.9**	**39.0**	**40.1**
R&D	**22.9**	**38.5**	**59.0**	**63.6**	**63.5**	**64.0**	**64.5**	**72.5**	**76.1**	**79.9**	**83.9**	**88.1**	**92.5**	**97.2**	**102.0**	**107.1**	**112.5**	**118.1**	**124.0**	**130.2**	**136.7**	**143.5**
SG&A	**5.0**	**7.5**	**13.5**	**14.0**	**14.3**	**14.6**	**31.6**	**39.5**	**39.8**	**40.5**	**41.2**	**41.9**	**43.0**	**44.2**	**44.9**	**45.7**	**46.6**	**47.4**	**48.2**	**49.1**	**50.0**	**50.9**
Total Operating expenses	**27.9**	**46.0**	**72.5**	**77.6**	**77.8**	**78.6**	**99.1**	**125.1**	**139.1**	**147.8**	**154.4**	**160.2**	**166.6**	**173.2**	**179.8**	**186.6**	**193.8**	**201.3**	**209.0**	**217.2**	**225.7**	**234.5**
Operating Income/Loss	**(21.0)**	**(0.8)**	**(30.1)**	**(16.8)**	**(51.7)**	**(43.6)**	**0.8**	**32.7**	**153.0**	**215.8**	**268.0**	**252.8**	**286.3**	**266.7**	**272.5**	**278.5**	**284.4**	**290.5**	**296.6**	**302.8**	**309.0**	**315.2**
Interest income	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	2.0	3.0	4.0	5.0
Interest expense	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	2.0	3.0	4.0	5.0
Other income (expense)	(0.0)	(0.1)	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	2.0	3.0	4.0	5.0
Pretax income	(21.0)	(0.7)	(30.1)	(16.8)	(51.7)	(43.6)	0.8	32.7	153.0	215.8	268.0	252.8	286.3	266.7	272.5	278.5	284.4	292.5	300.6	308.8	317.0	325.2
Income tax expense	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.6	15.3	62.6	93.8	88.5	100.2	93.3	95.4	97.5	99.6	102.4	105.2	108.1	110.9	113.8
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*8%*	*10%*	*29%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
Net loss attributable to common stock	**(21.0)**	**(1.2)**	**(30.3)**	**(16.8)**	**(51.7)**	**(43.6)**	**0.8**	**30.1**	**137.7**	**153.2**	**174.2**	**164.3**	**186.1**	**173.3**	**177.1**	**181.0**	**184.9**	**190.1**	**195.4**	**200.7**	**206.0**	**211.4**
EPS (basic)	**($14.65)**	**($0.72)**	**($1.11)**	**($0.51)**	**($1.38)**	**($1.12)**	**$0.02**	**$0.71**	**$3.14**	**$3.36**	**$3.67**	**$3.33**	**$3.62**	**$3.24**	**$3.19**	**$3.13**	**$3.08**	**$3.04**	**$3.01**	**$2.97**	**$2.93**	**$2.89**
EPS (diluted)	**($14.65)**	**($0.72)**	**($1.11)**	**($0.51)**	**($1.38)**	**($1.12)**	**$0.02**	**$0.63**	**$2.78**	**$2.97**	**$3.25**	**$2.95**	**$3.21**	**$2.87**	**$2.82**	**$2.77**	**$2.72**	**$2.69**	**$2.66**	**$2.63**	**$2.59**	**$2.56**
Basic shares	1.4	1.6	27.2	32.7	37.5	39.0	40.6	42.2	43.9	45.7	47.5	49.4	51.4	53.4	55.6	57.8	60.1	62.5	65.0	67.6	70.3	73.1
Diluted shares	1.4	1.6	30.6	37.4	42.4	44.1	45.9	47.7	49.6	51.6	53.6	55.8	58.0	60.3	62.8	65.3	67.9	70.6	73.4	76.4	79.4	82.6

Source: Cowen and Company

Epigenetics: A Quick Primer

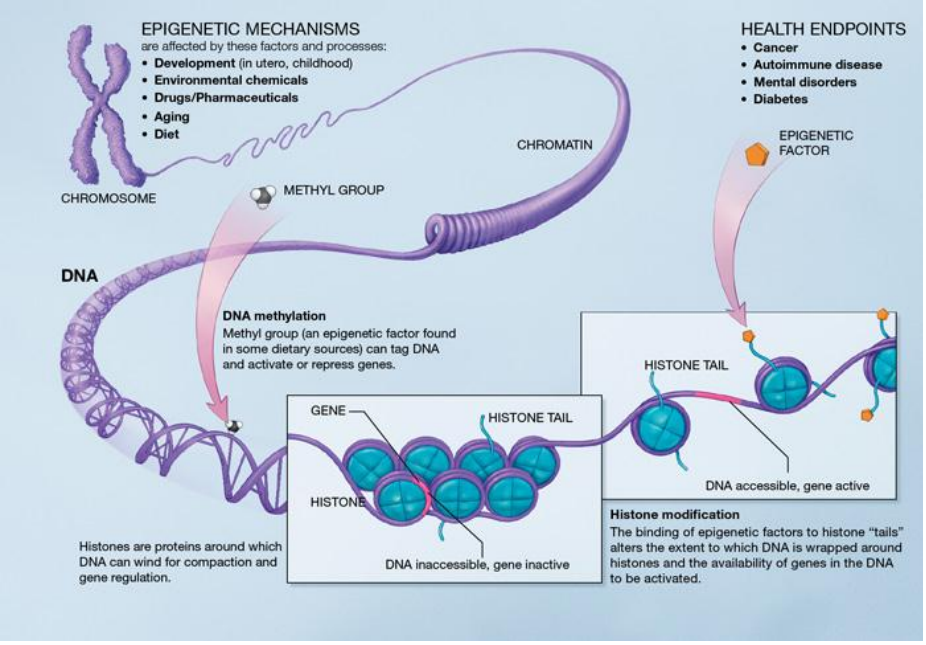
Epigenetics refers to the study of heritable changes in gene expression which occur independently of changes in the underlying DNA sequence. These changes may persist through multiple cell division cycles, allowing cells to have distinct identities while carrying the same genetic information. Thus, without changes to underlying DNA sequences (*i.e. genes*), certain factors can cause variations in gene expression. These factors regulating gene expression patterns are epigenetic modifications or "*marks*." Examples of epigenetic modifications include DNA methylation, histone protein modification, and nucleosome remodeling. These modifications serve as "*markers*" for recruitment of particular protein complexes which control gene expression. Epigenetic marks mediate cell diversity by regulating the access of transcribing machinery to genes, which results in activating or repressing gene expression (*i.e. turning genes "on" or "off"*).

Chromatin is the complex of DNA and proteins within the cell nucleus which organizes the genome (*the collection of all the genes in the cell*). Histones comprise the protein component of chromatin. Functionally, histones "package" and organize DNA into a structural unit called a nucleosome, which consists of approximately 146 base pairs of DNA wrapped around four core histones (H3, H4, H2A, H2B). Repeating units of nucleosomes form chromatin. This organized, compact, and dynamic structure influences gene expression by controlling access of transcription factors. An open chromatin structure makes DNA more accessible and generally supports gene transcription, while compaction, resulting in a closed configuration, typically favors transcriptional repression.

Histones contain C-terminal and N-terminal tail regions. The N-terminal tails of histones can be modified on specific amino acid residues (*an amino acid molecule which has lost a water molecule (H_2O) in becoming joined to another amino acid molecule*) through processes such as methylation or demethylation (*addition or removal of a methyl group, CH_3*) and acetylation or deacetylation (*addition or removal of an acetyl group, $COCH_3$*). The process of methylation occurs on lysine residues (K) and arginine residues (R). Lysine residues may be mono-, di-, or tri-methylated. The process of acetylation occurs on lysine residues. These histone modifications are regulated by enzymes. Histone methyltransferases (HMTs) add methyl groups, while histone demethylases (HDMs) remove methyl groups. Histone acetyltransferases (HATs) add acetyl groups, and histone deacetylases (HDACs) remove acetyl groups.

Influences on chromatin structure, and therefore on gene expression, include the acetylation and methylation status of amino acid residues within histones. Acetylation is generally associated with activation of transcription. The result of methylation depends on the degree of methylation and on the specific amino acid residue which is modified. For example, tri-methylation of lysine 4 on histone 3 (H3K4me3) and mono-methylation of lysine 9 on histone 3 (H3K9me1) are associated with an open chromatin configuration and activation of gene transcription. Tri-methylation of H3K9 (H3K9me3) and H3K27 (H3K27me3) is associated with a closed chromatin configuration and repression of gene expression.

Epigenetics Overview

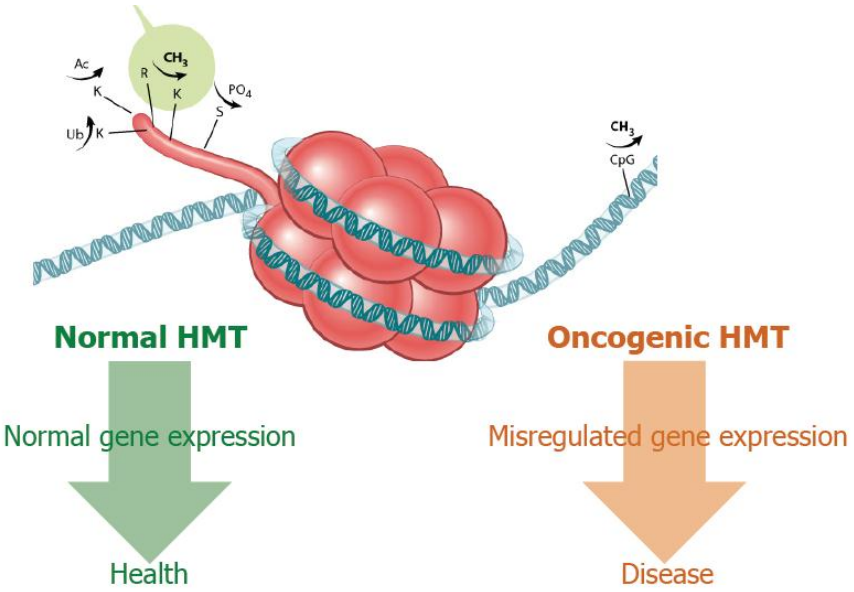


Source: Epizyme Presentation

Among protein groups which are involved in control of gene expression through chromatin modification, two protein families, the trithorax group (TrxG) and the polycomb group (PcG), have opposing roles. Methylation of H3K4 by some members of the TrxG family most often positively regulates gene expression, while methylation of H3K27 by PcG members represses gene expression. Abnormal functioning of TrxG or PcG proteins produces aberrant gene expression.

The epigenomic status of normal cells may be distorted in malignancies. Changes in epigenetic marks can result in dysregulated gene expression and consequently, inappropriate activation or inhibition of signaling pathways, which may support cancer development. Thus, in addition to genetic mutations, cancer cells may have epigenetic abnormalities. These genetic and epigenetic alterations may together promote cancer progression. For example, epigenetic changes may silence tumor suppressor genes or activate oncogenes. Epigenetic alterations may be selected and promoted in cancer cells, which are uncontrollably proliferating. Targeting epigenetic modifications may therefore have a therapeutic rationale in cancer.

Epigenetics and Cancer Development



Source: Epizyme Presentation

DOT1L: the HMT targeted by Epizyme's first clinical program

DOT1 (**d**isruptor **o**f **t**elomeric silencing) was initially discovered in yeast, and its corresponding mammalian protein is known as DOT1L (DOT1-**L**ike). DOT1L is a histone methyltransferase (HMT) which methylates H3K79 (histone 3 at lysine 79). HMTs which act at lysine residues can be categorized into two classes. One class contains a conserved amino acid sequence found in all organisms, known as a SET (**S**uppressor of variegation 3-9, **E**nhancer of Zeste, **T**rithorax) domain protein, which has methyltransferase activity and functionally transfers a methyl group from S-adenosylmethionine (SAM) to a lysine residue. The other class does not have a SET domain, but instead contains DOT1L.

DOT1L is not structurally related to the SET domain protein and is considered to be exclusively responsible for H3K79 methylation. DOT1L is also SAM-dependent, and enzymatically transfers a methyl group from SAM. H3K79 methylation is a marker of active gene transcription. In terms of transcriptional regulation, DOT1L is thought to be involved in transcriptional elongation, the stage of transcription between transcription initiation and termination, in which rapid transcription of long stretches of DNA by RNA polymerase occurs without dissociation. A number of multi-protein complexes, comprised by transcription elongation factors (such as ELL, AF4, AF9, AF10, pTEFb) supporting elongation, also contain DOT1L. These complexes are functionally associated with H3K79 methylation as well as phosphorylation of RNA polymerase II, which is required for the transition from the initiation to elongation phases of transcription. Thus, DOT1L is considered to have a role in transcription of some genes by facilitating transcriptional elongation.

DOT1L and MLL

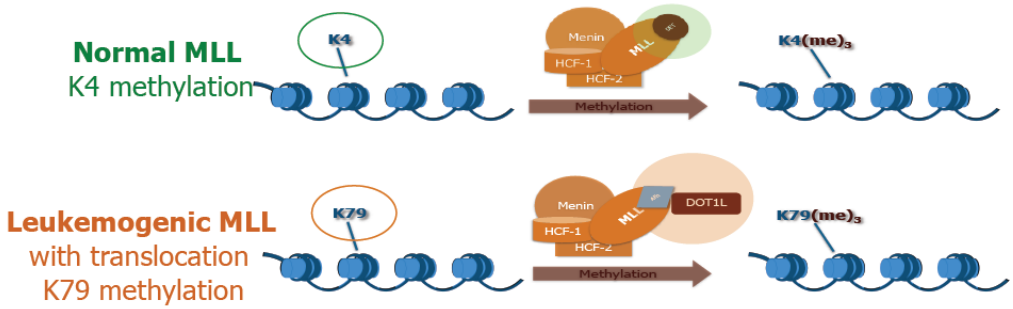
MLL is a member of the trithorax group (TrxG) family of proteins that positively regulate gene transcription through chromatin modification. The MLL gene encodes the MLL protein. The MLL protein, which contains a SET domain, is a HMT that normally methylates H3K4 (histone H3 at lysine 4) and positively controls the transcription of many genes, including the HOX (homeobox) genes (HOXA1, A3, A7, A9, A10, A11). HOX genes control embryonic development as well as tissue development, including differentiation of normal hematopoietic cells. Like other methyltransferases, the MLL protein is incorporated into a larger, multi-protein complex. The MLL complex modifies chromatin through histone methylation, histone acetylation, and nucleosome remodeling.

Genetic mutations of the MLL gene appear to preferentially occur in hematopoietic cells. In acute leukemias, chromosomal translocations which rearrange the MLL gene can occur, resulting in abnormal MLL fusion proteins, with disruption of the normal SET domain HMT function of MLL, replaced by functions of the fusion partner. The fusion proteins are transcriptional regulators which overtake control of targets normally controlled by MLL, such as the HOX genes. MLL fusion partner proteins include AF4, AF9, and AF10.

MLL fusion proteins have the ability to bind to several other proteins, activating transcription through chromatin modification. Histone H3 methylation at lysine 79 catalyzed by DOT1L is a hallmark of chromatin activated by MLL fusion proteins. The most frequent MLL fusion proteins, resulting from the most common MLL gene rearrangements, directly or indirectly bind DOT1L, and also coordinate DOT1L activity with the transcriptional elongation factor pTEFb (positive transcription elongation factor b), which acts on RNA polymerase II and supports the elongation phase of transcription.

The binding of DOT1L with MLL fusion proteins results in the misdirection of DOT1L to their gene targets, such as the HOX genes. Aberrant H3K79 methylation causes the target genes to be constitutively activated and thus overexpressed. This leads to malignant transformation of cells.

DOT1L and MLL



Source: Epizyme Presentation

MLL-rearranged leukemias have characteristic gene expression patterns, most notably high levels of HOX gene expression. HOX gene deregulation is likely a major underlying leukemogenic factor. HOX gene expression is typically high in stem cells and early precursor cells, and then down-regulated as cells mature. In malignant hematopoiesis, abnormal HOX gene overexpression blocks differentiation and promotes uncontrolled proliferation of immature leukemia cells. H3K79 methylation correlates with abnormal gene expression in MLL-rearranged leukemia. It is thus hypothesized that DOT1L may have an active role in maintenance of MLL fusion-mediated and leukemia-associated gene expression.

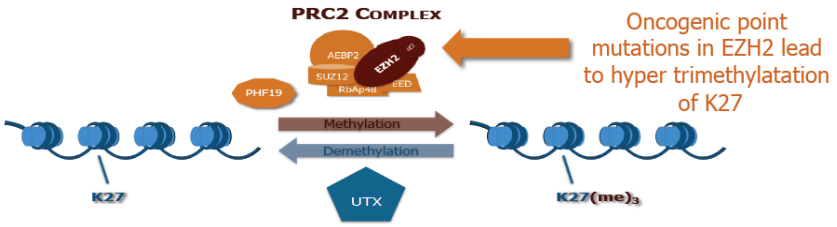
EZH2: the second HMT targeted by Epizyme

EZH2 (**E**nhancer of **Z**este **H**omolog **2**) forms the catalytic subunit of the PRC2 (**P**olycomb **R**epressive **C**omplex **2**) protein complex. Polycomb group (PcG) proteins are chromatin regulators which are transcriptional repressors. They are organized into two main protein complexes, PRC1 and PRC2, which repress multiple genes. EZH2 is a HMT and belongs to the SET domain protein methyltransferase family. EZH2, in cooperation with multiple PRC2 co-factors, catalyzes mono- through tri-methylation of H3K27. The tri-methylated H3K27 epigenetic mark is associated with repression of gene transcription. The histone modification also functions to recruit PRC1, which may additionally act independently of PRC2.

It has been established that EZH2 is overexpressed in some solid tumors, such as prostate and breast cancer, and functions as an oncogene, with increased expression characterizing malignant progression and advanced disease. Preclinical studies have demonstrated that disruption of PRC2/EZH2 reduces growth of cancer cells which highly express EZH2.

More recently, mutations in EZH2 with potential oncologic implications have been discovered. EZH2 is highly expressed in lymphoid precursor cells, and EZH2 deficiency causes developmental defects in lymphoid cells. EZH2 levels tend to decrease in resting B-cells, but increase when activated B-cells form germinal centers (GCs) and proliferate, suggesting a potential role of EZH2 in GC B-cell proliferative diseases, such as diffuse large B-cell lymphoma (DLBCL). Mutations which replace a single tyrosine (Y641) amino acid in the SET domain protein of EZH2 have been found in some patients with lymphomas deriving from GC B-cells, such as DLBCL (GCB-subtype) and follicular lymphoma (FL). These mutations result in the change of tyrosine (Y) 641 to phenylalanine (F), serine (S), asparagine (N), histidine (H), or cysteine (C), and cause increased H3K27 tri-methylation (hypermethylation), compared to the typically more efficient mono-methylation from wild-type EZH2. The consequence is inappropriate target gene repression. The current oncogenic model for EZH2/PRC2 suggests that abnormal activity results in elevated levels of tri-methylated H3K27, which may silence tumor suppressor gene expression and support cancer development.

EZH2 Mutation in Cancer

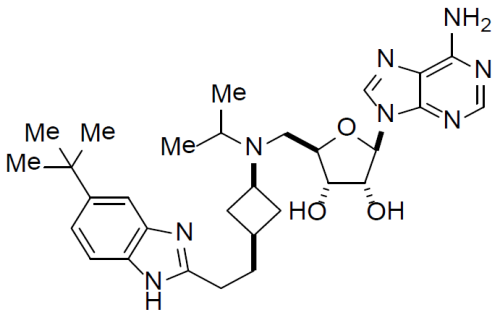


Source: Epizyme Presentation

EPZ-5676: A DOT1L Inhibitor

EPZ-5676 is an intravenously administered, small molecule inhibitor of DOT1L, a histone methyltransferase. EPZ-5676 is competitive with S-adenosylmethionine (SAM) for binding to DOT1L. As presented by Epizyme at ASH 2012, the compound has a Ki (*dissociation constant of inhibition*) of 0.08 nanomoles (nM) or 80 picomoles (pM) for DOT1L inhibition (*Ki being a thermodynamic measure of in vitro potency; a smaller Ki reflects tighter binding of an inhibitor, and a larger Ki reflects weaker binding).* Its drug-target residence time *(a measure of the lifetime of drug-target binding, considered a more appropriate measure of in vivo potency; in general, longer residence times correlate with stronger biological efficacy*) was also reported to be > 24 hours.

EPZ-5676 Chemical Structure

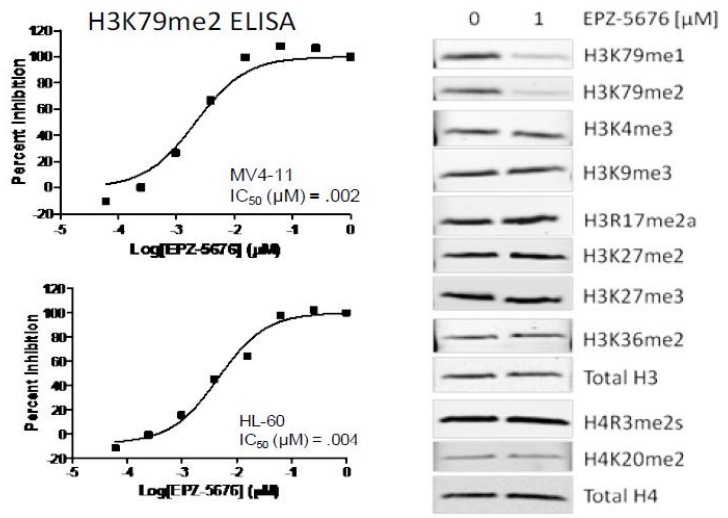


Source: Epizyme ASH 2012 poster

EPZ-5676 Preclinical Studies

In *in vitro* studies with cell lines including the MLL gene rearrangement, such as MV4-11 and HL-60 cells, EPZ-5676 treatment inhibited H3K79 methylation in a concentration dependent manner. EPZ-5676 was shown to be highly selective, inhibiting only DOT1L-associated H3K79 methylation, without affecting other histone methyl marks.

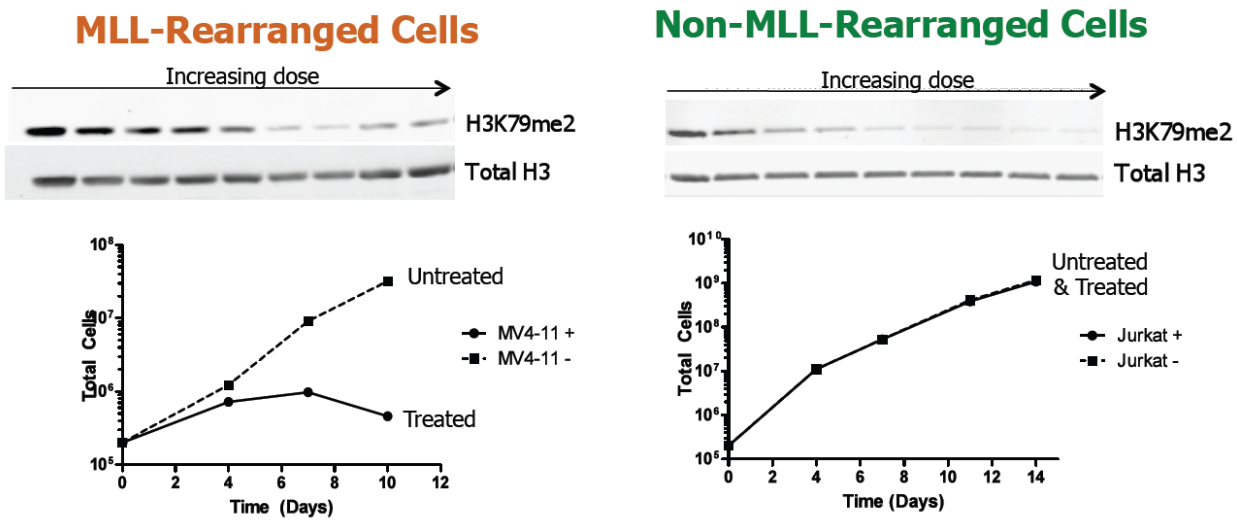
EPZ-5676 Inhibition of H3K79 Methylation



Source: Epizyme ASH 2012 poster

Additionally, in MLL-rearranged cells, EPZ-5676 treatment, which inhibited H3K79 methylation, killed cells and reduced cell proliferation. However, EPZ-5676 treatment in cells without MLL-rearrangement had minimal effect on cell proliferation, even though H3K79 methylation was inhibited. Thus, selective killing of MLL-rearranged cells was observed *in vitro* after treatment with EPZ-5676.

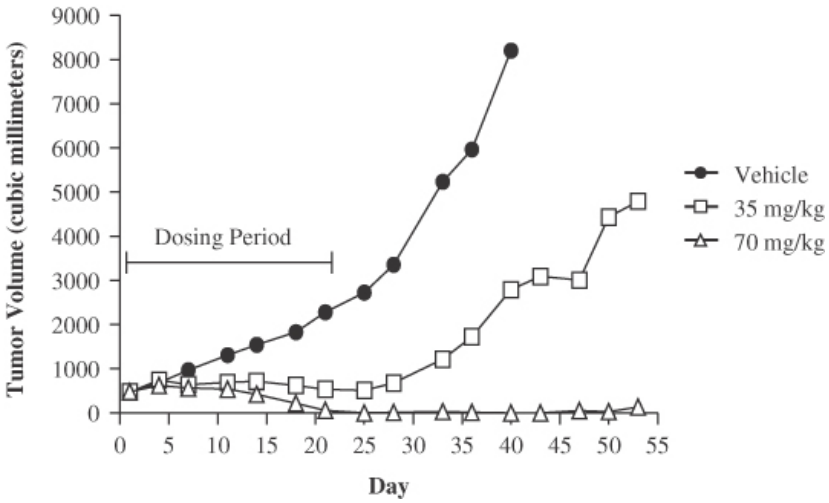
Selective Treatment Effect of EPZ-5676 *in vitro*



Source: Epizyme Presentation

In further *in vivo* preclinical studies, nude rat xenograft models were created through subcutaneous implantation of human MLL-rearranged cells, which formed tumors. EPZ-5676 was administered to the rats with continuous IV infusion for 21 days at three dose levels, with 10 animals each: 1) 35 mg/kg per day, 2) 70 mg/kg per day, and 3) no EPZ-5676, delivery vehicle alone. Rats receiving the 35 mg/kg dose showed inhibition of tumor growth, with stable disease in 7/10 animals, continuing for up to seven days after treatment discontinuation. At the 70 mg/kg dose, 9/10 rats had tumors reduced to undetectable volumes by the end of the treatment period, and there was no tumor regrowth in 8/9 of the rats through the end of the study, which occurred at day 53.

Tumor Volume Reduction with EPZ-5676 *in vivo* (rat xenograft model)



Source: Epizyme S-1

EPZ-5676 Clinical Development

Phase I Trial in Hematologic Malignancies, Including MLL-r Leukemia

- *Study started (dose escalation phase): September 2012*
- *Data expected: 2H13*
- *Expansion phase initiation: Expected 2H13*

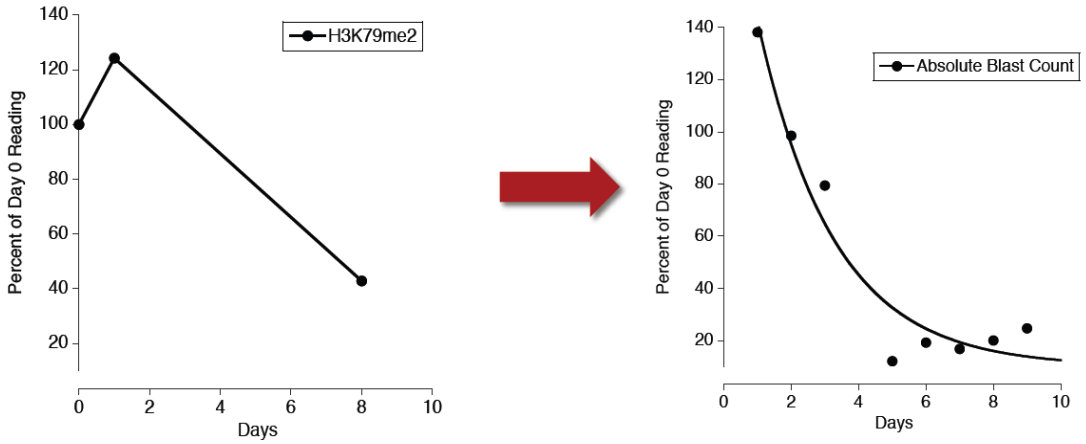
Phase I Trial Design and Population: This is an open label, multicenter, Phase I trial of EPZ-5676 which has two phases, enrolling approximately 40 patients. The first phase is a dose-escalation phase in patients with advanced hematologic malignancies, including some MLL-r leukemia patients. Patients will receive 21-day, continuous intravenous infusions of EPZ-5676. The second phase is an expansion phase, which will enroll only MLL-r leukemia patients and use the dose established in the first phase. Two clinical sites are currently enrolling patients, and there may ultimately be as many as 12 centers in the U.S. and E.U. participating in the expansion phase.

Study Endpoints: The primary endpoints of the trial are safety, tolerability, and determination of the maximum tolerated dose (MTD) of EPZ-5676. Secondary endpoints include assessments of preliminary efficacy, PK, and PD.

Trial Status Update: Two sites, Memorial Sloan-Kettering Cancer Center and Sarah Cannon Research Institute, are currently enrolling patients. As of April 30, 2013, four patients (one patient in the 1st dose cohort at 12 mg/m^2/day, and three patients in the 2nd dose cohort at 24 mg/m^2/day) have been dosed. There have been no grade > 2 AEs observed, and no dose limiting toxicities (DLTs) have been identified. There have been no modifications to dose or dosing schedule.

In one of the three patients in the 2nd dose cohort (24 mg/m^2/day) with a diagnosis of ALL with MLL-rearrangement, partial DOT1L inhibition was observed after treatment with EPZ-5676, as measured by ~ 60% decrease in the target methyl mark (H3K79me2) in white blood cells. The patient was noted to have a 90% reduction in circulating leukemic blast cells by the fifth day of treatment. By this day, the patient had resolution of fevers attributed to leukemia by the investigator. EPZ-5676 treatment was terminated on day 10 because of CNS disease progression. The patient had a single episode of transient hypertension, possibly related to EPZ-5676 treatment.

Early Phase I Results in 1 MLL-r Patient



Source: Epizyme Presentation

The other patients dosed as of April 30, 2013 (one patient in the 1st dose cohort and two patients in the 2nd dose cohort) did not have MLL-rearrangements. Methyl mark inhibition was not measured in the 1st dose cohort patient. In the other two patients from the 2nd dose cohort, there was partial target inhibition observed, as measured by reduction of the H3K79me2 methyl mark in white blood cells. However, there was no biological effect, i.e. reduction in leukemic blast cell count, observed in these patients who did not have MLL-rearrangements.

What's next for EPZ-5676? Data from the dose escalation phase of the Phase I trial are expected in 2H13. Also, the expansion phase of the trial is expected to be initiated in 2H13.

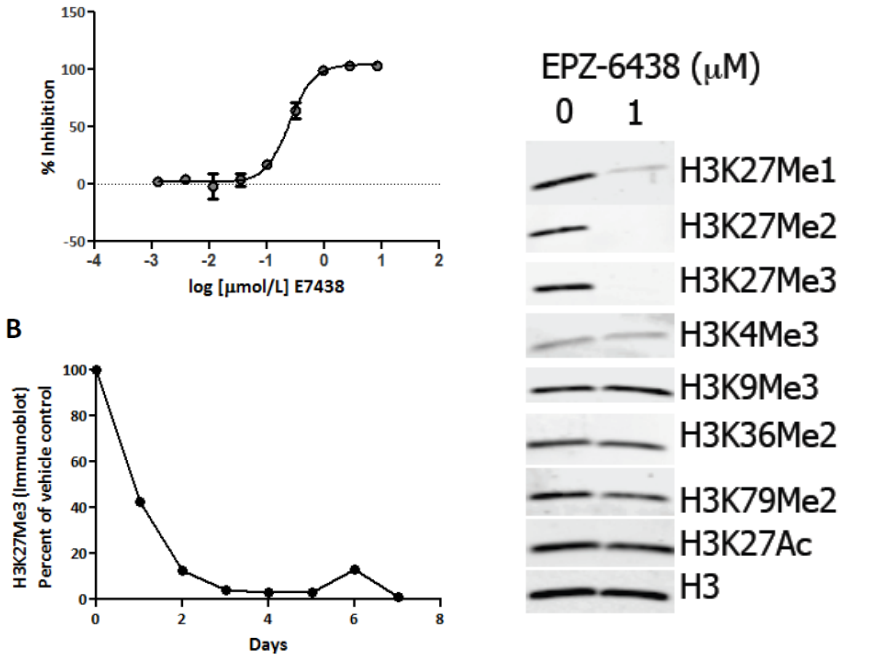
EPZ-6438: Behind DOT1L Comes an EZH2 Inhibitor

Epizyme's second development program is EPZ-6438, an orally available, small molecule inhibitor of EZH2, a well-characterized histone methyltransferase. Point mutations replacing a single tyrosine (Y641) amino acid in the SET domain protein of EZH2 are oncogenic and have been found in cases of lymphomas deriving from germinal center B-cells. Mutant EZH2 causes hypermethylation of H3K27. EPZ-6438 is competitive with S-adenosylmethionine (SAM) for binding to EZH2 in a mutually exclusive fashion, so that only one can bind to EZH2 at one time. As presented by Epizyme at ASH 2012, the compound has a Ki (*dissociation constant of inhibition*) of 2.5 nM for wild-type EZH2 inhibition. EPZ-6438 also inhibits, with similar potency (Ki), all known mutant forms of EZH2 that have been identified in lymphoma patient samples.

EPZ-6438 Preclinical Studies

In *in vitro* studies with NHL cell lines characterized by a point mutation in EZH2, such as WSU-DLCL2 cells with a Y641F mutation, EPZ-6438 (E7438, as designated by Eisai) treatment inhibited H3K27 methylation in a concentration dependent manner. EPZ-6438 was shown to be highly selective, inhibiting only EZH2-associated H3K27 methylation, without affecting other histone methyl marks.

EPZ-6438 is a Highly Selective Methylation Inhibitor

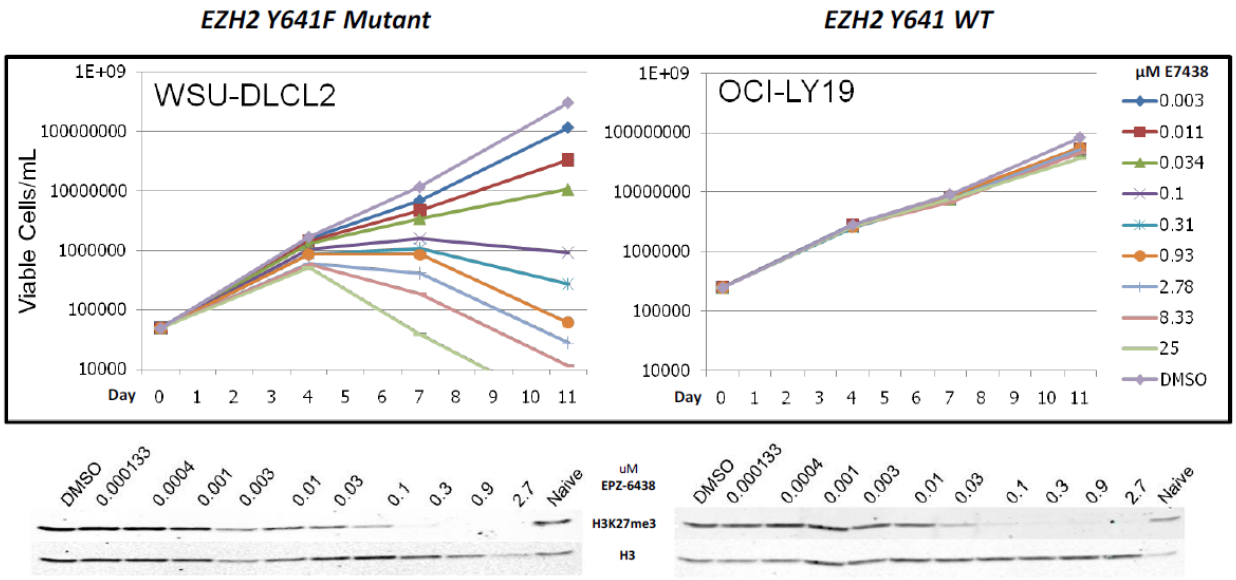


Source: Epizyme ASH 2012 poster

Additionally, when a lymphoma cell line containing an EZH2 mutation (WSU-DLCL2 with Y641F mutation) and a lymphoma cell line with wild-type EZH2 (OCI-LY19) were incubated with EPZ-6438 for 11 days, killing of only EZH2 mutant cells was observed, in a dose

dependent fashion. This resulted even though H3K27 methylation was inhibited to similar degrees in both cell lines. Thus, selective killing of cells bearing EZH2 mutations was observed *in vitro* after treatment with EPZ-6438.

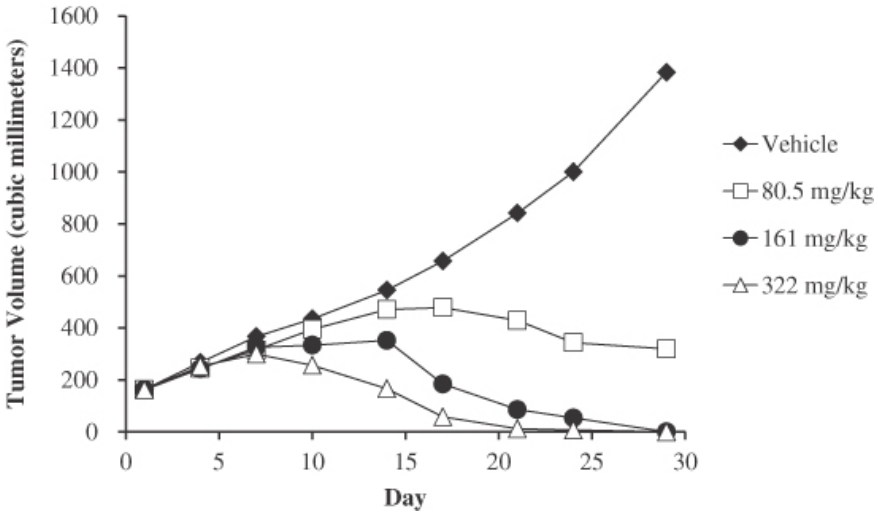
Selective Treatment Effect of EPZ-6438 on EZH2 Mutant Cells *in vitro*



Source: Epizyme ASH 2012 poster

In *in vivo* preclinical studies, mouse xenograft models were created through subcutaneous implantation of human NHL cells containing EZH2 mutations, which were allowed to form tumors. One model was created with KARPAS-422 xenografts containing the Y641N mutation. EPZ-6438 was orally administered twice daily for 28 days at four dose levels, with 9 animals in each dose group: 1) 80.5 mg/kg per dose, 2) 161 mg/kg per dose, 3) 322 mg/kg per dose, and 4) no EPZ-6438, delivery vehicle alone. Compared to mice receiving only the vehicle, mice treated with 80.5 mg/kg showed decreased tumor growth. The 161 mg/kg and 322 mg/kg treatment groups had reductions in tumors to undetectable volumes by the end of the 28 day treatment period.

Dose Dependent Tumor Volume Reduction with EPZ-6438 in mouse xenograft model



Source: Epizyme S-1

In a separate test, mice were again treated twice daily with EPZ-6438 at the highest (322 mg/kg) dose for 28 days. Tumor volume was measured during the 28 day treatment period and then further for 63 days beyond the treatment period, at which point the study ended. After 28 days, tumor volume in all animals was undetectable. Furthermore, there was no subsequent re-growth of tumor observed in any mice through the post-treatment period, up to the end of the study at 91 days.

EPZ-6438 Clinical Development

Phase I/II trial of EPZ-6438 in Advanced Solid Tumors and NHL

- *Phase I/II trial initiated: June 2013*
- *Data expected: 1H14*

Phase I/II Trial Design and Population: This Phase I/II trial of EPZ-6438 will be completed in two parts. The Phase I part of the trial consists of an open-label, dose escalation study in patients with advanced solid tumors or hematologic malignancies, including NHL with EZH2 mutations. Patients will receive single-agent EPZ-6438 twice daily in 28-day cycles. The primary endpoint of the Phase I trial is safety and determination of the MTD of EPZ-6438. Secondary endpoints include PK, PD, and preliminary efficacy assessment, including in patients with EZH2 mutations.

The Phase II trial, restricted to patients with relapsed or refractory EZH2-mutated NHL (DLBCL and grade 3 FL), will proceed in two phases. In the first phase, all patients will receive the MTD determined in the Phase I trial. Depending on the number of responses observed, the second phase of the Phase II trial may then be initiated, in which patients will be randomized 2:1 to

EPZ-6438 or standard of care treatment. The primary endpoint of the Phase II trial will be ORR. Secondary endpoints include PFS, disease control rate, clinical benefit rate, and safety.

What's next for EPZ-6438? Epizyme and Eisai initiated the Phase I/II trial in June 2013. Epizyme received a milestone payment of $6M, triggered on initiation of this trial. Data, including early indication of therapeutic efficacy, are expected in 1H14.

The Hematologist/Oncologist's Viewpoint

We interviewed a number of hematologists/oncologists specializing in leukemia and lymphoma treatment, all of whose research focused on epigenetics, and who were familiar with the preclinical and clinical data of the two Epizyme programs. Our consultants describe the early data for both HMT inhibitors as "*exciting*," "*encouraging*," "*persuasive*," and "*promising*." Relative to the other epigenetic therapies on the market, they consider these HMT inhibitors to be more "*precise*" and find the specificity of targeting to be a distinguishing feature. In particular, they are impressed by the selective activity of these small molecules against particular, genetically-defined subsets of disease. They remarked that the field of epigenetic therapy started as *"global"* therapy aimed at re-programming the epigenome to normalize cells through interventions focused on DNA methylation and histone acetylation. Our consultants view these approaches as relatively non-specific in terms of effect and indication. In contrast, they view EPZ-5676 and EPZ-6438 as truly *"targeted epigenetic therapies"* aimed at specific abnormalities. They like the fact that increased specificity may be associated with fewer global effects outside of tumor targets.

While acknowledging these data to be very early, our consultants believe that Epizyme's targeted epigenetic therapies, if confirmed as clinically active, may have utility in a number of settings (e.g., first-line, or as a prelude to stem cell transplant, or after failure of transplant), with the potential to change treatment paradigms. They expect these drugs will more likely be used in combination regimens and think that it is "*hard to imagine they will not have a place*" in leukemia and lymphoma treatment.

Our consultants have indicated that MLL-rearrangement is a well-known and recognized abnormality in acute leukemia, diagnosed by cytogenetic analysis, which is routinely used in all patients. All of our consultants view MLL-rearrangement as an indicator of poor prognosis and a leukemia which is more difficult to treat. Currently, they report that there is no specific treatment for this subset of patients, although stem cell transplant may be used earlier in the treatment sequence. As one of our consultants pointed out, *"if I had a MLL-targeted drug, I would use the targeted therapy."*

With regard to EZH2 mutations in lymphoma, our consultants indicate that, while now recognized, routine testing for this mutation is not performed. There is less genetic and molecular analysis overall in the lymphoma treatment paradigm. Our consultants stated that there are presently no data to determine the relevance of these mutations, and the *"clinical significance is not known"* of EZH2 mutation status to date. For patients with an EZH2

mutation, the current treatment approach does not differ from standard therapy. However, they acknowledge this may change, if there is a targeted therapy directed against the mutation.

While our consultants are truly excited about the potential of these therapies, they also temper their enthusiasm with the reality that clinical success is by no means guaranteed. As remarked, excitement *"does not translate into 'this is a drug.'"* With regard to EPZ-5676, the further advanced Epizyme program, two of our consultants pointed out that the *in vivo* models seemed to require high doses of the drug administered via continuous infusion for effect, which may indicate that this may be *"pharmacologically not a great compound"* in terms of formulation, half-life, and PK. They believe that clinically, the requirement for continuous IV infusion would not be optimal, both from a patient/physician convenience standpoint, as well as a cost issue. However, they felt that this may be less of an impediment in leukemia treatment, for which other continuously infused drugs are presently used (e.g., cytarabine for AML). Furthermore, for treatment of this lethal disease, *"if it works, people will definitely use it,"* even if less convenient. Nevertheless, one consultant brought up the question of the maintenance approach, should the drug be effective. While a one-time continuous treatment course may be effective and acceptable, the subsequent approach to maintaining patients with continuous infusion therapy may become a question which must be resolved.

With regard to the clinical success of EPZ-5676, our consultants believe that the very early and limited clinical data (in one MLL-r patient thus far) are impressive in terms of reduction in blast count, and they feel if this is seen in more patients, it will be *"promising and interesting."* However, as our consultants described, *"real clinical success"* is measured by the achievement of CR, with reduction in blast count to zero peripherally and in bone marrow, as well as recovery of neutrophil and platelet counts. Also, the durability of response was highlighted as an important clinical efficacy parameter, with desire to see response lasting more than 6 months, and optimally 1 year; *"CR lasting a month is meaningless."* While still too early to judge clinical efficacy, our consultants currently maintain an optimistic viewpoint.

Our consultants hold a similarly positive outlook for EPZ-6438 after reviewing the preclinical data, and they are awaiting information from the recently initiated Phase I/II clinical trial. They do point out some circumstantial differences with EPZ-5676. First, as noted previously, the clinical relevance of the EZH2 mutation is not as clear, compared to the significance of MLL rearrangement in MLL-r leukemia, which is well-known. Second, and more broadly, whereas cytogenetic and molecular testing are routinely performed for leukemia cases, such evaluations are less common in the lymphoma treatment paradigm, in which mutations have not generally been correlated with clinical prognosis. Finally, our consultants are aware of other companies developing EZH2 inhibitors (they have noted GSK and Constellation Pharmaceuticals), telling us that *"for EZH2, the field is more crowded,"* while they do not recognize any other companies commercially developing DOT1L inhibitors.

Epizyme's Preclinical Efforts Have Been Validated By Multiple Collaborations

In the five years since its November 2007 founding, Epizyme has attracted significant interest from big pharma. In the past two years, it has been able to secure partnerships with three different big pharma players for development of the company's novel small molecule HMT inhibitors.

Under the three current strategic alliances with GSK, Eisai, and Celgene, Epizyme has brought into the company approximately $150M in funding, and is further eligible to receive up to $1B in research, development, regulatory, and sales-based milestones, as well as royalties or profit sharing on any net product sales.

Summary of Epizyme's partnerships

Partner	GSK	Eisai	Celgene
Date announced	January 2011	April 2011	April 2012
Area of research	Small molecule HMT inhibitors directed against up to three undisclosed targets	HMT inhibitors directed to EZH2, including EPZ-6438	HMT inhibitors directed to DOT1L ex-US and options for ex-US to other HMT programs
Geography	GSK has WW rights	Epizyme retained an opt-in right to co-develop and co-commercialize in US	Epizyme has US rights
Upfront payment	$20M upfront	$3M upfront	$90M upfront ($65M in cash and $25M in equity)
Total milestones	**$630M ($210M/target)**	**$201M**	**$160M**
Clinical milestones	$21M in preclinical milestones $99M in clinical milestones	$31M	$60M
Regulatory milestones	$240M	$55M	$100M
Commercialization milestones	$270M	$115M	-
Royalties	Mid-single digits to the low double-digits	Mid-single digits to low double-digits in US; flat mid-single digit ex-US	Mid-single digits to the mid-teens
Development costs	Epizyme is responsible for research until target identification, GSK provides fixed research funding	Eisai funds 100% through POC	Epizyme funds 100% through Phase I, after that Celgene and Epizyme equally co-fund global development

Source: Cowen and Company, SEC filings

1) GSK partnership (established January 2011)

In January 2011, Epizyme and GSK entered into an agreement to discover, develop, and commercialize small molecule HMT inhibitors directed against up to three undisclosed targets from the Epizyme platform. Three targets have been selected and licensed by GSK.

Under the agreement, Epizyme received an upfront payment of $20M. Through March 31, 2013, Epizyme also received $4.5M in research funding and $8M in milestone payments. Epizyme is entitled to receive up to $630M in additional milestone payments. These milestones are based on stage of development as follows:

- Up to $360M in development milestones, as specified below:
    - $21M in preclinical R&D milestones
    - $99M in clinical development milestones
    - $240M in regulatory milestones
- Up to $270M in sales-based milestones

In addition, Epizyme will also receive royalties from GSK ranging from mid-single digits to the low double-digits on worldwide net product sales.

Under the agreement, for each of the three targets, Epizyme has primary responsibility for research until selection of the development candidate, at which point GSK has sole responsibility for development and commercialization. Epizyme must provide research for the targets during a research period which ends in January 2015. GSK provides a fixed amount of research funding during the second and third years of this research period. If Epizyme continues research activities in the fourth year of the period, GSK is obligated to fund 100% of research costs in that year.

Epizyme and GSK partnership summary

Partner	GSK
Date announced	January 2011
Area of research	Small molecule HMT inhibitors directed against up to three undisclosed targets
Geography	GSK has WW rights
Upfront payment	$20M upfront
Total milestones	**$630M ($210M/target)**
Clinical milestones	$21M in preclinical milestones $99M in clinical milestones
Regulatory milestones	$240M
Commercialization milestones	$270M
Royalties	Mid-single digits to the low double-digits
Development costs	Epizyme is responsible for research until target identification, GSK provides fixed research funding

Source: Cowen and Company, SEC filings

2) Eisai partnership (established April 2011)

In April 2011, Epizyme and Eisai entered into a collaboration and license agreement, providing Eisai with an exclusive WW license to Epizyme's small molecule HMT inhibitors directed

against EZH2, including EPZ-6438. Epizyme retained an opt-in right to co-develop, co-commercialize, and share profits with Eisai for licensed products in the U.S.

Under the agreement, Epizyme received a $3M upfront payment. Epizyme is further entitled to receive up to $201M in additional milestone payments. These milestones are based on stage of development as follows:

- Up to $86M in development milestones as specified below:
    - $31M in clinical development milestones
    - $55M in regulatory milestones
- Up to $115M in sales-based milestones

In addition, Epizyme will receive mid-single digits to low double-digits royalties on U.S. sales and flat mid-single digit royalties on ex-U.S. sales.

Eisai will fund all research, development, and commercialization costs. If Epizyme exercises its opt-in right for a licensed compound, it will be required to share ongoing U.S. development costs with Eisai. Eisai will also then be entitled to recover a portion of past development costs (25%) through a partial reduction of future milestone payments and royalties, and all subsequent milestone payments Epizyme is eligible to receive will be reduced by 50%.

A milestone payment of $6M was triggered in June 2013 on the initiation of the Phase I/II clinical trial. Through June 2013, Epizyme has received $11.3M in research funding payments and $13M in research milestone payments.

Epizyme and Eisai partnership summary

Partner	Eisai
Date announced	April 2011
Area of research	HMT inhibitors directed to EZH2, including EPZ-6438
Geography	Epizyme retained an opt-in right to co-develop and co-commercialize in US
Upfront payment	$3M upfront
Total milestones	**$201M**
Clinical milestones	$31M
Regulatory milestones	$55M
Commercialization milestones	$115M
Royalties	Mid-single digits to low double-digits in US; flat mid-single digit ex-US
Development costs	Eisai funds 100% through POC

Source: Cowen and Company, SEC filings

3) Celgene partnership (established April 2012)

In April 2012, Epizyme and Celgene entered into a collaboration and license agreement to discover, develop, and commercialize small molecule HMT inhibitors directed against DOT1L outside the U.S., including EPZ-5676. Celgene also has the option to license rights outside the U.S. for any other HMT programs, with the exception of HMT targets covered by Epizyme's collaborations with GSK and Eisai.

Under the terms of the agreement, Epizyme received a $65M upfront payment and $25M from the sale of Series C Preferred Stock. There are no commercial milestones under this agreement. Epizyme is eligible to earn up to $60M in clinical development milestones and $100M in regulatory milestones payments related to DOT1L.

Epizyme retains all product rights in the U.S. and is eligible to receive royalties at percentages ranging from mid-single digits to mid-teens on net product sales outside of the U.S., subject to reduction in specified circumstances. Under the agreement, Epizyme is responsible for funding the full cost of development through Phase I, after which global development costs will be shared equally by both the companies.

Epizyme is also eligible to receive up to $165M in option exercise fees and development/ regulatory milestones for each additional HMT target for which Celgene exercises its option, during an initial option period which ends in July 2015. Celgene can extend the option period until July 2016 by making a significant option extension payment. .

The first potential milestone payment of $25M would be triggered upon achieving proof-of-concept for the DOT1L inhibitor.

Epizyme and Celgene partnership summary

Partner	Celgene
Date announced	April 2012
Area of research	HMT inhibitors directed to DOT1L ex-US and options for ex-US to other HMT programs
Geography	Epizyme has US rights
Upfront payment	$90M upfront ($65M in cash and $25M in equity)
Total milestones	**$160M**
Clinical milestones	$60M
Regulatory milestones	$100M
Commercialization milestones	-
Royalties	Mid-single digits to the mid-teens
Development costs	Epizyme funds 100% through Phase I, after that Celgene and Epizyme equally co-fund global development

Source: Cowen and Company, SEC filings

Companion Diagnostic Collaborations

1) Roche (established December 2012)

In December 2012, Epizyme and Eisai entered into an agreement with Roche to develop and commercialize an EZH2 companion diagnostic for use with EPZ-6438. *Under the agreement, all development costs will be paid by Eisai*. If Epizyme exercise its opt-in right under the Eisai partnership agreement for EPZ-6438, the costs paid by Eisai under the Roche agreement will then be shared by Epizyme and Eisai.

Under the terms of the agreement, Eisai has agreed to pay Roche defined milestone payments of up to $21M to develop the companion diagnostic. The diagnostic is being developed in conjunction with the therapeutic, and is expected to be part of the approval process.

2) Abbott (established February 2013)

In February 2013, Epizyme entered into an agreement with Abbott to develop a companion diagnostic for EPZ-5676 to identify patients with MLL-rearrangement. Under the agreement, Epizyme paid an upfront fee of $0.9M to Abbott, and is also required to make aggregate milestone-based development payments of up to $6M. Epizyme will also reimburse specified costs, which are not to exceed $0.9M, incurred by Abbott in conducting clinical trials to obtain necessary regulatory approvals for the companion diagnostic.

Under the agreement, Abbott has exclusive rights to commercialize and retain all proceeds from the commercialization of the companion diagnostic. It is possible that this diagnostic, which is a currently used FISH (fluorescence in situ hybridization) test categorized as a Laboratory Developed Test (under jurisdiction of CMS pursuant to CLIA), may not require regulatory approval as an In Vitro Diagnostic (IVD). However, development of the diagnostic as an IVD is proceeding.

Competitors in the HMT Space

Constellation Pharmaceuticals: Epizyme's "sister company"; Compounds: preclinical EZH2 inhibitors and BET inhibitors

Constellation Pharmaceuticals, founded in 2008 and based in Cambridge, MA, is focused on the development of epigenetic therapies, and is currently engaged in identifying small molecule inhibitors of EZH2 and BET. This is a company that we would characterize as the "sister company" to Epizyme, given the number of important similarities between the two, including scientific and clinical area of focus, partnership(s) with premier biopharma players for significant upfront fees, and marquee name scientific founders, management team, board of directors and investors, among others.

Partnership with Genentech: $95M in upfront and the option to acquire Constellation. In January 2012, Constellation announced an exclusive epigenetics collaboration agreement with Genentech, under which the company received $95M in upfront fees and committed research and development funding for a three-year collaboration period. Constellation is eligible for substantial development and commercialization milestone payments and double digit royalties on product sales. Each company may retain exclusive rights to programs resulting from the collaboration. *Genentech was also granted an option to acquire Constellation based on pre-negotiated terms, including a significant initial acquisition payment plus contingent value rights payments*.

EZH2 inhibitors: As described in the company's pipeline information, Constellation is using multiple substrates, ranging from simple peptides to more complex, chemically modified oligonucleosomes, in biochemical assays to delineate genuine inhibitors of EZH2. The company also has described its proprietary assay technology, used to measure the physical binding of small molecule inhibitors to EZH2. Currently, Constellation is evaluating novel EZH2 inhibitors in preclinical studies.

BET inhibitors: Constellation is also developing inhibitors of BET bromodomains. There are four BET (**b**romodomain and **e**xtra-**t**erminal) proteins which contain bromodomains, BRD2, BRD3, BRD4, and BRDT. Bromodomains recognize acetylated lysine residues on histones, "reading" epigenetic marks. BET proteins bind to acetylated lysine residues and recruit transcription factors to regulate the expression of genes such as *MYC* and *BCL-2*, which have recognized roles in oncogenesis. As per the company's pipeline information, Constellation is evaluating small molecule BET inhibitors in preclinical studies.

In a 2011 publication (Mertz et al., *PNAS* 2011) detailing preclinical studies with representative small molecule inhibitors of BET, Constellation scientists demonstrated suppression of *MYC* gene transcription. In *in vitro* studies with a panel of cancer cell lines, treatment with a BET inhibitor (JQ1) inhibited proliferation of human leukemia, lymphoma, and myeloma cells. Gene expression profiling analysis of treated cells demonstrated the most down-regulated gene to be *MYC*, with expression reduced within 1 hour after treatment. In further *in vivo* studies with mouse tumor xenograft models created with Burkitt's lymphoma cells (Raji BL) or AML cells

(MV4-11), tumors in BET inhibitor-treated mice had significantly slower growth, compared to delivery vehicle-treated control mice. With BET inhibitor administration, the average tumor volume was reduced by 45% at 14 days in the Raji BL model, and by 20% at 32 days in the MV4-11 AML model.

Partnership with LLS: In September 2012, Constellation announced a strategic partnership with the Leukemia and Lymphoma Society (LLS) for the development of a novel BET inhibitor for the treatment of hematologic malignancies. Under the agreement, LLS, as part of its Therapy Acceleration Program, will provide up to $7.5M in funding to support Constellation's BET inhibitor development through the completion of Phase I clinical evaluation.

GlaxoSmithKline; Compound: GSK126

GlaxoSmithKline is developing GSK126, a small molecule inhibitor of EZH2, which is competitive with SAM for binding, and as reported by GSK, inhibits both wild-type and mutant EZH2. Results of preclinical studies were published in 2012 (McCabe et al., *Nature* 2012). In *in vitro* studies, GSK126 administration resulted in reduction of H3K27 trimethylation in EZH2 wild type and mutant DLBCL cell lines. Further evaluation of GSK126 on inhibition of cell proliferation in a panel of B-cell lymphoma cell lines from multiple subtypes demonstrated DLBCL cell lines to be most sensitive to treatment, with six of the seven most sensitive, including Pfeiffer, WSU-DLCL2, and KARPAS-422, noted to contain EZH2 mutations. In these cell lines, GSK126 inhibited proliferation and reduced cell numbers.

In *in vivo* studies, mouse tumor models were created using subcutaneous xenografts of KARPAS-422 and Pfeiffer cells. GSK126 was administered per the following dose groups: 1) 50 mg/kg once daily, 2) 150 mg/kg once daily, 3) 300 mg/kg twice per week, and 4) delivery vehicle alone, no GSK126. With 10 days of daily dosing, reduction of H3K27 trimethylation was observed in a dose dependent fashion. At the 50 mg/kg dose, there was complete tumor growth inhibition. Tumor regression was observed at the higher doses. After discontinuation of treatment, there was tumor stasis in the 50 mg/kg group, and undetectable tumor in the higher dose groups through study day 60. Further evaluation was completed using intermittent dosing regimens, weekly or including a 1 week drug holiday, with lower GSK126 doses in KARPAS-422 xenograft mice with large tumors. These intermittent dose schedules were also associated with inhibition of tumor growth (91–100%, p=0.0008–0.0024).

To date, there has been no announcement of a clinical trial with GSK126.

Novartis Institutes for Biomedical Research (China): Compound: EI1

In 2012, a published report (Qi et al., *PNAS* 2012) from the China Novartis Institutes for Biomedical Research described results from preclinical studies of EI1, a small molecule EZH2 inhibitor developed by the group. As indicated in the publication, EI1 is a SAM-competitive, EZH2-selective inhibitor which has similar potency against both wild-type and mutant EZH2 (Ki, 13 nM). In *in vitro* studies with cell lines, including DLBCL cells with EZH2 mutation (WSU-DLCL2) and wild type EZH2 (OCI-LY19), EI1 inhibited H3K27 di- and tri-methylation in dose

dependent fashion, while other H3 methyl marks were not affected. H3K27 tri-methylation was decreased 24 hours after EI1 administration, and reached the lowest levels after 4-5 days. Proliferation of EZH2 mutant cells was blocked by EI1 treatment, but there was no anti-proliferative effect observed in EZH2 wild-type cells. EI1 inhibition was associated with cell cycle arrest and apoptosis of EZH2 mutant DLBCL cells.

To date, we are not aware of further development announcements or trials of EI1. The compound is not currently listed as part of the Novartis oncology pipeline.

Current Epigenetic Therapy Landscape

The currently approved and marketed epigenetic therapies include two DNA methyltransferase (DNMT) inhibitors, Vidaza and Dacogen, and two histone deacetylase (HDAC) inhibitors, Zolinza and Istodax. HDACs remove acetyl groups from lysine residues on histones. Acetylation is generally associated with open chromatin configuration and activation of transcription. DNMTs methylate DNA on cytosine residues, typically at or near CG islands, DNA areas which have a high frequency of cytosine-guanine sequences. Hypermethylation of CG islands in tumor suppressor genes may inhibit expression and appears to be a mechanism for cancer development. Reversal of DNA methylation may restore silenced tumor suppressor gene expression. DNMT inhibitors are also known as hypomethylating agents.

DNA methyltransferase (DNMT) inhibitors: Vidaza and Dacogen are both approved for the treatment of myelodysplastic syndrome (MDS) in the U.S. and the E.U. The European approval for Vidaza also includes treatment for AML which has developed from MDS and only when the bone marrow has 20-30% abnormal cells. In the E.U., Dacogen is approved for first-line treatment of AML in adults age ≥ 65 years who are ineligible for standard chemotherapy.

Histone Deacetylase (HDAC) inhibitors: Zolinza is approved in the U.S. for the treatment of relapsed or refractory cutaneous T-cell lymphoma (CTCL) following two systemic therapies. In 2009, Merck withdrew its EMA application for Zolinza after preliminary review deemed data insufficient for approval. Istodax is approved in the U.S. for relapsed or refractory CTCL and peripheral T-cell lymphoma (PTCL), after at least one prior systemic therapy. In 2012, the CHMP of the EMA issued a negative opinion on Celgene's application for Istodax in PTCL (because of lack of a comparator treatment in the trial), which was further upheld after subsequent re-examination.

The Four Approved Epigenetic Therapies

Agent	Company	Mechanism	FDA Approval	Indication	2012 Sales
Vidaza (azacitidine)	Celgene	DNA methyltransferase inhibitor	2004	MDS	$823M
Dacogen (decitabine)	Eisai/Janssen	DNA methyltransferase inhibitor	2006	MDS	~$171M ($17.3B Yen)
Zolinza (vorinostat)	Merck	HDAC inhibitor	2006	R/R CTCL	$25M
Istodax (romidepsin)	Celgene	HDAC inhibitor	2009/2011	R/R CTCL, R/R PTCL	$50M

Source: Cowen and Company

Epigenetic Agents in Development for AML/ALL and NHL

There are several agents in development in the epigenetic arena, which are being evaluated in multiple oncology and hematology indications. HDAC inhibitors account for the majority of the compounds in more advanced phases of development. Looking specifically at AML/ALL and NHL, there are a number of agents in development, including some as listed below:

Pracinostat (MEI Pharma): MEI Pharma's HDAC inhibitor, pracinostat, will be evaluated in combination with Dacogen or Vidaza in a Phase II trial of 40 elderly, first-line AML patients, which is expected to begin in September 2013.

Entinostat (Syndax): Syndax's HDAC inhibitor, entinostat, is being evaluated in a Phase II trial of elderly (age > 60 years) AML patients intolerant of or declining chemotherapy, or relapsed after one prior regimen, in an overlapping or sequential combination with 5-azacytidine. The trial has an estimated enrollment of 108 patients and anticipated completion in 2014. Entinostat is also being evaluated in combination with clofarabine in a Phase I trial of adult, poor risk, Ph-negative ALL patients with newly diagnosed disease (age ≥ 40 years) or relapsed disease (age ≥ 21 years). The trial has an estimated enrollment of 34 patients and is expected to be complete at YE13.

Mocetinostat (Methylgene): At ASCO 2013, results from a Phase II combination trial of Methylgene's HDAC inhibitor, mocetinostat, with 5-azacytidine in patients with MDS and AML were presented. In 38 relapsed AML patients, the combination treatment resulted in an ORR of 32%, disease control rate of 84%, and OS of 5.1 months. Also at ASCO 2013, results from a Phase II trial of mocetinostat monotherapy in 72 patients with relapsed/refractory DLBCL and FL were presented. The median duration of treatment was 3 months. The ORR was 14% (17% in 41 DLBCL patients and 10% in 31 FL patients, with 1 patient in each group achieving CR). The median PFS was 2.7 months for the DLBCL subgroup, and 4 months for the FL subgroup. The most common Grade 3/4 AEs included fatigue (24%), neutropenia (14%), thrombocytopenia (13%), and anemia (7%).

SGI-110 (Astex): SGI-110, a small molecule DNMT inhibitor (hypomethylating agent) is a second generation, follow-on drug to Dacogen. A Phase I/II dose escalation study is evaluating SGI-110 in patients with high risk MDS or AML who are refractory to or relapsed after standard treatment. The dose expansion portion of the trial will include first-line AML patients, at least 65 years old, including those with poor cytogenetics.

BET inhibitors*:* The BET (**b**romodomain and **e**xtra-**t**erminal) proteins consist of four bromodomain-containing proteins, BRD2, BRD3, BRD4, and BRDT. Bromodomains recognize acetylated lysine residues on histones, thus "reading" the epigenetic mark. BET proteins bind to acetylated lysine residues and recruit transcription factors to regulate expression of genes such as *MYC* and *BCL-2*, which have recognized roles in oncogenesis. Small molecule inhibitors of BET appear to suppress transcription of these genes.

OTX015 (OncoEthix): The bromodomain inhibitor OTX015 is being evaluated in a Phase I trial in patients with relapsed/refractory acute leukemia and hematologic malignancies. In dose expansion cohorts, only patients with selected malignancies will be enrolled, including AML, ALL, and DLBCL. The trial has an estimated enrollment of 75 patients and anticipated completion in 2014.

JQ1 (Tensha): Preclinical study results for the BET inhibitor JQ1 were presented at ASCO 2013. JQ1 (100-500 nM) was studied alone and in combination with Novartis' HDAC inhibitor panobinostat in cultured and primary human AML blast cells, as well as in mouse xenograft tumor models created from AML cells. JQ1 treatment was associated with apoptosis of the cultured and primary AML cells, and combination with panobinostat was noted to be synergistic in this effect. The *in vivo* tumor model showed improved survival of mice treated with the combination of drugs, compared to mice treated with each agent alone or delivery vehicle alone.

Epigenetic Agents in Development for Oncology

Agent	Company	Mechanism	Development Phase	Indication
Panobinostat	Novartis	HDAC inhibitor	II/III	Multiple myeloma, HL, CTCL
Belinostat	Spectrum	HDAC inhibitor	II	PTCL, NHL, HCC, thymoma
Pracinostat	MEI Pharma	HDAC inhibitor	II	MDS, AML
Mocetinostat	Methylgene	HDAC inhibitor	II	MDS, AML, NHL, HL
Entinostat	Syndax	HDAC inhibitor	I/II	Leukemia, Breast ca, HL, NSCLC, RCC
Abexinostat	Pharmacyclics	HDAC inhibitor	I/II	NHL, sarcoma
CHR-3996	Chroma	HDAC inhibitor	I/II	Multiple myeloma
CHR-2845	Chroma	HDAC inhibitor	I/II	HCC
ACY-1215	Acetylon	HDAC inhibitor	I/II	Multiple myeloma
SGI-110	Astex	DNMT inhibitor	I/II	MDS/AML, OC, HCC
GSK525762	GSK	BET (bromodomain) inhibitor	I/II	NUT midline carcinoma
OTX015	OncoEthix	BET (bromodomain) inhibitor	I	Acute leukemia/hematologic
GSK126	GSK	HMT (EZH2) inhibitor	Preclinical	NHL
EZH2 inhibitors	Constellation	HMT (EZH2) inhibitor	Preclinical	Hematologic/solid tumors
BET inhibitors	Constellation	BET (bromodomain) inhibitor	Preclinical	Hematologic/solid tumors
JQ1	Tensha	BET (bromodomain) inhibitor	Preclinical	NUT midline carcinoma, AML
DUB inhibitor	CellCentric	Deubiquitinase inhibitor	Preclinical	Prostate ca

Source: Cowen and Company

Acute Leukemia: Brief Overview

Acute Myeloid Leukemia (AML)

AML is a heterogeneous hematologic malignancy marked by clonal expansion of myeloid blasts (precursor cells) in peripheral blood, bone marrow, and other tissues. AML represents the most common form of acute leukemia in adults. In the U.S., close to 14,000 patients were diagnosed with AML in 2012, and there were approximately 10,000 deaths. The median age of diagnosis is 66 years. More than half of patients (54%) are diagnosed at age ≥ 65 years, with approximately one-third diagnosed at age ≥ 75 years. AML is infrequent in children and represents 20% of childhood acute leukemias, with approximately 500 pediatric cases in the U.S. each year. An increasing subgroup of AML is comprised by patients with "therapy-related" myelodysplasia or myeloid leukemia (secondary MDS/AML) which has developed after previous treatment for cancer. Therapy-related AML is thought to account for 5%-20% of AML cases. It is more commonly associated with certain primary malignancies, such as breast cancer, gynecologic cancers, and lymphomas, and previous treatment with alkylating agents (such as cyclophosphamide) and topoisomerase inhibitors (such as etoposide). Therapy-related AML is generally associated with poor outcomes relative to de novo AML, which refers to AML in patients with no history of prior MDS, myeloproliferative disorder, or exposure to leukemogenic therapies.

Initial laboratory evaluation includes a complete blood count (CBC), which includes hemoglobin, hematocrit, platelets, and white blood cell (WBC) count, with differential (evaluation of levels of specific WBC types). Bone marrow analysis with cytogenetic analysis (karyotype and fluorescence in situ hybridization (FISH)) is necessary for diagnosis of AML. The presence of 20% or more blasts in the peripheral blood and/or bone marrow represents the threshold for diagnosis.

Classification of AML requires further diagnostic evaluation through immunohistochemistry (IHC), cytochemistry, and molecular genetics analysis. While 40-50% of de novo AML patients have normal karyotype, clinical outcomes can be heterogeneous because of molecular alterations. The most frequent mutations associated with AML occur in the FMS-like tyrosine kinase 3 (FLT3) gene, nucleophosmin (NPM1) gene, and the CEBPA gene, with the latter two being prognostically favorable. While providing prognostic information, these genetic changes do not affect initial treatment in AML.

AML Risk Status

Risk	Cytogenetics	Molecular Abnormalities
Better-risk	inv(16) or t(16;16) t(8;21) t(15;17)	*NPM1* mutation *CEBPA* mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11)	*c-KIT* mutation
Poor-risk	≥3 chromosomal abnormalities -5, 5q-, -7, 7q- 11q23 inv(3); t(3;3) t(6;9) t(9;22)	*FLT3* mutation

Source: Cowen and Company, NCCN Guidelines

AML Response Criteria: According to the International Working Group in AML, the definition of **complete remission (CR)** requires achievement of a morphologic leukemia-free state, meaning < 5% blasts in a bone marrow aspirate sample. Additionally, the patient should have an absolute neutrophil count > 1,000/mcL and platelet count ≥ 100,000/mcL. While there are no thresholds defined for hemoglobin and hematocrit count, transfusion independence is a requirement. Failure to achieve CR is considered to be a treatment failure. **Partial remission (PR)** is defined by at least a 50% decrease in the percentage of blasts in the bone marrow to 5% to 25%, with normalization of blood counts as in CR. **Relapse** after CR is defined as re-appearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow which is unrelated to any other cause. The re-appearance or development of extramedullary disease (outside of the bone marrow) also indicates relapse.

AML Response Criteria

Complete Remission (CR)	Partial Remission (PR)	Relapse
• <5% blasts in bone marrow • Transfusion independence • Absolute neutrophil count (ANC)>1,000/mcL • Platelet count ≥100,000/mcL • No extramedullary disease	• At least 50% decrease in blast percentage to 5% - 25% in bone marrow • ANC >1,000/mcL • Platelet count ?100,000/mcL	• Re-appearance of leukemic blasts in peripheral blood • ≥5% blasts in bone marrow, not related to other cause • Extramedullary disease

Source: Cowen and Company, NCCN Guidelines, International Working Group in AML

Treatment for Acute Leukemias: Acute leukemia treatment is divided into induction therapy and consolidation (post-remission) therapy. The goal of induction chemotherapy is reduction of

leukemic disease and restoration of normal hematopoiesis. More intensive treatments during consolidation are used to achieve durable control of disease. Without consolidation, patients will relapse, usually within 6 to 9 months. Higher risk patients generally receive more aggressive therapy. Poor risk factors for long term remission include 1) adverse cytogenetic and molecular lesions, 2) failure to achieve remission after one cycle of induction therapy, and 3) increased tumor burden (WBC ≥ 100,000/mcL).

Induction Therapy for AML: Induction therapy for AML is stratified by age greater or younger than 60 years. Patients in the older age group have a higher prevalence of unfavorable cytogenetic abnormalities, prior myelodysplasia, more frequent multi-drug resistance, more comorbid conditions reducing tolerance of intensive therapy, and increased treatment-related mortality. *Rates of CR typically are not greater than 70% in younger patients and 50% in older patients*.

In younger patients (age < 60 years) standard induction regimens are used. *AML induction regimens are based on the backbone of cytarabine and an anthracycline, such as daunorubicin or idarubicin*. Per NCCN guidelines, standard-dose cytarabine (100-200 mg/m^2 IV) for 7 days combined with either idarubicin (12 mg/m^2) for 3 days or escalated daunorubicin (90 mg/m^2) for 3 days is a recommended regimen supported by the highest level of evidence. In a Phase III ECOG study, the escalated daunorubicin dose (90 mg/m^2), when compared to standard dose (45 mg/m^2) was associated with increased CR rate (71% vs. 57%, p<0.001) and longer median OS (24 months vs. 16 months, p=0.003). Addition of the purine analog cladribine to a standard induction regimen may also be considered in patients younger than 60 years. The use of high dose cytarabine (2 g/m^2) may be associated with more rapid clearance of marrow blasts, but risks of neurotoxicity and renal impairment are increased. Whether high dose or standard dose cytarabine-based induction is used, between 20% and 45% of patients will not achieve remission. Poor risk patients have an even lower success rate, with only 40%-50% achieving CR with standard induction therapy.

For older AML patients (age > 60 years) with favorable risk, functional performance status (ECOG 0-2), and minimal comorbidities, standard therapy may provide benefit, irrespective of age. Remission rates of 40%-50% are expected in this population with standard induction. *Per NCCN guidelines, a reasonable induction regimen is comprised by standard dose cytarabine for 7 days and an anthracycline for 3 days*. Clofarabine, a purine analog, is another induction option for consideration, as an intermediate-intensity therapy. In a Phase II study from M.D. Anderson Cancer Center with older patients (median age 71 years), treatment with clofarabine 30 mg/m^2 IV for 5 days resulted in CR rate of 46% and a median OS of 72 weeks.

In patients who are not appropriate for standard or intermediate-intensity induction, *low intensity therapy options include low-dose cytarabine and the DNA methyltransferase inhibitors 5-azacytidine (Vidaza) and decitabine (Dacogen)*, which are FDA approved for treatment of MDS. In a Phase III study 5-azacytidine treatment in a subgroup of AML patients resulted in median OS of 24.5 months compared to 16 months with conventional treatment (HR 0.47, p=0.005). Otherwise, best supportive care, which includes blood and platelet transfusions and prophylactic antibiotic therapy, may also be reasonable.

AML Induction Therapy

Age	Induction Therapy	Response Rate
< 60 years	SD cytarabine x 7 days + idarubicin or daunorubicin X 3 days ***or*** SD cytarabine x 7 days + daunorubicin x 3 days + cladribine x 5 days ***or*** HD cytarabine + idarubicin or daunorubicin x 3 days	CR typically not greater than 70% (Poor risk CR 40%-50%)
> 60 years	SD cytarabine x 7 days + idarubicin or daunorubicin X 3 days or + mitoxantrone ***or*** Intermediate-intensity: clofarabine ***or*** Low-intensity: subcutaneous cytarabine, 5-azacytidine, decitabine	CR typically not greater than 50% (Poor risk CR 40%-50%)

Standard dose (SD); High dose (HD); Reduced Intensity Conditioning (RIC)

Source: Cowen and Company, NCCN Guidelines

Post-Induction Therapy for AML: Evaluation of the bone marrow should be completed 7 to 10 days following completion of induction. If residual blasts are demonstrated after standard induction, a second cycle of the same regimen may be used. Older patients may not have restoration of fully normal blood counts even with clearance of marrow blasts. In the case of significant residual blasts, escalation to high dose cytarabine can be considered. With failure of induction, patients can be treated in a clinical trial or proceed to allogeneic stem cell transplant (SCT), which may salvage 25-30% of these patients.

AML Post-Induction Therapy

Age	Post-Induction Therapy
< 60 years	HD cytarabine alone ***or*** SD cytarabine + idarubicin or daunorubicin
> 60 years	SD cytarabine + anthracycline or mitoxantrone ***or*** RIC allogeneic SCT

Standard dose (SD); High dose (HD); Reduced Intensity Conditioning (RIC)

Source: Cowen and Company, NCCN Guidelines

Consolidation Therapy for AML: Successful induction therapy will resolve leukemia in the marrow and restore normal hematopoiesis, but consolidation therapy is necessary to reduce any residual abnormal cells. *In patients age < 60 years, the standard consolidation therapy consists of 3 to 4 cycles of high dose cytarabine* (2 g/m^2 for 6 doses, total 18 g/m^2 per cycle). Other strategies for consolidation include one or more cycles of high dose cytarabine followed by autologous or allogeneic SCT. In favorable risk AML patients, potential benefit of allogeneic SCT may be reduced by risks of morbidity and death. Results with autologous SCT may be comparable. In a Phase III SWOG/ECOG study in younger (≤ 55 years) patients undergoing SCT, the 5-year survival rates for the autologous group (71%) and the allogeneic groups (63%) were similar. Thus, in favorable risk patients, autologous SCT is preferred, with allogeneic SCT reserved for salvage therapy. In patients with intermediate or poor risk, earlier use of allogeneic SCT may be considered.

Older patients achieving CR with induction therapy may also receive further consolidation with the same agents. The use of myeloablative allogeneic SCT may be limited in older patients because of comorbidities, but allogeneic SCT with reduced-intensity conditioning (RIC) may be feasible, with 2-year OS rates of 40%-60% reported from registry data. Per NCCN guidelines, this option can be considered in older patients who have achieved CR after induction or as treatment for induction failure.

AML Consolidation Therapy

Age	Consolidation Therapy
< 60 years	HD cytarabine x 3-4 cycles ***or*** HD cytarabine x 1-2 cycles, then autologous SCT for favorable and intermediate risk ***or*** Allogeneic SCT for intermediate and poor risk ***or*** Clinical trial
> 60 years	SD cytarabine ± anthracycline ***or*** HD cytarabine x 1-2 cycles ***or*** Low intensity regimens with 5-azacytidine or decitabine every 4-6 weeks until progression ***or*** RIC allogeneic SCT ***or*** Clinical trial

Standard dose (SD); High dose (HD); Reduced Intensity Conditioning (RIC)

Source: Cowen and Company, NCCN Guidelines

Salvage Therapy for Relapsed Disease: NCCN guidelines recommend monitoring of patients upon completion of consolidation therapy through laboratory evaluation (complete blood count, platelet count) every 1 to 3 months for 2 years, and then every 3 to 6 months for a total of 5 years. Enrollment in a clinical trial for treatment of relapse is strongly preferred. In case of relapse after a long duration of remission (> 12 months), re-treatment with the original induction regimen is an option.

Salvage chemotherapy followed by allogeneic SCT is another option, but transplantation should only be considered if the patient is in remission. Salvage chemotherapy options include high dose cytarabine with or without an anthracycline, as well as purine analog (fludarabine, cladribine, clofarabine)-based and etoposide-based combination regimens with cytarabine. These salvage regimens are considered aggressive therapies. Less aggressive options include low dose cytarabine and hypomethylating agents (DNA methyltransferase inhibitors).

AML Salvage Therapy

Age	Salvage Therapy	Response Rate
< 60 years	Clinical trial ***or*** Salvage chemotherapy, then allogeneic SCT ***or*** Repeat initial successful induction regimen ***or*** Best supportive care	CR 30%-45%
> 60 years	Clinical trial ***or*** Salvage chemotherapy, then allogeneic SCT ***or*** Repeat initial successful induction regimen ***or*** Best supportive care	

Standard dose (SD); High dose (HD); Reduced Intensity Conditioning (RIC)

Source: Cowen and Company, NCCN Guidelines

AML Treatment Summary

Age	Induction Therapy	Post-Induction Therapy	Consolidation Therapy	Salvage Therapy
< 60 years	SD cytarabine x 7 days + idarubicin or daunorubicin X 3 days ***or*** SD cytarabine x 7 days + daunorubicin x 3 days + cladribine x 5 days ***or*** HD cytarabine + idarubicin or daunorubicin x 3 days	HD cytarabine alone ***or*** SD cytarabine + idarubicin or daunorubicin	HD cytarabine x 3-4 cycles ***or*** HD cytarabine x 1-2 cycles, then autologous SCT for favorable and intermediate risk ***or*** Allogeneic SCT for intermediate and poor risk ***or*** Clinical trial	Clinical trial ***or*** Salvage chemotherapy, then allogeneic SCT ***or*** Repeat initial successful induction regimen ***or*** Best supportive care
> 60 years	SD cytarabine x 7 days + idarubicin or daunorubicin X 3 days or + mitoxantrone ***or*** Intermediate-intensity: clofarabine ***or*** Low-intensity: subcutaneous cytarabine, 5-azacytidine, decitabine	SD cytarabine + anthracycline or mitoxantrone ***or*** RIC allogeneic SCT	SD cytarabine ± anthracycline ***or*** HD cytarabine x 1-2 cycles ***or*** Low intensity regimens with 5-azacytidine or decitabine every 4-6 weeks until progression ***or*** RIC allogeneic SCT ***or*** Clinical trial	Clinical trial ***or*** Salvage chemotherapy, then allogeneic SCT ***or*** Repeat initial successful induction regimen ***or*** Best supportive care

Standard dose (SD); High dose (HD); Reduced Intensity Conditioning (RIC)

Source: Cowen and Company, NCCN Guidelines

Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy with proliferation of immature lymphoid cells in bone marrow and peripheral blood. In 2012, there were approximately 6,000 new ALL cases in the U.S. The median age at diagnosis is 14 years, and 60% of patients are younger than 20 years. ALL is the most common form of childhood leukemia and accounts for 80% of acute leukemias in the pediatric population, while it represents only 20% of leukemias in adults. Long term ALL prognosis has improved over time for children, and the cure rate is approximately 80%. However, outcomes for adults remain poor overall, with a cure rate of 30-40%. Differences in long term survival partly result from differences in cytogenetic subtypes among age groups.

Clinical presentation of ALL is usually non-specific and may include fatigue, lethargy, fevers, weight loss, infections, and easy bruising or bleeding. In children, pain in the joints and extremities can be presenting symptoms. Initial laboratory evaluation includes a complete blood count with differential. Diagnosis requires the presence of ≥ 20% lymphoblasts in the bone marrow. Evaluation includes morphologic examination of cells, immunophenotyping (flow cytometry), cytogenetic analysis (karyotype, FISH), and molecular analysis.

ALL is categorized as B-cell ALL or T-cell ALL. B-cell ALL accounts for the majority of cases in pediatric (88%) and adult (75%) groups. Recurrent chromosomal and molecular abnormalities are common. In children, the most common chromosomal abnormalities are hyperdiploidy (>

50 chromosomes) and *TEL-AML1* rearrangement from translocation t(12;21), both associated with favorable outcomes. Hypodiploidy (< 44 chromosomes) occurs in 1%-2% of patients and is associated with poor prognosis. In adults, the most common abnormality is the Philadelphia chromosome (t(9;22) translocation) causing *BCR-ABL* rearrangement, associated with poor prognosis.

Cytogenetic and Molecular Abnormalities in ALL

Cytogenetics	Gene	Adult Frequency	Pediatric Frequency
Hyperdiploidy	--	7%	25%
Hypodiploidy	--	2%	1%
t(9;22) Philadelphia	*BCR-ABL*	25%	3%
t(12;21)	*TEL-AML1*	2%	22%
t(v; 11q23)	***MLL***	***10%***	***8%***
t(1;19)	*E2A-PBX1*	3%	5%
t(5;14)	*IL3-IGH*	< 1%	< 1%
t(8;14)	*c-MYC*	4%	2%

Source: Cowen and Company, NCCN Guidelines

In the pediatric population, age range 1-10 years and white blood cell (WBC) count < 50 x 10^9/L define a standard risk group. High risk factors include T-cell ALL, Philadelphia chromosome-positive ALL (Ph-positive ALL), MLL gene rearrangement, hypodiploidy, and failure to achieve remission after induction. In adults, initial risk assessment is based on the presence or absence of the Philadelphia chromosome. Additional poor risk features include hypodiploidy, MLL gene rearrangements, complex karyotype (≥ 5 chromosomal abnormalities), and elevated WBC count (≥ 30 x 10^9/L for B-cell; ≥ 100 x 10^9/L for T-cell). Standard risk is defined as the absence of all these poor-risk factors.

ALL Response Criteria: CR in the bone marrow and peripheral blood is defined as the absence of circulating leukemic blasts, as well as absence of extramedullary disease, such as lymphadenopathy, splenomegaly, testicular mass, or CNS involvement. The bone marrow should have < 5% blasts. The absolute neutrophil count (ANC) must be > 1,000/mcL, and the platelet count must be > 100,000/mcL. There should be no recurrence observed for at least 4 weeks. Failure to achieve CR after induction therapy is considered to be **refractory disease**. **Progressive disease** is characterized by at least a 25% increase in the absolute number of circulating blasts in the blood or bone marrow blasts, or extramedullary disease development. The definition of **relapsed disease** is the re-appearance of blasts in blood or bone marrow (> 5%), or in any extramedullary site after CR achievement.

CNS disease in classified as: CNS-1, no lymphoblasts in cerebrospinal fluid (CSF); CNS-2, WBC count < 5/mcL in CSF with presence of blasts; or CNS-3, WBC count ≥ 5/mcL in CSF with presence of blasts. CNS relapse is defined as CNS-3 development or clinical signs of CNS leukemia, such as facial nerve palsy, and brain or eye involvement.

ALL Response Criteria

CR	CRi	Progressive Disease	Refractory Disease	Relapsed Disease
• No circulating blasts or extramedullary disease • Bone marrow with < 5% blasts • ANC > 1,000/mcL • Platelets > 100,000/mcL • No recurrence for 4 weeks	• CR with incomplete blood count recovery: • ANC < 1,000/mcL • Platelets < 100,000/mcL	• At least 25% increase in absolute number of circulating or bone marrow blasts, or development of extramedullary disease	• Failure to achieve CR at end of induction	• Reappearance of blasts in blood or bone marrow (>5%), or in any extramedullary site after CR

Source: Cowen and Company, NCCN Guidelines

Treatment for ALL: ALL treatment is categorized into induction, consolidation, and maintenance phases. Treatment regimens employ multi-agent chemotherapy. The goal of induction therapy is clearance of as many leukemic cells as possible from the bone marrow, in order to achieve remission. Consolidation therapy (also called *intensification therapy)*, is used to clear residual disease that may remain after induction. Maintenance therapy refers to extended treatment which is used to prevent relapse. All treatment regimens for ALL include CNS prophylaxis and treatment.

Induction Therapy for ALL: ALL induction consists of multi-agent chemotherapy regimens. *The typical therapy backbone includes the combination of vincristine, an anthracycline such as daunorubicin or doxorubicin, and a corticosteroid such as prednisone or dexamethasone, with or without L-asparaginase and/or cyclophosphamide*. Antimetabolites such as methotrexate, cytarabine, and mercaptopurine are also often administered during induction therapy for prophylaxis of CNS disease. Pediatric regimens are usually 3-drug or 4-drug combination regimens with vincristine, L-asparaginase, a corticosteroid, ± an anthracycline. Adult regimens consist of the 4-drug combination with these same agents or a 5-drug combination adding cyclophosphamide. In the CALGB 8811 trial, which evaluated the 5-drug induction regimen in 197 previously untreated ALL patients with median age of 32 years (range, 16-80 years; 29% Ph-positive), the median OS for all patients was 36 months, with 85% CR rate. Ph-negative patients had median OS of 39 months and a 3-year OS rate of 62%.

In pediatric and adult patients with Ph-positive ALL, NCCN guidelines recommend the addition of a tyrosine kinase inhibitor (TKI) to multi-agent chemotherapy. Imatinib mesylate (Gleevec) is a TKI which inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome translocation. The drug is approved for the treatment of previously untreated pediatric Ph-positive ALL patients and for adult patients with relapsed or refractory Ph-positive ALL. Dasatinib (Sprycel), nilotinib (Tasigna), and ponatinib (Iclusig) are second-generation TKI therapies which also inhibit BCR-ABL and may be alternatives to imatinib.

ALL Induction Therapy

Induction Therapy	Response Rate
Adults: Multi-agent chemo: daunorubicin, vincristine, pegaspargase, prednisone, ± cyclophosphamide **≥ 65 yrs:** multi-agent chemo or corticosteroids **Pediatric:** ± anthracycline **Ph-positive:** +TKI (imatinib or dasatinib)	***Adults:*** CR ~85% ***Pediatric:*** CR ~95%

Source: Cowen and Company, NCCN Guidelines

Consolidation Therapy for ALL: Once patients achieve remission with induction therapy, they receive consolidation, in order to eliminate any residual disease. The drug combinations and duration of therapy can vary among protocols. The chemotherapies used in this treatment phase can be similar to induction regimens. Also, high dose methotrexate, cytarabine, mercaptopurine, and L-asparaginase are frequently used, especially in the pediatric population. Treatment with allogeneic SCT may also be considered, especially in high risk cases, if the patient is appropriate (relatively fit, age < 65 years, no significant comorbidities) and a donor is available.

In Ph-positive ALL patients for whom a donor cannot be matched, consolidation therapy consists of continued multi-agent chemotherapy in combination with a TKI. Older patients or those with comorbidities may continue on a TKI, with or without chemotherapy.

ALL Consolidation Therapy

Consolidation Therapy
Continue multi-agent chemo ***or*** Consider allogeneic SCT **≥ 65 yrs:** chemo **Ph-positive:** TKI + chemo

Source: Cowen and Company, NCCN Guidelines

CNS Therapy for ALL: The CNS is an ALL "*sanctuary*" site, in which leukemic blasts are relatively protected from systemic chemotherapy effects. This results from the inability of therapies to cross the blood-brain barrier. CNS therapy is used to clear the CNS of leukemia cells, in order to prevent disease or relapse. Therapeutic options include cranial radiation therapy, intrathecal (*injected into the CSF*) chemotherapy, or high dose systemic

chemotherapy with agents that may penetrate the blood-brain barrier, such as methotrexate, cytarabine, mercaptopurine, and L-asparaginase. Patients generally receive CNS therapy throughout all phases of ALL treatment.

Maintenance Therapy for ALL: The core maintenance therapy in ALL consists of daily mercaptopurine and weekly methotrexate. Monthly pulses of vincristine and corticosteroid therapy are also typical. Ph-positive patients should have a maintenance regimen which includes a TKI. The duration of maintenance treatment is 2 years in adults, and 2-3 years in children.

ALL Maintenance Therapy

Maintenance Therapy
Daily 6-mercaptopurine + Weekly methotrexate + Monthly vincristine and prednisone pulses for 2-3 years **Ph-positive:** +TKI

Source: Cowen and Company, NCCN Guidelines

Salvage Therapy for Relapsed/Refractory ALL: *Approximately 20% of pediatric patients and about 60% of adults relapse after initial CR*. Of these relapsed patients, about 20%-30% will have long-term remission with second-line therapies. Early relapse, occurring < 18 months from diagnosis, is associated with an estimated approximately 20% five-year survival in children. In the MRC UKALL XII/ECOG 2993 study of 609 adults with ALL, the median OS after relapse was 4.5 to 6 months, with a 5-year OS rate of 7%-10%. Factors which favor better outcomes following salvage therapies include younger age (< 30 years) and duration of first CR > 2 years with first-line treatment.

ALL Salvage Therapy

Salvage Therapy	Efficacy
Clinical trial ***or*** Allogeneic SCT ***or*** Chemo: clofarabine, cytarabine, and alkylator containing regimens; augmented hyper-CVAD; vincristine **Ph-positive:** TKI (dasatinib, nilotinib, ponatinib) + chemo	***Adults:*** CR ~20%-30% 5-year survival 7%-10% ***Pediatric:*** CR ~30% 5-year survival ~20%

Source: Cowen and Company, NCCN Guidelines

Participation in a clinical trial is preferred for treatment of relapsed/refractory ALL. In patients with longer duration of initial response (relapse ≥ 36 months from initial diagnosis), re-treatment with the same induction regimen may be considered. Second-line therapy options include induction regimens which have not been previously used, as well as salvage chemotherapy with regimens containing clofarabine, cytarabine, or alkylating agents. Allogeneic SCT may also be an option in patients who are relatively fit, if a donor is available.

In Ph-positive ALL patients with relapsed/refractory disease, second-line therapy with an alternative TKI alone or TKI with multi-agent chemotherapy may be options. Alternative options include dasatinib, nilotinib, and ponatinib for patients who have received imatinib previously. Allogeneic SCT is also a consideration in appropriate patients with an available donor.

ALL Treatment Summary

Induction Therapy	Consolidation Therapy	Maintenance Therapy	Salvage Therapy
Adults: Multi-agent chemo: daunorubicin, vincristine, pegaspargase, prednisone, ± cyclophosphamide **≥ 65 yrs:** multi-agent chemo or corticosteroids **Pediatric:** ± anthracycline **Ph-positive:** +TKI (imatinib or dasatinib)	Continue multi-agent chemo ***or*** Consider allogeneic SCT **≥ 65 yrs:** chemo **Ph-positive:** TKI + chemo	Daily 6-mercaptopurine + Weekly methotrexate + Monthly vincristine and prednisone pulses for 2-3 years **Ph-positive:** +TKI	Clinical trial ***or*** Allogeneic SCT ***or*** Chemo: clofarabine, cytarabine, and alkylator containing regimens; augmented hyper-CVAD; vincristine **Ph-positive:** TKI (dasatinib, nilotinib, ponatinib) ± chemo

Source: Cowen and Company, NCCN Guidelines

MLL-rearranged (MLL-r) Leukemia

MLL-rearranged (MLL-r) leukemia is an aggressive subtype of acute leukemia (ALL and AML) which occurs frequently in the pediatric population, and is associated with a poor prognosis and early relapse. MLL-r leukemia also has a second peak incidence in older patients, especially those with "*therapy-related leukemia*" after previous treatment for unrelated cancers with agents such as topoisomerase inhibitors, e.g. etoposide. The *mixed lineage leukemia* (MLL) gene, normally located at chromosome 11q23, can be rearranged from chromosomal translocations occurring in acute leukemias. Abnormalities of 11q23 are found in up to 70% of infant ALL/AML and approximately 10% of all other ALL cases. Also, 11q23 translocations are observed in about 10% of therapy-related leukemia cases, which are usually AML, as well as 3% of de novo AML. *In total, approximately 10% of acute leukemias are associated with MLL gene rearrangement, which is a negative prognostic factor*.

The MLL protein, encoded by the MLL gene, is involved in regulation of chromatin. The MLL protein is a histone methyltransferase that binds DNA and methylates histone H3 at lysine 4 (H3K4), positively controlling the transcription of many genes, including the HOX (homeobox) genes (*HOXA1, A3, A7, A9, A10, A11*). Chromosomal translocations which rearrange the MLL

gene create MLL fusion proteins, which have loss of normal MLL function but retain the MLL targets. The most frequent MLL rearrangements, underlying 80% of all MLL-r leukemias, include: t(4;11), partnered with *AF4*; t(9;11), partnered with *AF9*; t(11;19), partnered with *ENL*; t(10;11), partnered with AF10; and t(6;11), partnered with *AF6*. The t(4;11) translocation occurs most often in ALL, while the t(9;11) translocation is frequent in AML.

Common MLL rearrangements

MLL rearrangement	Fusion partner	Comment
t(4;11)	***AF4***	***Most frequent in ALL***
t(9;11)	***AF9***	***Most frequent in AML***
t(11;19)	ENL	-
t(10;11	AF10	-
t(6;11)	AF6	-

Source: Cowen and Company, NCCN Guidelines

At least 64 MLL fusion proteins have been identified in a molecular study of 760 pediatric and adult MLL-r leukemia patients. *The most frequent MLL fusion proteins in MLL-r leukemias appear to directly or indirectly bind DOT1L, as well as coordinate DOT1L activity with positive transcription factors*.

MLL-r leukemia has characteristic gene expression patterns, most notably high level of *HOX* expression. HOX proteins, especially HOXA9 and its co-factor MEIS1, are oncoproteins which are overexpressed in leukemias. *HOX* genes are involved in differentiation of normal hematopoietic cells. *HOX* gene expression is high in stem cells and early precursor cells, and then downregulated as cells mature. In malignant hematopoiesis, aberrant *HOX* gene over-expression blocks differentiation and creates an expanded pool of early precursor cells which rapidly proliferate. H3K79 methylation by DOT1L correlates with abnormal gene expression in MLL-r leukemia.

MLL-r Treatment: *There is currently no specific therapy for MLL-r leukemia*. In general, treatment strategies for high risk ALL and AML are followed, consisting of multi-agent chemotherapy for induction and consolidation. Adult patients with MLL-r ALL and AML usually proceed to allogeneic SCT as soon as possible upon remission after induction therapy. Allogeneic SCT is the only potentially curative treatment, and is associated with approximately 30-40% survival. MLL-r patients have a high relapse rate. Relapsed patients may be treated with subsequent chemotherapy regimens or considered for primary or repeat transplant. In the pediatric population, allogeneic SCT has not been associated with improved prognosis and does not appear to provide significant clinical benefit.

Non-Hodgkin Lymphoma: Brief Overview

Lymphomas are solid tumors of the immune system. Hodgkin's lymphomas comprise approximately 10% of all lymphomas, and the remaining 90% are classified as non-Hodgkin lymphoma (NHL). NHL represents the 7th leading site of new cancer cases in adults, accounting for 4% of new cancer cases and 3% of cancer deaths. The majority of patients are older than 60 years in age. In the U.S., the American Cancer Society has estimated that in 2012, there were approximately 70,000 new NHL cases and 19,000 deaths. The incidence of NHL has been noted to be increasing in many regions worldwide.

A heterogeneous group of lymphoproliferative malignancies comprise NHL. B-cell lymphomas represent approximately 80-85% of the NHL subtypes, and T-cell lymphomas comprise 15-20%. Disease usually develops in lymph nodes, but almost any tissue may be affected. Any organ can be a primary NHL site. These diverse malignancies vary from indolent to aggressive diseases, which require different therapeutic approaches.

NHL Subtypes

Non-Hodgkin Lymphoma Subtypes
B-Cell Lymphomas (85%)
Diffuse large B-cell lymphoma (33%)
Follicular lymphoma (20%)
Chronic lymphocytic leukemia/small lymphocytic lymphoma (5-10%)
Mantle cell lymphoma (5%)
Marginal zone B-cell lymphomas (Extranodal/MALT, Nodal, Splenic) (5-10%)
Burkitt lymphoma (1-2%)
Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia) (1-2%)
Hairy cell leukemia (rare)
Primary (CNS) lymphoma (rare)
T-cell Lymphomas (15%)
Precursor T-lymphoblastic lymphoma/leukemia (1%)
Peripheral T-cell lymphomas
Cutaneous T-cell lymphoma (Sezary syndrome, mycosis fungoides) (5%)
Angioimmunoblastic T-cell lymphoma (3%)
Anaplastic large cell lymphoma (2%)
Extranodal natural killer/T-cell lymphoma, nasal type (rare)
Enteropathy type T-cell lymphoma
Peripheral T-cell lymphoma, unspecified

Source: Cowen and Company, www.cancer.org

NHL diagnosis: The clinical presentation of NHL depends on site of involvement, natural history of the subtype, and presence of B symptoms (weight loss > 10%, night sweats, elevated body temperature). Disease assessment above and below the diaphragm is accomplished with CT scan evaluation. PET (positron emission tomography) scan evaluation with 2-[18F]fluoro-2-deoxy-D-glucose (FDG) is also increasingly used, especially to measure

therapy response. Different NHL subtypes have variable avidity for FDG. NHL is staged according to the Ann Arbor classification system, summarized in the next table.

Ann Arbor Staging System for NHL

Stage	Definition
I	Involvement of one lymph node (LN) or one extranodal organ or site
II	Involvement of ≥ 2 LN regions on the same side of the diaphragm, or localized involvement of an extranodal site or organ and ≥ 1 LN regions on the same side of the diaphragm
III	Involvement of LN regions on both sides of the diaphragm, which might be accompanied by localized involvement of an extranodal organ or site, or spleen, or both; spleen is regarded as nodal
IV	Diffuse or disseminated involvement of ≥ 1 distant extranodal organs with or without associated LN involvement
Modifiers	**Definition**
A	Absence of B symptoms
B	Temperature > 38 degrees C, night sweats, and weight loss > 10% of body weight in the preceding 6 months

Source: Cowen and Company, NCCN Guidelines

Prognostic and Risk Factors: Patient prognosis is assessed by the International Prognostic Index (IPI), the most widely used prognostic model for NHL patients. The prognostic factors considered are: 1) age > 60 years, 2) serum LDH > 1 x normal, 3) performance status 2-4, 4) clinical stage III or IV, and 5) extranodal involvement of more than 1 site. Depending on the number of factors, patients are stratified by risk and classified as Low (0-1 factors), Low-intermediate (2), High-intermediate (3), or High (4-5). Survival varies by risk group.

Survival Rates by IPI Risk Group

Risk Group	Distribution (%)	5-year OS Rate (%)
Low	35	73
Low-intermediate	27	51
High-intermediate	22	43
High	16	26

Source: Cowen and Company, NCCN Guidelines

Response Assessment: Historically, the International Working Group (IWG) criteria were used as guidelines for assessment of response and outcomes in NHL. In 2007, updated criteria were published by the German Competence Network Malignant Lymphoma International Harmonization Project. In particular, these criteria accounted for the increasing use of PET scans using FDG as an imaging tool for staging and response assessment in lymphomas.

PET scan and FDG: PET (positron emission tomography) is a type of nuclear medicine examination in which a small dose of a radioactive chemical, called a radiotracer, is attached to a biologically active molecule and injected into the bloodstream and through imaging, used to measure functional activity in the body, such as blood flow, oxygen use, and glucose

metabolism. When FDG, (2-[18F]fluoro-2-deoxy-D-glucose), an analogue of glucose, is the biologically active molecule used for the PET scan, the radiotracer concentrations will show metabolic activity through glucose uptake. "*FDG-avidity*" refers to the degree of FDG uptake. Generally, FDG has high uptake in malignant tissue and low uptake in benign tissue. Compared with CT and MRI, PET may make be a more accurate tool for response assessment.

Different NHL subtypes have variable avidity for FDG, and some types of lymphoma tend to be fairly FDG-avid, such as DLBCL, FL, mantle cell lymphoma (MCL), and Hodgkin's lymphoma. A positive PET scan is defined as focal or diffuse uptake of FDG above background in a location which is not consistent with normal anatomy or physiology (normal function).

Complete Remission (CR) in NHL: The definition of CR in NHL requires the following: **1)** complete disappearance of all clinical evidence of disease and disease-related symptoms; **2)** for FDG-avid lymphomas (with either no previous or a positive pre-treatment PET), a post-treatment PET-negative residual mass of any size, or **3)** for lymphomas with variable or unknown FDG-avidity (with either no previous or a negative pre-treatment PET), decrease of all lymph nodes and nodal masses back to normal size on CT scan *(≤ 1.5 cm diameter if > 1.5 cm before treatment, or ≤ 1 cm diameter if 1.1-1.5 cm before treatment)*; **4)** spleen and liver, if enlarged before treatment, no longer palpable on exam and normal in size on imaging; and **5)** clearance of bone marrow involvement.

Partial Remission (PR) in NHL: The definition of PR in NHL requires the following: **1)** at least a 50% reduction in the sum of the product of the diameters (SPD) of up to 6 of the largest lymph nodes or nodal masses; **2)** no increase in size of other lymph nodes, liver, or spleen; **3)** nodules in the spleen and liver must decrease by ≥ 50% in SPD or greatest transverse diameter for a single mass; **4)** no measurable disease in other organs; **5)** no new sites of disease; **6)** for FDG-avid lymphomas (with either no previous or a positive pre-treatment PET), a post-treatment PET which is positive in at least one previously involved site, or **7)** for lymphomas with variable or unknown FDG-avidity (with either no previous or a negative pre-treatment PET), decrease of all lymph nodes and nodal masses back to normal size on CT scan *(≤ 1.5 cm diameter if > 1.5 cm before treatment, or ≤ 1 cm diameter if 1.1-1.5 cm before treatment)*.

Stable Disease (SD) in NHL: The definition of SD in NHL requires the following: **1)** failure to meet the criteria for CR or PR, as well as for progressive disease; **2)** for FDG-avid lymphomas (with either no previous or a positive pre-treatment PET), a post-treatment PET which is positive in previously involved areas, with no new sites, or **3)** for lymphomas with variable or unknown FDG-avidity (with either no previous or a negative pre-treatment PET), no change in size of previous masses.

Relapsed Disease and Progressive Disease (PD) in NHL: Relapsed (after CR) or progressive disease (after PR, SD) in NHL is defined by the following: **1)** a new mass > 1.5 cm in any axis during or after treatment; **2)** at least a 50% increase in the SPD of any previously involved lymph nodes or masses; **3)** at least a 50% increase in the longest diameter of any

single, previously identified lymph node > 1 cm; **4)** for FDG-avid lymphomas, or a previously positive mass on pre-treatment PET, the mass should be PET-positive, and **5)** new or recurrent bone marrow involvement. Lymph nodes are considered abnormal if the long axis is > 1.5 cm. A lymph node which is 1.1 to 1.5 cm in long axis is considered abnormal if > 1 cm in its short axis. Lymph nodes which are ≤ 1 cm x ≤ 1 cm are not considered abnormal.

Response Definitions in NHL

Response	Definition	Nodal Masses	Spleen and Liver	Bone Marrow
CR	Disappearance of all evidence of disease	• Any size PET-negative mass (in case of FDG-avid lymphoma, with no or positive pre-treatment PET) • Regression to normal size on CT (in case of FDG-variable lymphoma, with no or negative pre-treatment PET)	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; IHC negative if indeterminate on morphology
PR	Regression of measurable disease, and no new sites	• ≥ 50% decrease in SPD of up to 6 largest masses, and no increase in size of other nodes • 1 or more previously involved sites PET-positive (in case of FDG-avid lymphoma, with no or positive pre-treatment PET) • Regression on CT (in case of FDG-variable lymphoma, with no or negative pre-treatment PET)	• ≥ 50% decrease in SPD of nodules or in greatest transverse diameter for a single nodule • No increase in size of spleen or liver	Irrelevant if positive prior to treatment; specify cell type
SD	Failure to achieve CR/PR, or to meet PD criteria	• PET-positive at prior disease sites, and no new sites on CT/PET (in case of FDG-avid lymphoma, with no or positive pre-treatment PET) • No change in size of previous masses on CT (in case of FDG-variable lymphoma, with no or negative pre-treatment PET)	-	-
Relapsed Disease/ PD	Any new lesion or ≥ 50% increase in previously involved sites	• New mass > 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥ 50% increase in longest diamater of a previously identified node which was > 1 cm in short axis • PET-positive disease (in case of FDG-avid lymphoma, with no or positive pre-treatment PET)	> 50% increase in SPD of any previous masses	New or recurrent involvement

Source: Cowen and Company, NCCN Guidelines

Diffuse Large B-cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, accounting for approximately 30% of new cases. The median age at diagnosis is in the 60 years-range. Incidence increases with age, accounting for > 40% of NHL cases in elderly patients older than 75 years. Approximately 40% of patients present with systemic B symptoms, and presentation with disseminated disease is common, with frequent nodal and extra-nodal involvement.

DLBCL is characterized by significant heterogeneity. There are two broad molecular sub-groups: **G**erminal **C**enter **B**-cell-like (GCB) lymphomas and **A**ctivated **B**-**C**ell-like (ABC)

lymphomas. *ABC lymphomas are more aggressive clinically, with shorter survival compared to that for GCB.* With chemo-immunotherapy, three-year OS rates have been demonstrated to be 84% for GCB and 56% for the ABC.

The addition of rituximab to chemotherapy regimens has significantly improved survival in DLBCL. With modern therapy, approximately *2/3 of DLBCL patients can be cured.* Given that DLCBL is usually systemic at diagnosis, treatment with curative intent requires chemotherapy, regardless of stage.

First-Line Treatment: *In early stage disease, R-CHOP (3 cycles) chemo-immunotherapy with involved field radiation therapy (IFRT) or R-CHOP (6 cycles) with/without IFRT is standard first-line therapy*. The benefit of radiation for patients with early stage disease is not fully clear. In the phase III Mabthera International Trial (MInT), which compared a CHOP-like regimen with rituximab + CHOP-like chemotherapy in younger (< 60 years) DLBCL patients with good prognosis (3/4 with limited-stage disease), the 3-year OS was 93% with rituximab addition versus 84%. Personalization with regard to number of chemo-immunotherapy cycles and use of RT is recommended. Generally, bulky disease should be treated with a full 6-cycle course of R-CHOP ± consolidative RT. Non-bulky disease can be treated with a shorter 3-cycle R-CHOP course + RT.

For patients with advanced stage disease (Stage III and IV), R-CHOP-21 therapy (every 3 weeks, 6 cycles) is the standard regimen. The Groupe d'Etude Des Lymphomes De l'Adulte (GELA) LHN98-5 study was the first trial which established the benefit of rituximab addition to chemotherapy for first-line treatment of DLBCL. This trial enrolled DLBCL patients, age 60-80 years, with advanced stage disease. The 5-year OS rate with R-CHOP was 58% compared with 45% in patients treated with CHOP. Increased dose density of chemotherapy with CHOP-14 (every 2 weeks) may also be considered, but the R-CHOP-21 regimen remains the standard of care for patients with advanced stage disease.

For patients with CR after first-line therapy, observation is preferred, but consolidation with HDT (high dose chemotherapy)/ASCT (autologous stem cell transplant) may be considered in selected cases with high-risk disease. The German High Grade NHL Study Group evaluated first-line treatment in 262 younger (age ≤ 60 years) patients with aggressive disease, randomized to therapy with a R-CHOP-based regimen alone or followed by ASCT. Consolidation with ASCT did not produce any significant differences in rates of PFS (70% vs. 74% without consolidation) or OS (77% vs. 85%) at 3 years.

DLBCL First-Line Therapy

First-Line Therapy	First-Line Consolidation	Efficacy
• R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) • Dose-dense R-CHOP-14 • Dose-adjusted R-EPOCH (E=etoposide) • RCEPP (P=procarbazine) • RCDOP (D=liposomal doxorubicin) • RCNOP (N=mitoxantrone) • RCEOP	HDT/ASCT (consider in select patients)	CR ~60-70% 3-year OS (<60 years): ~90% 5-year OS (>60 years): ~60%

HDT/ASCT: High dose therapy and autologous stem cell transplant

Source: Cowen and Company, NCCN Guidelines

Second-Line Treatment, Relapsed/Refractory Disease: *Approximately 30-40% of DLBCL patients relapse after first-line chemotherapy*. The standard of care in the relapsed/refractory setting is second-line salvage chemotherapy followed by HDT/ASCT in chemo-sensitive patients. In the Phase III Parma Group trial, 109 relapsed DLBCL patients who were chemo-sensitive were randomized to second-line treatment with either combination chemotherapy (DHAP: dexamethasone, cisplatin, cytarabine) or HDT/ASCT. With transplantation, the ORR was 84% compared to 44% with chemotherapy alone. Five-year OS was significantly improved with transplantation (53%) compared to the rate without transplantation (32%, p=0.038).

Multiple second-line chemotherapy regimens may be used in this setting prior to HDT/ASCT, and no data have demonstrated superiority of any one. Thus, there is no preferred regimen at this time. These regimens may be administered with or without rituximab, with generally better outcomes in rituximab-naïve patients.

For patients who are not candidates for HDT/ASCT, enrollment in a clinical trial is recommended. Otherwise, treatment with single agent rituximab may be considered. Options also include other single agents with or without rituximab, such as bendamustine or lenalidomide (in non-GCB patients). A variety of multi-agent chemotherapy regimens can also be considered, with or without rituximab.

DLBCL Second-Line Therapy

Second-Line Therapy (candidates for HDT/ASCT)	Second-Line Therapy (not candidates for HDT/ASCT)	Efficacy
• DHAP (dexamethasone, cisplatin, cytarabine) ± R • ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± R • GDP (gemcitabine, dexamethasone, cisplatin) ± R • GemOx (gemcitabine, oxaliplatin) ± • ICE (isofosfamide, carboplatin, etoposide) ± R • MINE (M=mesna) ± R • Rituximab	• Clinical trial • Bendamustine ± R • CEPP ± R • DA-EPOCH ± R • CEOP ± R • GDP ± R • GemOx ± R • Lenalidomide ± R • Rituximab	CR ~50% 5-year OS (with ASCT): ~50% 5-year OS (without ASCT): ~30%

HDT/ASCT: High dose therapy and autologous stem cell transplant

Source: Cowen and Company, NCCN Guidelines

DLBCL Treatment Summary

First-Line Therapy	First-Line Consolidation	Second-Line Therapy (candidates for HDT/ASCT)	Second-Line Therapy (not candidates for HDT/ASCT)
• R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) • Dose-dense R-CHOP-14 • Dose-adjusted R-EPOCH (E=etoposide) • RCEPP (P=procarbazine) • RCDOP (D=liposomal doxorubicin) • RCNOP (N=mitoxantrone) • RCEOP	HDT/ASCT (consider in select patients)	• DHAP (dexamethasone, cisplatin, cytarabine) ± R • ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± R • GDP (gemcitabine, dexamethasone, cisplatin) ± R • GemOx (gemcitabine, oxaliplatin) ± • ICE (isofosfamide, carboplatin, etoposide) ± R • MINE (M=mesna) ± R • Rituximab	• Clinical trial • Bendamustine ± R • CEPP ± R • DA-EPOCH ± R • CEOP ± R • GDP ± R • GemOx ± R • Lenalidomide ± R • Rituximab

HDT/ASCT: High dose therapy and autologous stem cell transplant

Source: Cowen and Company, NCCN Guidelines

Follicular Lymphoma (FL)

Follicular lymphoma (FL) is the second most common type of lymphoma, representing approximately 20% of NHL cases. The median age at diagnosis is 60 years, and the clinical course is typically relapsing and remitting. FL is the most common indolent form of NHL. Some patients may not require treatment for years. Other patients may have significant organ or nodal involvement requiring intervention. Histologic transformation to a diffuse, aggressive lymphoma can occur, which is associated with a poor prognosis. *FL is usually not curable with conventional treatment.*

FL prognosis: Prognosis is determined through the Follicular Lymphoma International Prognostic Index (FLIPI), based on age ≥ 60 years, clinical stage III or IV, ≥ 5 involved nodal sites, hemoglobin level < 12 g/dl, and serum LDH level > upper limit of normal. Patients are

stratified into three risk groups, according to the number of risk factors: low (0-1), intermediate (2), and high (≥ 3).

Survival by FLIPI Risk Group

Risk	Distribution (%)	5-year OS (%)	10-year OS (%)
Low	36	90.6	70.7
Intermediate	37	77.6	50.9
High	27	52.5	35.5

Source: Cowen and Company

First-Line Treatment: In early stage disease (Ann Arbor stage I/II), involved-field radiation therapy (IFRT) is the preferred treatment. RT is potentially curative, although disease may recur in areas outside of the radiation fields. Because of potential toxicity associated with RT in particular areas, observation ("watchful waiting") may also be an acceptable approach.

For advanced stage disease, *initiation of treatment in FL* is guided by the Groupe d'Etudes des Lymphomes Folliculaires **(GELF) criteria**, which include: **1)** symptomatic disease, not limited to B-symptoms; **2)** threatened end-organ function, **3)** cytopenia resulting from lymphoma; **4)** bulky disease, single mass > 7 cm, or three or more masses, each > 3 cm, **5)** splenomegaly, and **6)** steady progression over at least 6 months.

In patients requiring systemic therapy, chemoimmunotherapy with rituximab is the standard of care. In a Phase III study conducted by the German Low-Grade Lymphoma Study Group, 428 previously untreated FL patients were randomized to treatment with R-CHOP or CHOP. The ORR with R-CHOP was 96%, compared with 90% (p=0.011), and the estimated 2-year OS rate was higher with R-CHOP, 95% vs. 90% (p=0.016). Different chemotherapy base regimens, such as CVP (cyclophosphamide, vincristine, prednisone), fludarabine combinations, and bendamustine, can be used. The superiority of any one particular chemoimmunotherapy regimen has not been demonstrated.

Most patients have disease recurrence within 3 to 5 years. Following complete or partial response to first-line therapy, patients can be observed or treated with consolidation therapy.

First-Line Consolidation: *Rituximab therapy extending to 2 years is recommended for patients responding to first-line chemoimmunotherapy*. The addition of 2 years of rituximab maintenance therapy, compared to observation, in 1,018 FL patients responsive to first-line R-CVP, R-CHOP, or R-FCM was evaluated in the Phase III PRIMA study. At a median follow up of 36 months, the 3-year PFS rate of 75% with maintenance therapy was significantly better than the rate of 58% without maintenance (p=0.0001).

Tositumomab and ibritumomab tiutexan are radiolabeled anti-CD20 antibodies. Radioimmunotherapy (RIT) has been investigated as consolidation therapy, but its role following first-line FL therapy has not been well established. RIT may be considered for patients responding to first-line chemotherapy. In the Phase III FIT (First-line Indolent Trial)

study, 414 FL patients who responded to first-line treatment were randomized to a single course of ibritumomab tiutexan or observation. Patients receiving consolidation had an ORR of 87% and median PFS of 49 months versus 14 months in the observation arm.

FL First-Line Therapy

First-Line Therapy	First-Line Consolidation
• R-CHOP • R-CVP (rituximab, cyclophophamide, vincristine, prednisone) • BR • FR • RFND (rituximab, fludarabine, mitoxantrone, dexamethasone) • Radioimmunotherapy • Rituximab	• Radioimmunotherapy (after chemotherapy) • Rituximab up to 2 years (after chemo-immunotherapy)

HDT/ASCT: High dose therapy and autologous stem cell transplant

Source: Cowen and Company, NCCN Guidelines

Second-Line Treatment, Relapsed/Refractory Disease: As in first-line treatment, initiation of second-line treatment is guided by the GELF criteria. Therapeutic options for second-line treatment include chemoimmunotherapy regimens used in first-line therapy, fludarabine-based regimens combined with rituximab, RIT, or any second-line DLBCL agents.

Second-Line Consolidation: In patients responsive to second-line therapy, further consolidative therapy with rituximab has clinical benefit. In the phase III EORTC 20981 study, rituximab maintenance treatment in 334 relapsed/refractory FL patients responding to CHOP or R-CHOP was associated with a longer median PFS compared to observation alone, 3.7 years vs. 1.3 years ($p<0.001$).

Additionally, HDT/ASCT may also be beneficial for consolidation after second or third remission. In a retrospective analysis conducted by the Groupe d'Etude des Lymphomes de l'Adulte (GELA), rituximab-based second-line treatment followed by HDT/ASCT was associated with a 5-year OS rate of 90% after relapse. Allogeneic SCT may also be considered for consolidation therapy in select patients.

FL Second-Line Therapy

Second-Line Therapy	Second-Line Consolidation
• Chemoimmunotherapy • FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) • Radioimmunotherapy • Second-line DLBCL agents	• Rituximab maintenance • HDT/ASCT • Allogeneic SCT in select patients

HDT/ASCT: High dose therapy and autologous stem cell transplant

Source: Cowen and Company, NCCN Guidelines

FL Transformation to DLBCL: Patients with FL have a risk of transformation to DLBCL. This occurs with a 3% rate annually for 15 years, but then the risk of transformation declines for unknown reasons. DLBCL transformation generally results in poor outcomes, with median OS < 2 years. Treatment options include RIT, chemotherapy with or without rituximab, IFRT, or best supportive care.

FL Treatment Summary

First-Line Therapy	First-Line Consolidation	Second-Line Therapy	Second-Line Consolidation
• R-CHOP • R-CVP (rituximab, cyclophophamide, vincristine, prednisone) • BR • FR • RFND (rituximab, fludarabine, mitoxantrone, dexamethasone) • Radioimmunotherapy • Rituximab	• Radioimmunotherapy (after chemotherapy) • Rituximab up to 2 years (after chemo-immunotherapy)	• Chemoimmunotherapy • FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) • Radioimmunotherapy • Second-line DLBCL agents	• Rituximab maintenance • HDT/ASCT • Allogeneic SCT in select patients

HDT/ASCT: High dose therapy and autologous stem cell transplant

Source: Cowen and Company, NCCN Guidelines

Epizyme's Intellectual Property Estate

Epizyme has built and is continuing to build an IP portfolio around its product candidates targeting human methyltransferases (HMTs), including DOT1L and EZH2. The company has 3 issued and 4 pending U.S. patents and patent applications. Epizyme also has 21 issued and 5 pending related PCT applications and international patents and patent applications. Epizyme has filed a patent application covering the composition of matter of EPZ-5676, which, if issued, will expire in 2031. The company also has an issued patent (U.S. Patent # 8,410,088) covering the composition of matter of EPZ-6438 which expires in 2032.

DOT1L: For the DOT1L patent portfolio, Epizyme has one pending U.S. patent application covering the composition of or methods of making or using EPZ-5676, which, if issued, will expire in 2031. A related patent application has been filed with several countries. Any patents resulting from these patent applications, if issued, will expire in 2031.

EZH2: For the EZH2 patent portfolio, Epizyme holds U.S. Patent # 8,410,088, titled "*Aryl- or heteroaryl-substituted benzene compounds*". As stated in the patent abstract "*The present invention relates to aryl- or heteroaryl-substituted benzene compounds. The present invention also relates to pharmaceutical compositions containing these compounds and methods of treating cancer by administering these compounds and pharmaceutical compositions to subjects in need thereof. The present invention also relates to the use of such compounds for research or other non-therapeutic purposes*." This patent covers the composition of matter claims for EPZ-6438 and related compounds and expires in 2032. The company also has three pending patent applications, which, if issued, will expire in the 2031-2032 window.

Valuation Methodology & Investment Risks

Valuation Methodology

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Company Specific Risks

Risks to our Outperform rating on EPZM shares include: 1) clinical setbacks in the ongoing trials of EPZ-5676 and EPZ-6438, 2) the possibility of additional financings, and 3) a change in appetite for early-company risk among biotech investors.

Addendum

STOCKS MENTIONED IN IMPORTANT DISCLOSURES

Ticker	Company Name
EPZM	Epizyme Inc

Analyst Certification

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Cowen and Company Rating System effective May 25, 2013

Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013

Buy – The fundamentals/valuations of the subject company are improving and the investment return is expected to be 5 to 15 percentage points higher than the general market return

Sell – The fundamentals/valuations of the subject company are deteriorating and the investment return is expected to be 5 to 15 percentage points lower than the general market return

Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

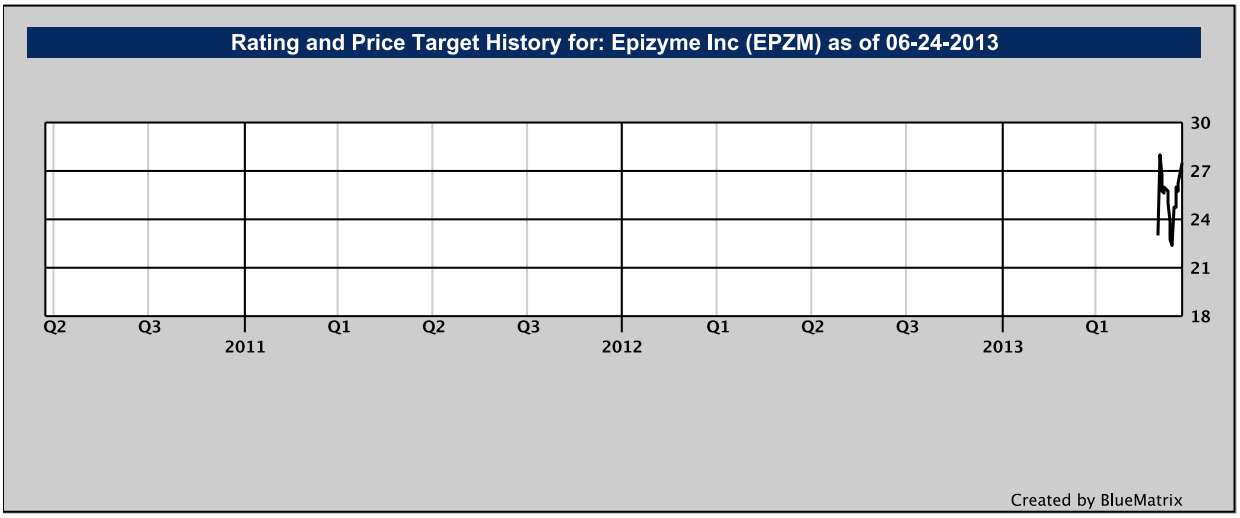
COWEN AND COMPANY RATING ALLOCATION

Distribution of Ratings/Investment Banking Services (IB) as of 05/27/13

Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	380	55.96%	51	13.42%
Hold (b)	276	40.64%	2	0.72%
Sell (c)	23	3.38%	1	4.34%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

Note: "Buy", "Hold" and "Sell" are not terms that Cowen and Company, LLC uses in its ratings system and should not be construed as investment options. Rather, these ratings terms are used illustratively to comply with FINRA and NYSE regulations.



Legend for Price Chart:

I = Initation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | T = Terminated Coverage | $xx = Price Target | NA = Not Available