FLASH NOTE
Biotechnology
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Simos Simeonidis, Ph.D.
simos.simeonidis@cowen.com 646.562.1386

Yatin Suneja
yatin.suneja@cowen.com 646.562.1388

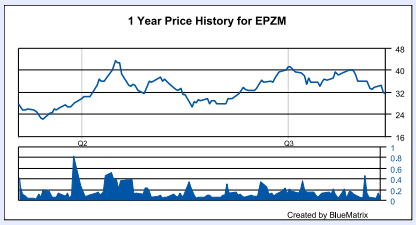
Raymond Chang, M.D.
raymond.chang@cowen.com 646.562.1337

**Recommendation**

| | |
|---|---|
| Rating: | Outperform |
| Price Target: | NA |

**Stock Statistics as of 11/13/2013**

| | |
|---|---|
| Price: | $31.71 |
| 52W Range: | $45.72-$15.00 |
| Shares Out (MM): | 33.4 |
| Market Cap (MM): | $901.2 |
| Net Debt (MM): | $(98.0) |
| Net Cash Per Share: | $4.18 |




# EPIZYME INC (NASDAQ:EPZM)

# EPZ5676 data panic investors; we think it's too early for this type of reaction

**The news:** Epizyme announced initial results from the ongoing Phase I dose-escalation study of DOT1L inhibitor EPZ-5676. Four dose cohorts (12, 24, 36 and 54 mg/m$^2$/day on a 21-day on/7-day off administration schedule) have been completed with 16 heavily pre-treated patients, 8 of whom had acute leukemia with MLL-r. The fifth dose cohort (80 mg/m$^2$) is currently enrolling. There have been no DLTs observed, and the MTD has not been reached. Early evidence of treatment effects have been observed in 4 out of the 8 acute leukemia MLL-r patients, who were in the 2$^{nd}$ (24 mg/m$^2$, n=1), 3$^{rd}$ (36 mg/m$^2$, n=2), and 4$^{th}$ (54 mg/m$^2$, n=1) dose cohorts. These effects included reduction in circulating blast (2$^{nd}$ cohort), reduction in marrow blasts (4$^{th}$ dose cohort), maturation in blood and marrow (3$^{rd}$ and 4$^{th}$ cohorts), as well as symptomatic improvements, such as resolution of fevers and cachexia. Treatment effects appear to be selective, as no effects were observed in non-MLL-r patients.

**Our take on the news:** Overall, we believe these data are too early to draw strong conclusions from, one way or another, since **1)** it appears that we are probably still in the dose and schedule finding portion of its development, and **2)** we're still dealing with very small numbers of patients.

**The positives from the data:** We view the fact that 4/8 "target" patients responded, as positive. So far, we only had data from a single "target" (MLL-r) patient and they were a responder; moving to a larger, albeit *still very small* sample of patients, it is not at all surprising that the response in MLL-r patients moved to 50% (4/8 patients). We also view as positive the fact that there was methyl mark inhibition during the 21-day administration of the drug, and that there was a rebound during the 7-day holiday: this means that the drug works molecularly the way it is supposed to work, i.e. it's hitting its target. Safety doesn't appear to be an issue, the MTD has not yet been reached, and we view the fact that the company believes, based on what they've seen, that it can dose escalate further and also move to a continuous dose schedule as a positive.

**The question marks:** On the other hand, we don't have a good answer as to why the other four of out the eight MLL-r patients didn't respond. Also, the fact that 7 out of the 8 MLL-r patients progressed during the first few cycles could be due to a number of reasons, including that these patients may be too advanced in their disease to be helped by this treatment, it could be that a higher dose is needed, or that a continuous dose schedule that will continuously inhibit the target is necessary, for at least more cycles, in order to get to a sustained response.

**Throwing the baby out with the bathwater?** EPZM is down 40% intraday based on these data. Reasonable investors can disagree about whether EPZM was appropriately valued *before* these data were released; however, we believe that given *these data*, a 40% reduction

Please see addendum of this report for important disclosures.

in its value isn't warranted, since we view these data as still preliminary and as providing incremental information, some of which is positive, and some of which raises some questions that we cannot answer. However, we believe that it is too early draw this much of a negative conclusion on this drug, and the stock, given that 1) its proposed molecular MOA appears intact, and is in fact confirmed by these data, and 2) that there appears to be room for dose escalation and continuous dosing, especially given its safety. We will await further data, especially the data from the 80mg/m2 continuous dosing schedule expansion arm that will start in December.

**Next steps for EPZM-5676:** In December, Epizyme plans to initiate the expansion stage of the Phase I trial, including only MLL-r patients, at an 80 mg/m2/day dose on an uninterrupted schedule (no drug holiday), with continued dose escalation possible. This expansion stage is expected to assess the clinical efficacy of EPZ-5676 in MLL-r patients with drug administration in an optimal manner. In early 2014, Epizyme plans to initiate a Phase I study in pediatric MLL-r (similar in design, with dose-escalation and expansion stage) as well as a trial in MLL-PTD patients.

**What's next for EPZM?** 1) Initiation of the expansion portion (MLL-r patients only) of the Phase I trial of EPZ-5676, December 2013; 2) Initiation of Phase I trial of EPZ-5676 in pediatric MLL-r patients, early 2014; 3) Initiation of clinical study of EPZ-5676 in MLL-PTD subset of AML, early 2014; 4) Completion of Phase I dose-escalation study of EPZ-6438 and initiation of the Phase II portion (EZH2-mutated patients only) of the Phase I/II trial, 2014; and 5) Initiation of proof-of-concept trials of EPZ-6438 in INI1-deficient tumors, including synovial sarcoma, 2014.

**Patient Demographics:** The median age of the enrolled patients was 55 years (range, 22-81 years). Fifteen of the 16 patients had a diagnosis of acute leukemia, with the majority (n=13) having AML and the remaining with ALL (n=2). There was one patient with chronic myelomonocytic leukemia (CMML). Of the acute leukemia patients, 8 had MLL-rearrangement. Patients were heavily pre-treated, with a median of 4 prior therapies (range, 1-8). There were 6 patients who had relapsed after prior allogeneic stem cell transplant.

**Phase I dose-escalation trial of EPZ-5676: Patient Demographics**

| | |
|---|---|
| Age Median (range) | 55 (22-81) |
| Gender | Male: 11<br>Female: 5 |
| Diagnosis | AML: 13 (7 MLL-r)<br>ALL: 1 (MLL-r)<br>ALL (Ph +): 1<br>CMML: 1 (MLL-r) * |
| # Prior Therapies Median (range) | 4 (1-8) |
| Prior Allogeneic SCT | Yes: 6<br>No: 10 |

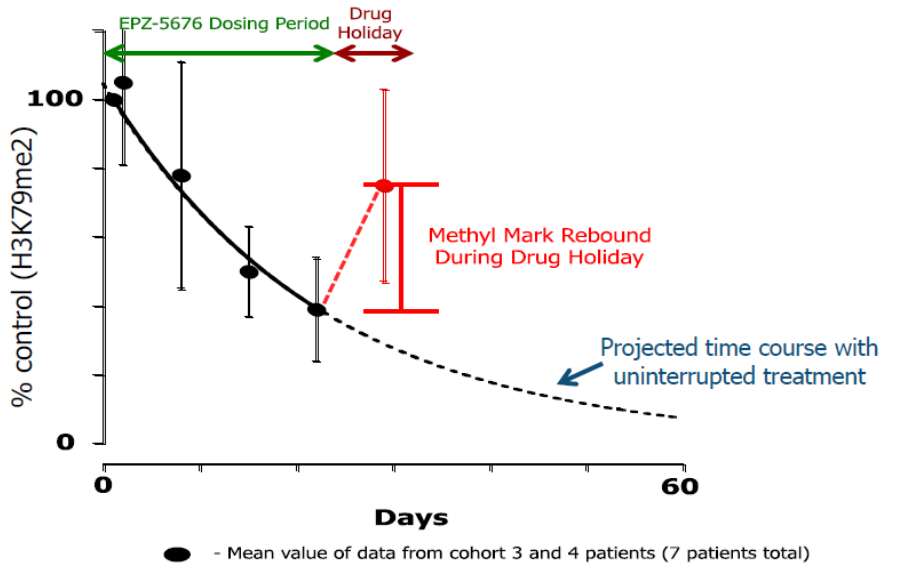
*CMML patient in transformation with MLL-r translocation

Source: Cowen and Company, Epizyme Presentation

**Safety Data:** There have been no DLTs observed, and the MTD has not been reached. There is no evidence of a dose-toxicity relationship to date. No AEs have required dose interruption or dose reduction. One AE-related discontinuation (patient with intracranial bleeding in the setting of thrombocytopenia) was not considered drug-related. There has been one Grade 3 AE, neutropenia occurring in a patient in the fourth dose cohort, who continues on treatment, considered to possibly be drug-related and not treatment-limiting.

**PK and PD Data:** PK data demonstrated dose-proportional exposure. In terms of PD effects, methyl mark inhibition was noted to be both dose- and time-dependent. Epizyme indicated that at doses ≥ 36 mg/m$^2$, the target methyl mark is inhibited. All patients who had treatment effects were noted to have had methyl mark inhibition. The methyl mark was noted to continue declining throughout the 21-day treatment period and rebounded, approaching baseline, after the 7-day drug holiday. Management guided that these results suggest a continuous treatment regimen over multiple cycles may be necessary.

**Phase I dose-escalation trial of EPZ-5676: Pharmacodynamic Summary**




Source: Epizyme Presentation

**Efficacy Data:** All patients with treatment effects manifested these effects within the first treatment cycle, and all these patients were noted to have had methyl mark inhibition. Treatment effects were noted in the 2nd (n=1), 3rd (n=2), and 4th (n=1) dose cohorts. These included reduction of circulating blasts and resolution of fevers (cohort 2 patient), maturation in blood and bone marrow with resolution of cachexia and leukemia cutis (two cohort 3 patients), and reduction in marrow blasts as well as marrow maturation (cohort 4 patient). The longest treatment course to date has been 4 cycles. The patient in the 4th cohort with treatment effects continues on study.

**Phase I dose-escalation trial of EPZ-5676: Treatment Effects**

| Dose Cohort | Diagnosis | Treatment Effects | Cycles Completed |
|---|---|---|---|
| n=2 (24 mg/m$^2$) | ALL | 90% circulating blast reduction (no bone marrow aspirate available); Resolution of fevers | Cycle 1+ |
| | AML | None observed | Cycle 1+ |
| n=3 (36 mg/m$^2$) | AML | Maturation in blood and marrow (no change % marrow blasts); Leukocytosis; Resolution of cachexia | Cycle 3+ |
| | AML | Maturation in blood (no change % marrow blasts) Leukocytosis; Resolution of leukemia cutis | Cycle 2+ |
| | AML | None observed | Cycle 1+ |
| n=4 (54 mg/m$^2$) | AML | None observed | Cycle 2+ |
| | AML | Maturation in marrow % marrow blast decrease (20% to 2%) | On study (2nd cycle) |
| | AML | None observed | Cycle 1+ |
| | CMML | Too early to evaluate | On study (2nd cycle) |

+Discontinuation due to disease progression

Source: Cowen and Company, Epizyme Presentation

# Valuation Methodology & Investment Risks

## Valuation Methodology

**Biotechnology:**

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

**Biotechnology:**

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

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| Ticker | Company Name |
|---|---|
| EPZM | Epizyme Inc |

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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 09/30/13

| Rating | Count | Ratings Distribution | Count | IB Services/Past 12 Months |
|---|---|---|---|---|
| Buy (a) | 394 | 58.72% | 54 | 13.71% |
| Hold (b) | 255 | 38.00% | 5 | 1.96% |
| Sell (c) | 22 | 3.28% | 1 | 4.55% |

(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.

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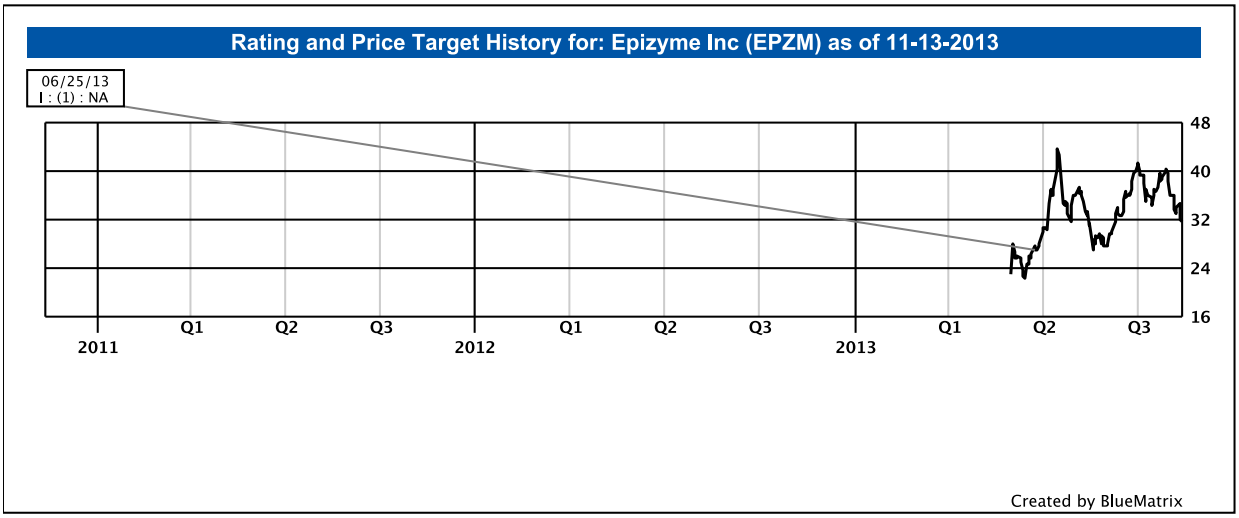


**Legend for Price Chart:**

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