Epizyme In Vivo Data Shows Promise in Personalized Therapeutics Programs for Acute Leukemia and Lymphoma

Pre-Clinical Study Results to be Presented at ASH 2012 Show Selectivity, Efficacy of DOT1L and EZH2 Inhibitors

Cambridge, Mass. – November 29, 2012 – Epizyme, Inc., a biopharmaceutical company leading the creation of personalized therapeutics to treat genetically defined cancers, today announced the presentation of data evaluating the preclinical safety and efficacy of two of the Company’s novel, potent and selective small molecule inhibitors. These inhibitors individually target DOT1L and EZH2, members of a class of enzymes called histone methyltransferases (HMTs). Genetically altered or misregulated HMTs are oncogenic and therefore important targets for drug development. Data will be presented in poster sessions at the 54th Annual Meeting of the American Society of Hematology (ASH) in Atlanta, GA from December 8 – 11, 2012.

“The data Epizyme is presenting at ASH demonstrate substantial progress in our DOT1L and EZH2 inhibitor programs,” said Robert J. Gould, Ph.D., President and CEO, Epizyme. “Building on our proprietary product platform, these findings show the efficacy and selectivity of our compounds in animal models of leukemia and lymphoma, in each case demonstrating robust antitumor activity in genetically defined preclinical models. We expect to report Phase I clinical data for our DOT1L program within 12 to 18 months, and to initiate clinical development for the EZH2 program shortly.”

Preclinical Characterization of a Potent, Selective Inhibitor of the Protein Methyltransferase DOT1L for Use in the Treatment of MLL-Rearranged Leukemia (Abstract #2379)

Poster Session: Sunday, December 9, 2012, 6:00 p.m.-8:00 p.m. ET, Hall B1-B2, Level 1, Building B, Georgia World Congress Center

Aberrant activity of the histone methyltransferase DOT1L has been shown to be the driving genetic lesion in MLL-rearranged (MLL-r) leukemia. In this abstract, preclinical results of treatment with EPZ-5676, a S-adenosyl methionine competitive DOT1L inhibitor, in a genetically defined rat model of MLL-rearranged leukemia are reported. Continuous intravenous infusion of EPZ-5676 for 21 days in this model led to dose-dependent antitumor activity, resulting in complete tumor regression with the highest dose tested. This complete tumor regression was sustained after cessation of treatment.

EPZ-5676 is highly selective for DOT1L, demonstrating greater than 37,000-fold selectivity against all other HMTs tested. Treatment of leukemia cells with EPZ-5676 resulted in concentration- and time-dependent reduction of H3K79 methylation, the target histone for aberrant DOT1L activity in MLL-r leukemia, without impacting other histone sites. The reduction of H3K79 methylation led to inhibition of key MLL target genes, and selective cell killing of MLL-r leukemia cells with no activity against non-MLL-r leukemia cells.

Epizyme initiated a Phase I study in September 2012 to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of EPZ-5676 and will provide a preliminary assessment of efficacy in an expansion cohort of patients with MLL-r leukemia. Clinical data for this trial is anticipated within 12 to 18 months. Epizyme has 100% of the US development and commercialization rights to this program, which is
partnered with Celgene ex-US.

Supplementary DOT1L Data

Two additional posters presented at ASH 2012 expand the spectrum of genetic alterations potentially treatable by DOT1L inhibitors.

- Abrogation of MLL-AF10 and CALM-AF10 Mediated Transformation Through Genetic Inactivation or Pharmacological Inhibition of the H3K79 Methyltransferase DOT1L (Abstract #2384; Poster Session: Sunday, December 9, 2012, 6:00 p.m.-8:00 p.m. ET, Hall B1-B2, Level 1, Building B, Georgia World Congress Center)
- MLL-AF6 Mediated Transformation Is Dependent On the H3K79 Methyltransferase DOT1L (Abstract #3502; Poster session: Monday, December 10, 2012, 6:00 p.m.-8:00 p.m. ET, Hall B1-B2, Level 1, Building B, Georgia World Congress Center)

Patients with MLL-AF10, CALM-AF10 or MLL-AF6 chromosomal rearrangements have a particularly poor outcome compared to patients whose leukemia cells do not contain these translocations. Findings in abstract #2384 showed that DOT1L inhibition impairs the in vitro and in vivo oncogenic activity of the MLL-AF10 and CALM-AF10 fusion oncogenes. Results in abstract #3502 demonstrated that the MLL-AF6 oncoprotein requires the activity of DOT1L for abnormal transcription of downstream target oncogenes.

Preclinical Characterization of E7438, a Potent, Selective Inhibitor of Protein Methyltransferase EZH2 with Robust Antitumor Activity Against EZH2 Mutated Non-Hodgkin Lymphoma Xenografts in Mice (Abstract #3712)

Poster Session: Monday, December 10, 2012, 6:00 p.m.-8:00 p.m. ET, Hall B1-B2, Level 1, Building B, Georgia World Congress Center

Building on previous research demonstrating that a small molecule inhibitor of EZH2 selectively kills lymphoma cells bearing EZH2 mutations with minimal effect on non-mutant lymphoma cells, Epizyme researchers developed E7438, a selective inhibitor of EZH2 with properties consistent with a viable drug candidate. The compound potently and selectively inhibits all mutants of EZH2 that have been identified in non-Hodgkin lymphoma (NHL) patient samples with 35-fold selectivity against the closely related enzyme EZH1 and greater than 4,500-fold selectivity compared to all other histone methyltransferases tested.

In the abstract, oral administration of E7438 resulted in significant antitumor activity in nude, SCID or NSG mice implanted subcutaneously with various EZH2 mutant-bearing human lymphomas. Importantly, tumor regression was shown to be sustained following discontinuation of E7438. E7438 administration was well-tolerated at doses representing high multiples of doses in which antitumor activity was demonstrated. Activity against the EZH2 target histone H3K27, demonstrated by reduction in trimethylation status of H3K27 by ELISA in samples of tumor, bone marrow, skin and peripheral blood mononuclear cells (PBMCs), indicated the potential for a non-invasive biomarker for use in human clinical trials.

Epizyme has partnered the EZH2 program with Eisai Co., Ltd., Tokyo, Japan with Epizyme retaining US profit
share and co-commercialization rights, and expects to initiate the Phase I trial for E7438 in the near future.

**About Epizyme, Inc.**

Epizyme is leading the creation of small molecule histone methyltransferase inhibitors (HMTi), a new class of personalized therapeutics for patients with genetically defined cancers. Genetic alterations in HMTs, a class of epigenetic enzymes, drive multiple human diseases. Our approach represents the future of healthcare by matching better medicines with the right patients.

Epizyme has benchmark alliances with Celgene, GSK and Eisai and receives funding and strategic support from the Multiple Myeloma Research Foundation (MMRF) and the Leukemia & Lymphoma Society (LLS). For more information, visit [www.epizyme.com](http://www.epizyme.com).

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