Epizyme, Inc.
Form 424B5
March 18, 2015
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As Filed Pursuant to Rule 424(b)(5)
Registration No. 333-196692

Prospectus Supplement

(To Prospectus Dated June 27, 2014)

6,000,000 Shares

Epizyme, Inc.

Common Stock

$20.75 Per Share

We are offering 6,000,000 shares of our common stock. Our common stock is listed on The NASDAQ Global Market under the symbol EPZM. The last reported sale price of our common stock on The NASDAQ Global Market on March 17, 2015 was $21.13 per share.

Investing in our common stock involves risks. See Risk Factors beginning on page S-19.

We are an emerging growth company under applicable Securities and Exchange Commission rules and are eligible for reduced public company disclosure requirements. See Prospectus Supplement Summary Implications of Being an Emerging Growth Company.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Per Share	Total
Public offering price	$ 20.75	$ 124,500,000
Underwriting discount(1)	$ 1.245	$ 7,470,000
Proceeds, before expenses, to Epizyme, Inc.	$ 19.505	$ 117,030,000

(1) We refer you to Underwriting beginning on page S-59 of this prospectus supplement for additional information regarding total underwriter compensation.

We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to 900,000 additional shares of our common stock. See Underwriting for more information.

The underwriters expect to deliver the shares to purchasers on or about March 23, 2015 through the book-entry facilities of The Depository Trust Company.

Joint Book-Running Managers

Leerink Partners | **Cowen and Company** *Lead Manager* | **RBC Capital Markets**

JMP Securities

Co-Managers

SunTrust Robinson Humphrey | **Mizuho Securities**

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PROSPECTUS SUPPLEMENT

PROSPECTUS

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein or therein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled Where You Can Find More Information and Incorporation of Certain Information by Reference in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless otherwise stated, all references in this prospectus supplement and the accompanying prospectus to we, us, our, Epizyme, the Company and similar designations refer, collectively, to Epizyme, Inc., a Delaware corporation, and its

consolidated subsidiary.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predic target, potential, will, would, could, should, continue, and similar expressions are intended to identify forw statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus supplement include, among other things, statements about:

- our plans to develop and commercialize novel epigenetic therapies for cancer patients;
- our ongoing and planned clinical trials, including the timing of initiation of and enrollment in the trials, the timing of availability of data from the trials and the anticipated results of the trials;
- our ability to receive research funding and achieve anticipated milestones under our collaborations;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of our products;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property portfolio;
- our expectations related to the use of proceeds for this offering; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus supplement, particularly in the Risk Factors section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements.

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under Risk Factors beginning on page S-19 of this prospectus supplement, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision.

Company Overview

We are a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize novel epigenetic therapies for cancer patients. We have built a proprietary product platform that we use to create small molecule inhibitors of a 96-member class of enzymes known as histone methyltransferases, or HMTs. HMTs are part of the system of gene regulation, referred to as epigenetics, that controls gene expression. Genetic alterations can result in changes to the activity of HMTs, making them oncogenic. These altered HMTs are referred to as oncogenes. The HMT target class has many potential oncogenes and, we believe, presents the opportunity to create, develop and commercialize multiple epigenetic therapeutics.

Our lead product candidate, EPZ-6438, is an inhibitor that targets the EZH2 HMT. We are currently conducting a Phase 1/2 clinical trial of EPZ-6438 in patients with relapsed or refractory B-cell lymphoma or advanced solid tumors. In 2014, we and our collaboration partner Eisai Co. Ltd., or Eisai, completed enrollment in the dose escalation portion of this Phase 1/2 clinical trial and disclosed the first clinical responses to treatment with EPZ-6438 from this ongoing Phase 1/2 clinical trial. These clinical responses were observed in heavily pretreated and relapsed or refractory patients with non-Hodgkin lymphoma, including of both germinal center and non-germinal center cells-of-origin, and in a patient with an INI1-deficient tumor. In March 2015, we reacquired global rights to develop, manufacture and commercialize EPZ-6438 outside of Japan from Eisai. As we begin the process of transitioning the ongoing development and manufacturing activities of EPZ-6438 to us, we are continuing to dose patients under both the dose escalation and dose expansion portions of the Phase 1/2 study and plan to commence a five-arm Phase 2 portion of the Phase 1/2 trial in Europe in the second quarter of 2015. We expect to enroll approximately 150 patients in this trial in both relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma patients, prospectively stratified by cell of origin and EZH2 mutational status. We also plan to commence a Phase 2 trial in adult patients with INI1-deficient tumors and a Phase 1 trial in pediatric patients with INI1-deficient tumors in the second half of 2015.

Our therapeutic strategy is to treat the underlying causes of specific cancers by blocking the misregulated activity of oncogenic HMTs. HMTs regulate gene expression by adding marks, called methyl groups, to specific locations on the proteins of human chromosomes, or histones, a process known as methylation. Oncogenic HMTs inappropriately mark these locations. As a result, the gene expression necessary for healthy, normally functioning cells is altered, thereby causing disease. Oncogenic HMTs drive multiple types of cancer, including hematological cancers and solid tumors.

In 2011, our scientists defined the 96-member HMT target class, which is referred to as the HMTome. Previously, specific HMTs were known, but a comprehensive identification of the entire target class did not exist. We subsequently analyzed cancer genome databases to enable us to prioritize these HMTs for our drug discovery activities based on the potential oncogenic role of these HMTs, the clinical need of patients with the relevant cancers and the possible clinical development and regulatory pathway for related inhibitors. The clinical development plan for each of our therapeutic product candidates is directed towards targeted cancer patient

populations. Because we are tailoring our epigenetic therapeutics for discrete, identifiable patient populations with specific cancers, we believe that many of our products may qualify for orphan drug designation in the United States, the European Union and other regions.

We currently have two HMT inhibitors in clinical development for the treatment of patients with certain cancers and believe we are the first company to conduct clinical trials of HMT inhibitors and demonstrate objective responses in patients in such a trial. In 2012 we initiated a Phase 1 clinical trial of EPZ-5676, an inhibitor targeting the DOT1L HMT and our second most advanced product candidate, in adult patients with MLL-r, an acute leukemia with genetic alterations of the *MLL* gene. In 2013, we completed enrollment in the dose escalation portion of this Phase 1 clinical trial and, in 2014, we completed enrollment in a 90 mg/m^2/day expansion cohort and disclosed the first clinical responses to treatment with EPZ-5676 in heavily pretreated and relapsed or refractory patients with MLL-r. We are currently enrolling up to an additional 20 MLL-r patients in an expansion cohort to investigate the activity of EPZ-5676 at a dose of 54 mg/m^2/day. We are also conducting a Phase 1 clinical trial of EPZ-5676 in pediatric patients with MLL-r, which we initiated in 2014.

In 2015, we plan to execute on the following clinical plans:

- Continue dosing patients who remain on study in the dose escalation portion of our ongoing Phase 1/2 clinical trial of EPZ-6438 in adult patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma;

- Continue dosing patients in two fully enrolled six-patient expansion cohorts in our ongoing Phase 1/2 clinical trial of EPZ-6438 in adult patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma, with one cohort at 800 mg and one cohort at 1600 mg;

- Initiate the Phase 2 portion of our Phase 1/2 clinical trial of EPZ-6438 in Europe in adult non-Hodgkin B-cell lymphoma patients in which patients will be prospectively stratified based on cell of origin and EZH2 mutational status into one of five arms;

- Initiate a Phase 2 clinical trial of EPZ-6438 in adult patients with INI1-deficient tumors such as synovial sarcoma;

- Initiate a Phase 1 clinical trial of EPZ-6438 in pediatric patients with INI1-deficient tumors such as malignant rhabdoid tumors, or MRT;

- Initiate standard clinical pharmacology studies of EPZ-6438;

- Complete enrollment in a 20 patient expansion cohort in our ongoing Phase 1 clinical trial of EPZ-5676 in adult MLL-r patients at 54 mg/m^2/day; and

Complete enrollment in the ongoing Phase 1 clinical trial of EPZ-5676 in pediatric MLL-r patients.

In addition to our clinical programs, we also have a pipeline of HMT inhibitors in preclinical development that target our other prioritized HMTs in the HMTome. These programs are directed to specific cancers, including both hematological and solid tumors. Three of these HMT programs, including our compounds directed to the PRMT5 HMT, are currently partnered with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK.

If we see evidence of a therapeutic effect in any of our programs, we intend to meet with regulatory authorities to discuss the possibility of an expedited clinical development and regulatory pathway for the applicable program. If eligible, we intend to apply for expedited review and approval programs from the United States Food and Drug Administration, or FDA, including breakthrough therapy and fast track designations.

In March 2015, we entered into an amended and restated collaboration and license agreement with Eisai, under which we reacquired worldwide rights, excluding Japan, to our EZH2 program, including EPZ-6438.

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Under the original collaboration and license agreement, we had granted Eisai an exclusive worldwide license to our EZH2 program, including EPZ-6438, while retaining an opt-in right to co-develop, co-commercialize and share profits with Eisai as to licensed products in the United States. Under the amended and restated collaboration and license agreement, we will be responsible for global development, manufacturing and commercialization outside of Japan of EPZ-6438 and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture EPZ-6438 and any other EZH2 product candidates in Japan. In connection with the amended and restated agreement, we agreed to pay Eisai an upfront payment of $40.0 million, specified milestone payments based on our development and commercialization of EZH2 products outside of Japan and royalties on net sales of EZH2 products outside of Japan.

In addition to our collaborations with Eisai and GSK, we are also a party to a collaboration agreement with Celgene. These collaborations have provided us with $188.7 million in non-equity funding through December 31, 2014. Our collaborations with Celgene and GSK also provide us with the potential for significant research, development, regulatory and sales-based milestone payments, as well as royalties on any net product sales. Our key therapeutic collaborations are as follows:

- A collaboration with Celgene under which we have granted Celgene a license outside of the United States to our DOT1L program, which includes EPZ-5676, and the option during a defined period that expires in July 2015 to license other HMT programs outside of the United States. Celgene has the right to extend the option period until July 2016 by making a significant option extension payment. We retain all United States development and commercialization rights for our DOT1L program and any other programs that we license to Celgene under this collaboration.

- A collaboration with GSK under which we have granted GSK a worldwide license to three specified HMT targets, including the PRMT5 HMT. Potential inhibitors of these targets are currently in preclinical development with GSK.

- An amended and restated collaboration with Eisai, under which we have granted Eisai a license to our EZH2 program in Japan, including EPZ-6438. We have retained worldwide development, manufacturing and commercialization rights, excluding Japan. In the event that we seek to license rights to a third party to develop or commercialize an EZH2 product in any country in Asia other than Japan, Eisai has a limited right of first negotiation for such rights.

We have also entered into an agreement with Roche Molecular Systems, Inc., or Roche, for the development of a companion diagnostic for use with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations.

Strategy

Our goal is to be a leader in the discovery, development and commercialization of novel epigenetic therapies for cancer patients. We systematically identify the genetic alterations that create oncogenes, select patients in whom the identified genetic alteration is found and then design small molecule therapies to inhibit the oncogenic activity. Our approach is part of a broader trend towards personalized therapeutics based on first identifying the underlying cause of a disease afflicting specific patient populations, applying rational drug design tools to create a therapeutic to inhibit a molecular target in the identified disease pathway and using diagnostic methods to select the right patients for treatment. Because we are tailoring our therapeutics for targeted cancer patient populations, we believe that many of

our products may qualify for orphan drug designation in the United States, the European Union and other regions and have been granted orphan drug designation in the United States and the European Union for EPZ-5676.

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Key elements of our strategy to achieve our goal are to:

Rapidly Advance the Clinical Development of Our Two Lead Product Candidates. We are conducting a Phase 1/2 clinical trial of EPZ-6438 for the treatment of non-Hodgkin lymphoma and advanced solid tumors including INI1-deficient tumors, such as synovial sarcoma and malignant rhabdoid tumors and plan to initiate the Phase 2 portion of the Phase 1/2 trial in patients with non-Hodgkin lymphoma in Europe in the second quarter of 2015, as well as a Phase 1 trial in pediatric patients with INI1-deficient tumors in the second half of 2015 and a Phase 2 trial in adult patients with INI1-deficient tumors in the second half of 2015. We are also conducting two Phase 1 clinical trials of EPZ-5676 for the treatment of MLL-r in both adult and pediatric patients. If we see compelling early evidence of a therapeutic effect in any of these trials, we plan to meet with regulatory authorities to discuss the possibility of an expedited clinical development and regulatory pathway for the applicable program. This approach is similar to the clinical development pathway that was used by the sponsor of the cancer therapeutic Zelboraf® which was included by the FDA in its 2011 report on Innovative Drug Approvals and which received marketing approval from the FDA within five years of initiating Phase 1 clinical trials. If safe and sufficiently active in the target patient populations, we believe that our two lead product candidates may be able to rely on an expedited regulatory approval process because these product candidates have the potential to satisfy the requirements that applied to other targeted cancer therapeutics as well as the FDA s new breakthrough therapy designation, such as treating a life-threatening disease and providing a major advance in treatment. We cannot predict whether or when any of our product candidates will prove effective or safe in humans, if they will receive regulatory approval or if we will be able to participate in FDA expedited review and approval programs, including breakthrough and fast track designation.

Pursue Expansion Indications for our Two Lead Product Candidates. We apply our proprietary product platform to identify additional cancers that may be treated with each of our product candidates beyond the initial indication of interest. For instance, INI1-deficient tumors are a potential expansion indication for EPZ-6438 that we identified internally. We are also continuing to look at other genetic alterations affecting EZH2, and its role in oncogenesis in a range of other hematological malignancies and solid tumors.

Establish Commercialization and Marketing Capabilities in the United States. We have retained commercialization rights in the United States for all of our programs other than the three programs in our GSK collaboration. We plan to seek to retain similar rights in connection with any future oncology collaborations. We intend to build a focused specialty sales force and marketing capabilities to commercialize any of our oncology drugs that receive regulatory approval in the United States.

Use Our Product Platform to Build a Pipeline of Proprietary HMT Inhibitors. There are 96 HMT enzymes in the HMTome. We regularly prioritize these HMTs based on their potential as attractive targets for personalized therapeutics. We are using our intellectual property, expertise and knowledge to create small molecule inhibitors of the HMT targets that we have prioritized. To date, we have invented novel, potent small molecule inhibitors for 17 HMTs. We intend to advance certain of these inhibitors into clinical trials.

Leverage Collaborations. We have established therapeutic collaborations with Celgene, GSK and Eisai for our most advanced HMT programs. These collaborations provide us with access to the considerable scientific, development, regulatory and commercial capabilities of our collaborators. Our collaborations with Celgene and GSK potentially provide us with significant funding for both our specific development programs and our product platform. We believe that collaborations like these can contribute to our ability to rapidly advance our product candidates, build our product platform and concurrently progress a wide range of discovery and development programs, and may seek to enter into additional therapeutic collaborations in the future.

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Develop Companion Diagnostics for Use with Our Therapeutic Product Candidates. For many of our therapeutic product candidates, we may seek to develop a companion diagnostic for the identification of patients with the cancers that we seek to treat with our therapeutic product candidates. We believe that this approach may enable us to accelerate the clinical development and regulatory timelines for our therapeutic product candidates and, for any of our therapeutic product candidates that receive marketing approval, improve patient care by identifying patients who will benefit from the therapy. We intend to develop diagnostics based on currently available diagnostic technologies to the extent possible in order to minimize development and regulatory risk of our diagnostic programs. We are working with Roche to develop a companion diagnostic, based on currently available technology, for use with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations and are relying on existing laboratory tests for use with EPZ-5676 to identify MLL-r patients.

The Epizyme Approach

We are discovering and developing HMT inhibitors as novel epigenetic therapeutics for cancer patients. We are applying our approach to the HMTome, with a focus on HMTs that we believe have the potential to be oncogenic, due to a variety of genetic alterations.

Background of Epigenetics. Epigenetics is a regulatory system that controls gene expression without altering the makeup of the genes themselves. Genes are composed of DNA. When properly read and translated, genes provide the blueprint for making individual proteins of the body. Epigenetic control of gene expression relies on a well-orchestrated collection of enzymes to perform precisely timed and located chemical reactions. When the function of these epigenetic enzymes is altered, the program of gene expression is changed in ways that often leads to disease.

Like thread wrapped around a spool, the DNA of chromosomes is packed into cell nuclei by wrapping around groups of proteins called histones, together forming packages of combined DNA and histone units known as nucleosomes. How tightly packed the nucleosomes are determines how easily individual genes on the DNA may be expressed. The tightness of the packing is controlled by the placement of small chemical groups acetyl groups, methyl groups and others onto specific sites in the DNA and the histone proteins by particular epigenetic enzymes. Where, when and how many of these small chemical groups are deposited determines which genes in a cell are turned on or off at any particular time.

Cancer and HMTs. The HMT class of enzymes is particularly attractive for drug therapy for several reasons. First, there are a large number of HMTs in humans 96 in total because these enzymes are needed to conduct all of the methylation reactions at distinct locations within the histones. As a result, this class provides a large number of potential drug targets. Second, because HMTs regulate gene expression in a precise fashion, they provide the potential for creation of an inhibitor that can have a desired biological effect. Third, genome discovery efforts have demonstrated that the activity of many of the HMTs is changed due to genetic alterations in cancers in such a way as to make the individual cancers strongly dependent on the enzyme activity of specific HMTs, thereby potentially improving the likelihood that an inhibitor will have a therapeutic effect.

While HMTs are a particularly attractive target class of enzymes for drug therapy, in our experience it requires significant effort and scientific knowledge to successfully pursue drug development programs directed at these targets. Key steps in these programs include:

screening cancer genome sequences specifically to identify alterations directly in HMTs or in related pathways;

defining an oncogenic hypothesis for the affected HMT;

developing assays to test the oncogenic hypothesis; and

creating and optimizing drug-like molecules to inhibit the selected HMT.

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The Epizyme Product Platform

When Epizyme was founded, we recognized that the HMT target class might contain many potential oncogenes and, therefore, presented the opportunity to create, develop and commercialize multiple epigenetic therapeutics. To realize this potential opportunity, we created and continue to expand and enhance our proprietary product platform. Our product platform includes intellectual property, know-how, expertise, proprietary biological information, biochemical assays, a library of novel HMT inhibitors and crystal structures of HMT enzymes bound with our small molecules. We have used, and continue to apply, our product platform to:

- define the HMTome;
- determine the roles of HMTs as oncogenes;
- identify potent and selective small molecule inhibitors of prioritized HMTs;
- optimize those small molecules as potential drug candidates; and
- develop companion diagnostics with our collaborators, where needed, for use with our therapeutic product candidates.

We invented EPZ-6438 and EPZ-5676, our two lead product candidates, and our pipeline of preclinical drug candidates using our proprietary product platform.

Define the HMTome. We defined the HMTome and published our findings in *Chemical Biology & Drug Design* in August 2011. The HMTome represents an unusually large target class, and therefore presents a broad opportunity to identify therapeutic applications.

Determine HMT Oncogenicity. After comprehensively defining the HMTome, we applied a rigorous analysis to prioritize HMTs for our drug discovery programs. Specifically:

- We generated hypotheses as to the oncogenic nature of particular HMTs based on our proprietary experimental data as well as public databases, such as The Cancer Genome Atlas, a project to catalogue genetic mutations responsible for cancer supervised by the National Cancer Institute and the National Human Genome Research Institute. We published our findings regarding our hypotheses as to the oncogenic nature of particular HMTs in *Oncogene* in February 2013.
- We designed and created proprietary *in vitro* biochemical and cellular assays to confirm the enzymatic function and oncogenic mechanism of various HMTs. For example, using these assays, we discovered the oncogenic role in a genetically defined subtype of non-Hodgkin lymphoma played by a point mutation in EZH2. A point mutation is a type of genetic alteration in which a single nucleotide base in a gene is

substituted, added or deleted. This discovery formed the basis of our program in which we identified EPZ-6438. Our research on the EZH2 point mutation was published in the *Proceedings of the National Academy of Sciences* in December 2010.

Similarly, in *in vitro* preclinical studies conducted by us, EPZ-6438 induced apoptotic cell death and, in preclinical animal models conducted by us, EPZ-6438 caused dose-dependent regression of malignant rhabdoid tumors and prevention of tumor regrowth after dosing cessation. Our research on tumor regressions in genetically altered malignant rhabdoid tumors by inhibition of EZH2 was published in the *Proceedings of the National Academy of Sciences* in April 2013.

We identified the patient populations with the oncogenic HMTs to determine that we were pursuing areas of significant unmet medical need.

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Identify Potent and Selective Small Molecule Inhibitors. We then screened for potent and selective inhibitors that have the potential to be novel, safe and effective pharmaceuticals. Specifically:

- We have designed and built proprietary biochemical assays that we use to screen for potent and selective inhibitors of the prioritized HMTs. We refer to these assays together as our HMTome cross screen. Our HMTome cross screen includes our high priority HMTs. We have also included a number of other HMTs to determine whether the compounds that we screen inhibit the HMT of interest selectively.

- We have created more than 650 proprietary crystal structures of enzymes bound with HMT inhibitors. We use these structures to guide our efforts to select HMT inhibitors that we believe have the potential to be developed into safe and effective pharmaceuticals and to optimize these inhibitors through medicinal chemistry efforts.

Optimize Small Molecule Compounds. We have created a proprietary library of more than 29,000 compounds in 27 distinct chemical series. Within these 27 distinct series, there are examples of multiple modes of inhibition of HMTs, thereby increasing the likelihood of their binding to a target HMT in a manner that may have a pharmaceutical effect. We have further optimized many of these small molecule compounds to have drug-like properties, including the ability to be absorbed and maintained at blood levels necessary to treat cancers. Many of these compounds are highly selective for specific HMTs.

Develop Companion Diagnostics. One element of our approach to cancer treatment is to develop a companion diagnostic for use with each therapeutic product candidate we develop, unless we believe existing, available technology may be sufficient to identify the patients we seek to treat. We are working with a collaborator to develop one such companion diagnostic, applying our knowledge about the target HMT and using currently available diagnostic technologies to the extent possible in order to minimize development and regulatory risk of our diagnostic programs. We believe that this approach will help us to access the best technology for each program and control diagnostic development costs. We intend to use the companion diagnostic to identify and stratify patients for our clinical trials who have the target cancers that we are seeking to treat with our therapeutic product candidate. We believe that including these patients may increase the likelihood that we will see early evidence of a therapeutic effect in our trials.

We believe that our product platform provides us with an important competitive advantage in identifying oncogenic HMTs and creating novel epigenetic therapeutics to treat the cancers caused by these HMTs.

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Product Pipeline

The following table summarizes key information about our two most advanced product candidates:

Product Candidate	Clinical Populations	Stage of Development	Commercial Rights	Diagnostic Collaborator
EPZ-6438 (EZH2 inhibitor)	Non-Hodgkin lymphomas, including germinal center diffuse large B-cell lymphoma and follicular lymphoma as well as non-germinal center DLBCL, including primary mediastinal B-cell lymphoma (EZH2)	Phase 1/2 clinical trial ongoing Phase 1 dose escalation complete; Phase 1 dose expansion fully enrolled at the highest two tested dose levels Phase 2 trial for expanded population of non-Hodgkin lymphoma patients expected to initiate in the second quarter of 2015	Epizyme: Worldwide rights, ex-Japan Eisai: Japan	Roche (Non-Hodgkin lymphoma with EZH2 point mutations)
	Other solid tumors such as synovial sarcoma and MRT (INI1-deficient)	Phase 1 trial for pediatric patients with INI1-deficient tumors, including MRT, expected to initiate in the second half of 2015 Phase 2 trial for adult patients with INI1-deficient tumors, including synovial sarcoma, expected to initiate in the second half of 2015 Clinical pharmacology studies evaluating food effects and drug/drug interactions expected to initiate in 2015		None - existing standard of care immunohistochemical testing used at time of diagnosis to be utilized for studies in INI1-deficient tumors

EPZ-5676 (DOT1L inhibitor)	Acute leukemias with alterations in the *MLL* gene MLL-r subtype of acute myeloid leukemia, or AML, and acute lymphoblastic leukemia, or ALL, in adult patients (Chromosomal translocation involving the *MLL* gene) MLL-r in pediatric patients (Chromosomal translocation involving the *MLL* gene)	Phase 1 MLL-r adult patient trial ongoing Dose escalation fully enrolled in MLL-r adult patient trial MLL-r only adult expansion enrolling Phase 1 MLL-r pediatric patient trial enrolling	Epizyme: United States Celgene: Rest of world	None - existing standard of care molecular testing used at time of diagnosis to be utilized for studies in MLL-r leukemia

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In addition to the therapeutic programs listed above, we are working with GSK on three specified HMT inhibitors, including inhibitors directed to the PRMT5 HMT, that are in preclinical development and for which GSK holds commercial rights. We also have active drug discovery programs for other HMTs that we consider to be priority targets.

EPZ-6438 EZH2 Inhibitor

Overview. We are developing EPZ-6438 as an orally available small molecule inhibitor of EZH2 for the treatment of non-Hodgkin lymphoma patients and for the treatment of patients with INI1-deficient solid tumors, such as synovial sarcoma, a soft tissue sarcoma, and malignant rhabdoid tumor, a primarily pediatric cancer with high unmet medical need. In June 2013, Eisai and we initiated a Phase 1/2 clinical trial of EPZ-6438 in adult patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma. In March 2015, we completed enrollment of two expansion cohorts of the Phase 1 dose escalation portion of the trial at clinical sites in France. In November 2014, we and Eisai released data from the Phase 1 dose escalation portion of the trial. In this portion of the trial, EPZ-6438 exhibited favorable safety and tolerability as well as monotherapy activity in non-Hodgkin lymphoma, including germinal center and non-germinal center B-cell lymphomas with wild-type EZH2, and INI1-deficient tumors. On the basis of these trial results, a recommended Phase 2 dose has been selected. We expect to initiate the Phase 2 portion of the trial in non-Hodgkin lymphoma patients in which patients will be prospectively stratified based on cell of origin and EZH2 mutational status in Europe in the second quarter of 2015 as well as a Phase 2 trial for the treatment of adults with INI1-deficient tumors, including synovial sarcoma, in the second half of 2015. These two Phase 2 trials are intended to provide an initial assessment of efficacy, or proof-of-concept, in two cancer types that we currently seek to treat with EPZ-6438. Additionally, in the second half of 2015, we plan to initiate a Phase 1 dose escalation study of EPZ-6438 in pediatric patients with INI1-deficient tumors, including MRT.

In March 2015, we entered into an amended and restated collaboration and license agreement with Eisai, under which we reacquired worldwide rights, excluding Japan, to our EZH2 program, including EPZ-6438. Under the original collaboration and license agreement, we had granted Eisai an exclusive worldwide license to our EZH2 program, including EPZ-6438, while retaining an opt-in right to co-develop, co-commercialize and share profits with Eisai as to licensed products in the United States. Under the amended and restated collaboration and license agreement, we will be responsible for global development, manufacturing and commercialization, outside of Japan, of EPZ-6438 and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture EPZ-6438 and any other EZH2 product candidates in Japan. In connection with the amended and restated agreement, we agreed to pay Eisai an upfront payment of $40.0 million, specified milestone payments based on our development and commercialization of EZH2 products outside of Japan and royalties on net sales of EZH2 products outside of Japan.

Clinical Development. We are conducting our ongoing Phase 1/2 clinical trial of EPZ-6438 in two parts. The Phase 1 portion of this first-in-human clinical trial is an open label dose escalation trial. The Phase 2 portion will be conducted in two stages. All patients in the Phase 2 trial will be dosed at the recommended Phase 2 dose as determined in the Phase 1 clinical trial. If the pre-specified number of responses are observed in the first stage of the Phase 2 part of this clinical trial, enrollment will continue into the second stage. Both the Phase 1 and Phase 2 clinical trials provide for the assessment of the safety and tolerability and pharmacokinetics of EPZ-6438 and include various exploratory pharmacodynamics and translational research objectives.

The primary objective of the Phase 1 clinical trial is to evaluate the safety and tolerability of EPZ-6438 and to determine the recommended dose for Phase 2 trials.

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Secondary objectives of the Phase 1 clinical trial are to:

- explore the pharmacokinetic activity, including evaluating the fraction of orally administered drug that reaches systemic circulation, of EPZ-6438;
- explore the pharmacodynamic activity of EPZ-6438; and
- evaluate early evidence of anti-tumor activity in patients.

In the Phase 1 trial, EPZ-6438 is being administered orally as a monotherapy, twice daily in 28-day cycles in patients with advanced solid tumors or with relapsed or refractory B-cell lymphoma. A total of 24 patients were enrolled in one of five dose cohorts at dose levels of 100, 200, 400, 800, or 1600 mg. This dose escalation portion of the trial allowed for, but did not require, the enrollment of patients with non-Hodgkin lymphoma and INI1-deficient tumors. Of the 24 enrolled patients, 12 patients had a diagnosis of non-Hodgkin lymphoma and 12 patients had advanced solid tumors, two of which were INI1-deficient. This patient population was heavily pre-treated, with 14 patients having received between two and four prior therapies and nine having received more than four prior therapies. As of an October 2014 data cut-off, 10 of the non-Hodgkin lymphoma patients and two of the INI1-deficient patients were evaluable for efficacy. Four of the 10 non-Hodgkin lymphoma patients evaluable for efficacy achieved a partial response or better, including one complete response, which remained ongoing at 14 months as of January 23, 2015, and one of the two evaluable INI1-deficient patients achieved a complete response, which remained ongoing at nearly nine months as of January 23, 2015. Four of the 10 non-Hodgkin lymphoma patients and one INI1-deficient patient from the dose escalation remain on study with treatment durations ranging from seven to 14 months as of January 23, 2015. Confirmatory sequencing in a central laboratory showed that all 10 non-Hodgkin lymphoma patients evaluable for efficacy had wild-type EZH2.

In the trial results to date, EPZ-6438 has exhibited a favorable safety and tolerability profile. Specifically, one dose-limiting toxicity at 1600 mg has been reported. This safety and tolerability profile suggest that combination with a range of other non-Hodgkin lymphoma therapies may be possible. We are currently evaluating a range of potential combinations preclinically.

Based on the Phase 1 dose escalation results, a recommended Phase 2 dose of 800 mg was selected. We have fully enrolled two ongoing six-patient expansion cohorts, one at 800 mg and one at 1600 mg. We plan to provide an update on data from the dose escalation portion of the study at a medical conference in mid-2015 and data from these expansion cohorts by the end of 2015.

Subject to our ongoing discussions with regulatory authorities, we expect to initiate the Phase 2 portion of this trial in non-Hodgkin B-cell lymphoma patients in the European Union in the second quarter of 2015. Our plan for this Phase 2 portion of the clinical trial provides for prospective stratification of patients based on cell of origin and EZH2 mutational status and will enroll five distinct patient populations in five clinical trial arms, allowing us to discretely assess EPZ-6438 in the following patient groups: germinal center DLBCL with wild-type EZH2, non-germinal center B-cell DLBCL, germinal center DLBCL with mutated EZH2, FL with wild-type EZH2 and FL with mutated EZH2. We expect to enroll approximately 30 patients in each trial arm, for a total of approximately 150 patients, assuming each arm of the study achieves its primary response rate goal in its first stage. We expect to disclose data from the germinal center DLBCL with wild-type EZH2 and non-germinal center B-cell DLBCL trial arms in mid-2016 and from the FL with wild-type EZH2 trial arm in the first half of 2017. We will not be able to reasonably estimate the

timing of the mutated EZH2 arms until we have completed an initial evaluation of enrollment rates; however, we expect that enrollment in these trial arms will be slower than the wild-type EZH2 arms based on the estimated incidence of mutated EZH2.

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The primary objective of the Phase 2 clinical trial will be to assess the objective response rate of EPZ-6438 in patients who have confirmed relapsed or refractory DLBCL or FL. The secondary objectives of the Phase 2 clinical trial will be to assess duration of response and progression-free survival of EPZ-6438 as a monotherapy.

It is important to note that the objective responses and treatment effects observed in the dose escalation portion of the study were experienced by only some of the lymphoma and INI1-deficient tumor patients enrolled in the trial, were observed in an open-label setting and might not be experienced by other patients treated with EPZ-6438. Additionally, the disease did progress in other lymphoma and INI1-deficient tumor patients enrolled in the dose escalation study. This Phase 1/2 trial is not designed to show results with statistical significance. Statistical significance means that an effect is unlikely to have occurred by chance. Clinical trial results are considered statistically significant when the probability of the results occurring by chance, rather than from the efficacy of the drug candidate, is sufficiently low. Since the trial is not powered to show results with statistical significance, the results from the trial may be attributable to chance and not the clinical efficacy of EPZ-6438. We plan to design any later stage trials that are intended to support marketing approval applications to show statistical significance. We would do so by enrolling a larger number of patients than enrolled in earlier trials.

We plan to launch the Phase 2 portion of our EPZ-6438 trial in non-Hodgkin B-cell lymphoma in the second quarter of 2015 in the European Union.

In the course of our ongoing preclinical safety studies for EPZ-6438, we observed the development of lymphoma in a single study in Sprague Dawley rats. We did not observe this finding in our parallel preclinical safety studies of EPZ-6438, which were conducted in primates. Additionally, we have not observed any similar findings in our ongoing Phase 1/2 clinical study of EPZ-6438. We have informed the relevant European regulatory authorities and the clinical investigators of this finding. We continued to enroll patients in the expansion cohorts of our Phase 1 study in France, with updated data from the dose escalation patients expected in mid-2015 and data on the expansion cohort patients expected by the end of 2015.

Expansion of trials of EPZ-6438 to the United States will require that we submit an investigational new drug application, or IND, and that we address this matter to the satisfaction of the FDA within the context of patient risk-benefit and in view of the safety and efficacy data from our ongoing Phase 1/2 clinical study. We are in discussions with the FDA, and we are conducting additional preclinical studies to understand this observation more fully, prior to submitting our IND. If we are unable to adequately address this matter, we may be unable to expand our planned clinical trials of EPZ-6438 into the United States, our trials may be limited to certain patient populations or our ability to conduct trials in the United States may be delayed.

In the second half of 2015, we plan to initiate a Phase 1 trial of EPZ-6438 for the treatment of INI1-deficient tumors, such as MRT, in pediatric patients and a Phase 2 trial of EPZ-6438 for the treatment of INI1-deficient tumors, such as synovial sarcoma, in adult patients. These trials will only enroll patients with the targeted disease. The Phase 1 trial is currently designed to evaluate the safety, tolerability and preliminary efficacy of EPZ-6438 and to determine its maximum tolerated dose in children. The Phase 2 trial is currently designed to provide an initial assessment of efficacy, or proof-of-concept, in this adult patient population. We also plan to initiate in 2015 standard clinical pharmacology studies designed to evaluate the food effects and any potential drug-to-drug interactions of EPZ-6438.

Companion Diagnostic. We are working with Roche to develop an *in vitro* based diagnostic for use as a companion diagnostic with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations and plan to use this diagnostic in the prospective screening of patients for stratification in the Phase 2 portion of our EPZ-6438 clinical trial. The agreement with Roche calls for the development of a diagnostic to test for the presence of an oncogenic point mutation in EZH2. Under the agreement, Roche will have the right to commercialize the companion diagnostic

with EPZ-6438. We anticipate that we and Roche will coordinate our marketing and sales

activities for EPZ-6438 and the companion diagnostic. We have not yet determined whether companion diagnostics will be necessary for the INI1-deficient tumors as the EZH2 sensitivity may be inherent in the clinical diagnosis for most of the patient population.

EPZ-5676 DOT1L Inhibitor

Overview. We are developing EPZ-5676 as an intravenously administered small molecule inhibitor of DOT1L for the treatment of acute leukemias with alterations in the *MLL* gene, specifically rearrangements of *MLL* as a consequence of chromosomal translocation, referred to as MLL-r, which includes partial tandem duplications of the *MLL* gene, referred to as MLL-PTD. We invented EPZ-5676 using our proprietary product platform and initiated a Phase 1 clinical trial of this product candidate in September 2012. The dose escalation portion of this trial included patients with advanced hematologic malignancies, including, but not restricted to patients with alterations involving the *MLL* gene. The dose escalation was fully enrolled as of December 31, 2013, and, from December 2013 to November 2014, we enrolled patients in a 90 mg/m^2/day expansion cohort in the Phase 1 trial. The expansion cohort only included patients with MLL-r or MLL-PTD. Based on the results seen through the 90 mg/m^2/day expansion cohort, in January 2015, we initiated enrollment of adult MLL-r patients in a 54 mg/m^2/day expansion cohort to gain further clinical experience at this dose level. We chose this dose level based on complete responses observed in MLL-r patients at this dose level in the dose escalation portion of the Phase 1 trial.

In May 2014, we initiated a Phase 1 trial of EPZ-5676 in pediatric patients with MLL-r. This Phase 1 study is designed to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of EPZ-5676 in patients between the ages of three months and 18 years. This trial is also designed to provide a preliminary assessment of efficacy.

We retain all U.S. rights to EPZ-5676. We have granted Celgene an exclusive license to EPZ-5676 outside of the United States.

In August 2013, we were granted orphan drug designation for EPZ-5676 for the treatment of acute myeloid leukemia, or AML, and acute lymphoblastic leukemia, or ALL, by the FDA, and in January 2014, the European Commission granted orphan drug designation for EPZ-5676 for the treatment of AML and ALL.

Phase 1 Clinical Trial in Adult Patients. Our Phase 1 clinical trial of EPZ-5676 is a first-in-human open label, multicenter trial that is being conducted in two parts. The first part involves dose escalation in patients with advanced hematologic malignancies, including, but not restricted to, MLL-r patients. The second part involves expansion cohorts that only enroll MLL-r patients. We are currently enrolling a second expansion cohort of up to 20 MLL-r patients at a dose of 54 mg/m^2/day using an uninterrupted administration schedule and expect to disclose top-line data from this expansion cohort in the second half of 2015. We are currently conducting this trial at seven sites in the United States and one site in the European Union.

The primary objectives of the trial are to evaluate the safety and tolerability of EPZ-5676 and to determine its maximum tolerated dose. Secondary objectives of this trial are to:

- determine the pharmacokinetics of EPZ-5676;

assess the biochemical and physiological effects of EPZ-5676 on the human body, which is referred to as pharmacodynamics, including methylation in peripheral blood mononuclear cells and leukemia cells; and

evaluate preliminary anti-tumor activity in patients with MLL-r.

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Dose Escalation. We began enrolling patients in the dose escalation portion of the Phase 1 trial in September 2012 and completed enrollment in December 2013. A total of 25 patients were enrolled in one of six dose cohorts at dose levels of 12, 24, 36, 54, 80, or 90 mg/m^2/day, with patients in the 12, 24, 36, and 54 mg/m^2/day dose cohorts receiving EPZ-5676 on a 21-day on drug, seven-day off drug schedule via continuous intravenous administration and patients in the 80 and 90 mg/m^2/day dose cohorts receiving continued intravenous administration without a drug holiday. The dose escalation allowed for, but did not require, the enrollment of patients with the targeted MLL-r genetic alterations. The majority of patients had a diagnosis of AML. Other diagnoses included ALL and chronic myelomonocytic leukemia, or CMML. In December 2013, two patients in the 54 mg/m^2/day dose cohort of the dose escalation achieved complete responses. Based on preclinical data suggesting greater biological activity of uninterrupted drug exposure, these patients were switched from the original intravenous administration schedule, which included a seven-day drug holiday, to an uninterrupted intravenous administration schedule. One of these patients was diagnosed with AML with an MLL-r translocation. The other patient was diagnosed with CMML with an MLL-r translocation.

During the dose escalation portion of the trial, in addition to the two objective responses, we observed treatment effects of EPZ-5676 in other patients with MLL-r, such as treatment-related leukocytosis, cellular differentiation and maturation in blood and bone marrow and resolution of leukemia-related symptoms such as cachexia, fevers, and leukemia cutis that are consistent with anti-leukemic effects in MLL-r patients.

Expansion Cohorts. We enrolled 17 MLL-r patients in an expansion cohort at 90 mg/m^2/day from December 2013 to November 2014. These patients received EPZ-5676 with uninterrupted intravenous administration. Of the 17 patients enrolled in the 90 mg/m^2/day expansion cohort, one patient achieved a partial response.

The patients enrolled into the dose escalation cohorts and 90 mg/m^2/day expansion cohort were heavily pre-treated. Of the 42 patients enrolled through these two stages, 29 had received two or more prior therapies. Sixteen of the 42 patients had received at least one prior allogeneic hematopoietic cell transplant.

In the trial results to date, EPZ-5676 has exhibited a favorable safety and tolerability profile. Specifically, two dose-limiting toxicities in 23 total patients treated at the 90 mg/m^2/day dose level have been reported. Leukocytosis, an elevated white blood cell count, has been observed in some patients and is considered treatment-related, but consistent with the therapeutic mechanism of action of EPZ-5676, thus is not considered an adverse event.

The Phase 1 clinical trial is not powered to demonstrate efficacy with statistical significance. However, pending the results of this Phase 1 clinical trial, we plan to use the results of the trial to design any later stage trials that are intended to demonstrate statistical significance and potentially support marketing approval applications. We would do so by enrolling a larger number of patients than enrolled in earlier trials.

Based on the collective findings of the dose escalation experience, and especially that of the 54 mg/m^2/day dose cohort, we have initiated a second expansion cohort, at 54 mg/m^2/day, in 2015, to gain more experience at this dose level. This planned expansion cohort will enroll up to an additional 20 MLL-r patients.

Phase 1 Clinical Trial in Pediatric Patients. In May 2014, we initiated a Phase 1 clinical trial of EPZ-5676 in pediatric patients. This clinical trial is restricted to pediatric patients with MLL-r acute leukemia and is similar in design to the adult trial, with a dose escalation and an expansion cohort that we would expect will enable us to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of EPZ-5676 in patients between the ages of three months and 18 years and also provide a preliminary assessment of efficacy. Patients in this trial are receiving uninterrupted administration of EPZ-5676. We expect to complete enrollment in this Phase 1 trial in the second half of 2015.

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Companion Diagnostic. We are currently relying on commercially available diagnostics that are commonly used by clinicians to identify and diagnose MLL-r patients.

HMT Collaborations

We have entered into three strategic collaborations for our therapeutic programs. These therapeutic collaborations have provided us with $188.7 million in non-equity funding through December 31, 2014. In addition, as of December 31, 2014, we were owed an additional $2.1 million under these collaborations for research and development services revenue earned and global development co-funding. Our therapeutic collaborations also provide us with development co-funding and the potential for significant research, development, regulatory and sales-based milestone payments as well as royalties or profit sharing on net product sales. In addition, we have entered into a collaboration to develop a companion diagnostic with Roche. Key terms of these collaborations are summarized below.

Celgene

In April 2012, we entered into a collaboration and license agreement with Celgene to discover, develop and commercialize, in all countries other than the United States, small molecule HMT inhibitors targeting DOT1L, including EPZ-5676, and any other HMT targets from our product platform, excluding the EZH2 HMT and targets covered by our GSK collaboration, which we refer to as the available targets.