

Epizyme, Inc.
Form 424B4
February 05, 2014
Table of Contents

Filed Pursuant to Rule 424(b)(4)
Registration No. 333-193569

PROSPECTUS

4,492,679 Shares

Epizyme, Inc.

Common Stock

\$29.25 per share

We are selling 3,000,000 shares of our common stock and the selling stockholders are selling 1,492,679 shares of our common stock. We will not receive any proceeds from the sale of shares by the selling stockholders.

To the extent that the underwriters sell more than 4,492,679 shares of common stock, the underwriters have an option to purchase up to 673,901 additional shares from us at the public offering price, after deducting underwriting discounts and commissions.

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 February 4, 2014 was \$30.00 per share.

Investing in our common stock involves risks. See Risk Factors beginning on page 12.

We are an emerging growth company under applicable Securities and Exchange Commission rules and are eligible for reduced public company disclosure requirements. See 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	\$ 29.25	\$ 131,410,861
Underwriting Discount(1)	\$ 1.681875	\$ 7,446,972
Proceeds to Epizyme (before expenses)	\$ 27.568125	\$ 82,704,375
Proceeds to selling stockholders	\$ 27.64125	\$ 41,259,514

(1) The underwriting discount for the shares of common stock sold by Epizyme is \$1.681875 per share and the underwriting discount for the shares of common stock sold by the selling stockholders is \$1.608750 per share. We refer you to Underwriting beginning on page 149 for additional information regarding underwriting compensation.

Celgene European Investment Company LLC, or CEIC, which is affiliated with one of our collaborators and is an existing investor, has agreed to purchase 340,000 shares of our common stock in this offering at the public offering price. The underwriters will receive the same underwriting discount on any shares purchased by CEIC as they will on any other shares sold to the public in this offering.

The underwriters expect to deliver the shares to purchasers on or about February 10, 2014 through the book-entry facilities of The Depository Trust Company.

Citigroup

Cowen and Company

Leerink Partners

JMP Securities

Wedbush PacGrow Life Sciences

BTIG

February 4, 2014

Table of Contents

We and the selling stockholders are responsible for the information contained in this prospectus. We and the selling stockholders have not authorized anyone to provide you with different information, and we take no responsibility for any other information others may give you. If anyone provides you with different or inconsistent information, you should not rely on it. We and the selling stockholders are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained in this prospectus is accurate as of any date other than the date on the front of this prospectus.

TABLE OF CONTENTS

	Page
<u>Summary</u>	1
<u>Risk Factors</u>	12
<u>Special Note Regarding Forward-Looking Statements and Industry Data</u>	43
<u>Use of Proceeds</u>	44
<u>Price Range of Common Stock</u>	45
<u>Dividend Policy</u>	45
<u>Capitalization</u>	46
<u>Dilution</u>	47
<u>Selected Consolidated Financial Data</u>	48
<u>Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	49
<u>Business</u>	74
<u>Management</u>	113
<u>Executive Compensation</u>	119
<u>Transactions with Related Persons</u>	131
<u>Principal and Selling Stockholders</u>	135
<u>Description of Capital Stock</u>	139
<u>Shares Eligible for Future Sale</u>	143
<u>Material U.S. Tax Considerations for Non-U.S. Holders of Common Stock</u>	145
<u>Underwriting</u>	149
<u>Legal Matters</u>	154
<u>Experts</u>	154
<u>Where You Can Find More Information</u>	154
<u>Index to Consolidated Financial Statements</u>	F-1

Table of Contents

SUMMARY

The following summary highlights information contained elsewhere in this prospectus and is qualified in its entirety by the more detailed information and consolidated financial statements included elsewhere in this prospectus. This summary does not contain all of the information that may be important to you. You should read and carefully consider the following summary together with the entire prospectus, including our consolidated financial statements and the notes thereto appearing elsewhere in this prospectus and the matters discussed in the sections in this prospectus entitled Risk Factors, Selected Consolidated Financial Data and Management's Discussion and Analysis of Financial Condition and Results of Operations before deciding to invest in our common stock. Some of the statements in this prospectus constitute forward-looking statements that involve risks and uncertainties. See Special Note Regarding Forward-Looking Statements and Industry Data. Our actual results could differ materially from those anticipated in such forward-looking statements as a result of certain factors, including those discussed in the Risk Factors and other sections of this prospectus.

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus to Epizyme, the company, we, us and our refer to Epizyme, Inc., together with its consolidated subsidiary.

Company Overview

We are a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize innovative personalized therapeutics for patients with genetically defined cancers. We systematically identify the genetic alterations that create cancer causing genes, called oncogenes, select patients in whom the identified genetic alteration is found and then design small molecule therapeutics to inhibit the oncogene. The clinical development plan for each of our product candidates is directed towards patients with a particular genetically defined cancer. 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 bind with a molecular target in the identified disease pathway and using a companion diagnostic to select the right patients for treatment.

We have built a proprietary product platform that we use to create small molecule inhibitors of a 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. In 2011, our scientists defined the 96-member HMT target class, which is referred to as the HMTome. Genetic alterations can result in changes to the activity of HMTs, making them oncogenic. 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 personalized therapeutics.

We currently have two HMT inhibitors in clinical development for the treatment of patients with genetically defined cancers and believe we are the first company to conduct a clinical trial of an HMT inhibitor. We are conducting a Phase 1 clinical trial of our most advanced product candidate, EPZ-5676, an inhibitor targeting the DOT1L HMT, being developed for the treatment of acute leukemias with genetic alterations of the MLL gene, referred to as MLL-r and MLL-PTD. On January 6, 2014, we announced that we had earned a \$25.0 million proof-of-concept milestone in our collaboration with Celgene Corporation and Celgene International Sàrl, collectively referred to as Celgene, in December 2013 by achieving objective responses in two MLL-r patients enrolled in the dose escalation stage of our Phase 1 trial. We are also conducting a Phase 1/2 clinical trial of our second most advanced product candidate, EPZ-6438, an inhibitor targeting the EZH2 HMT, being developed for the treatment of a genetically defined subtype of non-Hodgkin lymphoma and solid tumors including INI1-deficient tumors, such as synovial sarcoma and malignant rhabdoid tumors, or MRT.

Table of Contents

In 2014, we plan to have four clinical trials ongoing that are intended to assess the proof of concept of our product candidates in five genetically defined cancer patient groups:

The expansion stage of our ongoing Phase 1 clinical trial of EPZ-5676 in MLL-r adult patients and MLL-PTD adult patients;

Our planned Phase 1b clinical trial of EPZ-5676 in MLL-r pediatric patients;

Our planned Phase 2 clinical trial of EPZ-6438 in non-Hodgkin lymphoma patients with EZH2 point mutations as part of our ongoing Phase 1/2 clinical trial of EPZ-6438; and

Our planned Phase 2 clinical trial of EPZ-6438 in synovial sarcoma patients.

The initiation of our proof-of-concept trials of EPZ-6438 is subject to our review of the data from the Phase 1 clinical trial of EPZ-6438 that we are conducting as part of our ongoing Phase 1/2 clinical trial of EPZ-6438.

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 genetically defined cancers, both hematological and solid tumors. As we announced on January 6, 2014, one of these preclinical HMT inhibitors achieved a development candidate milestone in December 2013, earning a \$4.0 million milestone in our collaboration with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK.

For many of our therapeutic product candidates, we plan to develop a companion diagnostic for the identification of patients with the genetically defined cancers that we seek to treat with our therapeutic product candidates. Because we are tailoring our personalized therapeutics for discrete patient populations with genetically defined 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 believe our personalized therapeutic product candidates offer the promise of treatment for patients with genetically defined cancers by blocking the incorrect function of oncogenic HMTs.

We were founded in November 2007 and are led by a management team with extensive experience in the pharmaceutical industry. We have entered into therapeutic collaborations with Celgene, Eisai Co., Ltd., or Eisai, and GSK, that have provided us with \$133.3 million in non-equity funding through September 30, 2013. As of September 30, 2013, we had \$139.6 million in cash and cash equivalents. We estimate that our cash, cash equivalents and accounts receivable balance as of December 31, 2013 will be between \$155.0 million and \$160.0 million. We have provided a range, rather than a specific amount, for our estimate of cash, cash equivalents and accounts receivable primarily because we have not yet completed our year-end closing procedures for the year ended December 31, 2013. It is possible that our cash, cash equivalents and accounts receivable balance will not be in this range. We will not complete our year-end closing procedures until after this offering is complete. Our independent registered accounting firm, Ernst & Young LLP, has not audited or reviewed, and does not express an opinion with respect to, this estimate.

Role of Epigenetics and HMTs

Edgar Filing: Epizyme, Inc. - Form 424B4

Epigenetics is a regulatory system that controls gene expression. When properly read and translated, genes provide the blueprint for making the individual proteins of the body. Epigenetic control of gene expression relies on the precisely orchestrated activity of a collection of enzymes. When the function of these epigenetic enzymes is altered, gene expression is changed in ways that often leads to disease.

HMTs are a type of epigenetic enzyme that regulate gene expression by adding marks, called methyl groups, to specific locations on chromosomes, a process known as methylation. Oncogenic HMTs inappropriately mark these locations, driving multiple types of cancer, including hematological cancers and solid tumors. Out of the 96 enzymes in the HMTome, we have prioritized 20 HMTs as attractive targets for personalized therapeutics based on their oncogenic potential.

Table of Contents

Our Strategy

Our goal is to be a leader in the discovery, development and commercialization of personalized therapeutics for the treatment of patients with genetically defined cancers. We believe that many of our products may qualify for orphan drug designation in the United States, the European Union and other regions.

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

Rapidly advance the clinical development of our two lead product candidates. We have designed the Phase 1 clinical trial of EPZ-5676 and the Phase 1/2 clinical trial of EPZ-6438 to include some patients with the genetically defined cancer that we are seeking to treat. If we see evidence of a therapeutic effect in either 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 genetically defined population, 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 these other 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 genetically defined cancers that may be treated with each of our product candidates beyond the initial indication of interest. MLL-PTD is an expansion indication for the EPZ-5676 product candidate that we identified internally. Similarly, we identified INI1-deficient tumors as potential expansion indications for EPZ-6438.

Leverage our existing collaborations. We have established therapeutic collaborations with Celgene, Eisai and GSK for our most advanced HMT programs. We believe that our collaborations 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. In the case of the Celgene and Eisai arrangements, we have retained commercialization or co-commercialization rights in the United States.

Establish commercialization and marketing capabilities in the United States. We have retained commercialization or co-commercialization rights in the United States for all of our programs other than the three programs in our GSK collaboration. We intend to build a focused specialty sales force and marketing capabilities in the United States to commercialize any of our oncology drugs that receive regulatory approval.

Use our product platform to build a pipeline of proprietary HMT inhibitors. We are using our intellectual property, expertise and knowledge to create small molecule inhibitors of the 20 HMT targets that we have prioritized. We have invented novel, potent small molecule inhibitors of 15 of these 20 prioritized HMTs. We intend to advance multiple other product candidates into clinical trials.

Develop companion diagnostics for use with our therapeutic product candidates. For many of our therapeutic product candidates, we plan to develop a companion diagnostic for the identification of patients with the genetically defined cancers that we seek to treat with our therapeutic product candidates. 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.

Table of Contents

Our Lead Product Candidates

We invented our two lead product candidates using our proprietary product platform. We designed these product candidates to treat genetically defined cancers for which there is a significant unmet medical need.

EPZ-5676 DOT1L Inhibitor

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, or MLL-r, and partial tandem duplications of the *MLL* gene, or MLL-PTD. We initiated a Phase 1 clinical trial of this product candidate in September 2012. Our Phase 1 clinical trial of EPZ-5676 is an open label, multicenter trial that has two stages. The first stage is a dose escalation stage that includes some MLL-r patients. The second stage is an expansion stage that will only include MLL-r and MLL-PTD patients. We also plan to initiate a Phase 1b trial of EPZ-5676 in pediatric patients with MLL-r in 2014.

The primary objectives of the ongoing Phase 1 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 process by which EPZ-5676 is distributed and metabolized in the body, which is referred to as pharmacokinetics;

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 any early evidence of anti-tumor activity in patients with MLL-r.

The dose escalation stage of this trial was fully enrolled as of December 31, 2013. A total of five dose cohorts were enrolled at doses of 12, 24, 36, 54, and 80 mg/m²/day, with a total of 19 patients enrolled. The dose escalation stage allowed for but did not require the enrollment of patients with the targeted *MLL* genetic alterations, MLL-r and MLL-PTD. The majority of patients had a diagnosis of acute myeloid leukemia, or AML. Other diagnoses included acute lymphoblastic leukemia, or ALL, and chronic myelomonocytic leukemia, or CMML. Based on the trial results to date, EPZ-5676 has demonstrated a favorable safety and tolerability profile. Specifically, no dose-limiting toxicities, drug-related trial discontinuations, or serious adverse events considered by the clinical site investigators to be related to EPZ-5676 have been reported.

In December 2013, two patients in the fourth dose cohort of the ongoing Phase 1 trial had objective responses. These patients had demonstrated treatment-related effects and were switched from the original intravenous administration schedule, which provided for cycles of 21 days of continuous intravenous administration followed by seven days with no treatment, 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. In addition to the two objective responses, we observed treatment effects of EPZ-5676 in some other patients with MLL-r in the trial, such as treatment-related leukocytosis, cellular 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. Consistent with the genetically defined therapeutic mechanism of action of EPZ-5676, no treatment effects were seen in the non-MLL-r patients. We have not reported results for the fifth dose cohort, which is still ongoing.

Edgar Filing: Epizyme, Inc. - Form 424B4

Based on the initial findings from the dose escalation stage of the ongoing Phase 1 trial, we began enrolling the MLL-r/MLL-PTD expansion stage in December 2013. This stage of the trial will only enroll MLL-r and MLL-PTD patients and is designed to provide an initial assessment of efficacy, or proof of concept, in these two distinct patient populations. We plan to enroll in the trial 15 to 20 MLL-r patients and 15 to 20 MLL-PTD patients. These patients will receive EPZ-5676 with uninterrupted intravenous administration. This trial has a starting dose at 90 mg/m²/day and allows for dose escalation. We plan to provide data from the Phase 1 clinical trial, including from the dose escalation stage and the MLL-r/MLL-PTD expansion stage, in 2014.

Table of Contents

We retain all U.S. rights to EPZ-5676. We have granted Celgene an exclusive license to EPZ-5676 outside of the United States. We are working with Abbott Molecular Inc., or Abbott, to develop a companion diagnostic to identify patients with the MLL-r genetic alteration for this program. We may seek to collaborate with an established diagnostic company to develop a companion diagnostic to identify patients with the MLL-PTD genetic alteration for this program.

EPZ-6438 EZH2 Inhibitor

We are developing EPZ-6438 as an orally available small molecule inhibitor of EZH2 for the treatment of non-Hodgkin lymphoma patients who have an oncogenic point mutation in EZH2 and for the treatment of certain INI1-deficient solid tumors, such as synovial sarcoma, a soft tissue sarcoma, and malignant rhabdoid tumor, a pediatric cancer. In June 2013, Eisai and we initiated a Phase 1/2 clinical trial of EPZ-6438.

The Phase 1/2 clinical trial of EPZ-6438 is being conducted in two parts. The Phase 1 clinical trial is an open label dose escalation trial that includes some patients with an EZH2 point mutation. This trial is currently enrolling patients with advanced solid tumors or with relapsed or refractory B cell lymphoma at clinical sites in France. The primary objective of the Phase 1 clinical trial is to evaluate the safety and tolerability of EPZ-6438 and to determine its maximum tolerated dose when administered as a single agent twice daily in 28-day cycles. Secondary objectives of the Phase 1 clinical trial are to:

determine the oral bioavailability, meaning the fraction of an orally administered drug that reaches systemic circulation, of EPZ-6438;

determine the potential for drug/drug interactions with EPZ-6438;

preliminarily assess activity of EPZ-6438; and

evaluate any early evidence of anti-tumor activity in patients with an EZH2 point mutation.

Subject to enrolling patients on our planned schedule, we expect to announce top-line results from the Phase 1 clinical trial in 2014.

The current design for the Phase 2 clinical trial is focused on the evaluation of EPZ-6438 for the treatment of non-Hodgkin lymphoma patients with a point mutation in EZH2. The Phase 2 clinical trial will consist exclusively of patients with an EZH2 point mutation. 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 diffuse large B-cell lymphoma of germinal-center origin, or DLBCL, or follicular lymphoma, or FL, and an EZH2 point mutation. The secondary objective of the Phase 2 clinical trial will be to assess progression-free survival, disease control rate and the clinical benefit rate of EPZ-6438 as a single agent. The Phase 2 clinical trial will be conducted in two stages. In the first stage, all patients will be dosed at the maximum tolerated dose as determined in the Phase 1 clinical trial. Depending upon the number of responses observed in the first stage of the Phase 2 part of this clinical trial, we may initiate a second stage in which patients will be randomized in a 2:1 manner to receive either EPZ-6438 or the existing standard of care treatment.

Pending our review of the data from the ongoing Phase 1 trial, we expect to initiate the Phase 2 trial in 2014 using the dose selected in the dose escalation phase. Additionally, in 2014, we plan to expand our clinical trials of EPZ-6438 to include a Phase 2 trial of EPZ-6438 for the

Edgar Filing: Epizyme, Inc. - Form 424B4

treatment of synovial sarcoma. These two Phase 2 trials are intended to provide an initial assessment of efficacy, or proof of concept, in the two genetically defined cancers that we currently seek to treat with EPZ-6438.

We have a collaboration agreement with Eisai for our EZH2 program. Under this collaboration, we have a right to opt in to a 50/50 co-development, co-commercialization and profit share arrangement in the United

Table of Contents

States prior to the initiation of a registration trial. Subject to this right, we have granted Eisai a worldwide license to our EZH2 program, including EPZ-6438. We are working with Roche Molecular Systems, Inc., or Roche, and Eisai to develop a companion diagnostic for this program.

Our Therapeutic Collaborations

We have entered into a number of strategic collaborations for our therapeutic programs and corresponding companion diagnostics. Our therapeutic collaborations have provided us with \$133.3 million in non-equity funding through September 30, 2013. With the additional \$29.0 million in milestones earned from Celgene and GSK in December 2013, our therapeutic collaborations will have provided us with a total of \$162.3 million in non-equity funding. Our therapeutic collaborations also provide us with research funding and the potential for more than \$1.0 billion of research, development, regulatory and sales-based milestone payments, as well as royalties or profit sharing on any net product sales. We have retained commercialization or co-commercialization rights in the United States for all of our programs other than the three programs in our GSK collaboration.

We have established the following three therapeutic collaborations:

Celgene. In April 2012, we entered into a collaboration and license agreement with Celgene under which we granted Celgene an exclusive license to our DOT1L program outside of the United States, including EPZ-5676. We also granted Celgene the option to license rights outside the United States to other HMT programs, excluding HMT targets covered by our two other existing therapeutic collaborations. We are eligible to receive royalties on net product sales outside of the United States.

Under the terms of the agreement, we received a \$65.0 million upfront payment and \$25.0 million from the sale of our series C preferred stock to an affiliate of Celgene, and in December 2013, we earned a \$25.0 million clinical development milestone. In addition, we are eligible to earn up to \$135.0 million in additional clinical development and regulatory milestone payments related to DOT1L and up to \$165.0 million in option exercise fees and clinical development and regulatory milestone payments related to each additional target as to which Celgene exercises its option during an initial option period ending in July 2015. Celgene has the right to extend the option period until July 2016 by making a significant option extension payment.

Eisai. In April 2011, we entered into a collaboration and license agreement with Eisai under which we 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 terms of the agreement, we have received a \$3.0 million upfront payment, \$7.0 million in preclinical research and development milestone payments, and a \$6.0 million clinical development milestone payment and recorded cash payments and accounts receivable totaling \$16.5 million for research and development services through September 30, 2013. We are eligible to receive up to \$195.0 million in additional milestone payments, comprising aggregate clinical development and regulatory milestone payments of up to \$80.0 million and sales-based milestone payments of up to \$115.0 million. We are also eligible to receive royalties on any net product sales. Eisai solely funds all research, development and commercialization costs for licensed compounds. If we exercise our opt-in right to co-develop, co-commercialize and share profits with Eisai, we are required to share ongoing U.S. development costs with Eisai, Eisai is entitled to recover a portion of past development costs as a partial reduction of future milestone payments and royalties, and the milestone payments we are eligible to receive in the future are reduced.

GSK. In January 2011, we entered into a collaboration and license agreement with GSK to discover, develop and commercialize novel small molecule HMT inhibitors directed to available targets from our product platform. Under the terms of the agreement, we granted GSK exclusive worldwide license rights to HMT inhibitors directed to three targets. Additionally, as part of the research collaboration provided for in the

Table of Contents

agreement, we agreed to provide research and development services related to the licensed targets pursuant to agreed upon research plans during a research term that extends to the earlier of January 8, 2015 or the achievement of development candidate declaration as to each selected target.

Under the agreement, we have received an upfront payment of \$20.0 million. Through September 30, 2013, we also received \$6.0 million of research funding and \$8.0 million of preclinical research and development milestone payments, and in December 2013, we earned a \$4.0 million preclinical research and development milestone. We are eligible to receive up to \$626.0 million in additional milestone payments, comprising aggregate preclinical research and development, clinical development and regulatory milestone payments of up to \$356.0 million and sales-based milestone payments of up to \$270.0 million. In addition, GSK is required to pay us royalties on worldwide net product sales.

Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the Risk Factors section of this prospectus. These risks include the following:

We have incurred significant losses since our inception. Our accumulated deficit was \$72.0 million as of September 30, 2013, representing our cumulative losses since our inception in 2007. We expect to incur losses over the next several years and may never achieve or maintain profitability.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

Our research and development is focused on the creation of personalized therapeutics for patients with genetically defined cancers, which is a rapidly evolving area of science, and the approach we are taking to discover and develop drugs is novel and may never lead to marketable products. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. We believe we are the first company to conduct a clinical trial of an HMT inhibitor.

The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, it is important to note that the objective responses observed in the dose escalation phase of our Phase 1 clinical trial of EPZ-5676 were achieved by only two of the MLL-r patients enrolled in the trial through the fourth dose cohort, were observed in an open-label setting, are not statistically significant and might not be achieved by any other patient treated with EPZ-5676. We have not yet reported results of the fifth dose cohort, which is ongoing.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

If we are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience significant delays in doing so, we may not achieve marketing approval or realize the full commercial potential of our therapeutic product candidates.

Edgar Filing: Epizyme, Inc. - Form 424B4

Our existing therapeutic collaborations are important to our business, and future collaborations may also be important to us. If we are unable to maintain any of these collaborations, or if these collaborations are not successful, our business could be adversely affected.

Table of Contents

If we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.

Our Corporate Information

We were incorporated under the laws of the state of Delaware on November 1, 2007 under the name Epizyme, Inc. Our principal executive offices are located at 400 Technology Square, Cambridge, Massachusetts 02139 and our telephone number is (617) 229-5872. Our website address is www.epizyme.com. The information contained on, or that can be accessed through, our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

Epizyme® and the Epizyme logo are our registered trademarks. The other trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

Implications of Being an Emerging Growth Company

As a company with less than \$1.0 billion in revenue during our last fiscal year, we qualify as an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from specified disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced Management's Discussion and Analysis of Financial Condition and Results of Operations disclosure;

not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;

not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;

reduced disclosure obligations regarding executive compensation; and

exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We may take advantage of these provisions through 2018 or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than \$1.0 billion in annual revenues, have more than \$700.0 million in market value of our capital stock held by non-affiliates as of specified times or issue more than \$1.0 billion of non-convertible debt over a three-year period. We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of some reduced reporting burdens

Edgar Filing: Epizyme, Inc. - Form 424B4

in this prospectus. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an emerging growth company to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Table of Contents

THE OFFERING

Common stock offered by us	3,000,000 shares
Common stock offered by the selling stockholders	1,492,679 shares
Common stock to be outstanding immediately following this offering	31,617,947 shares
Option to purchase additional shares	The underwriters have an option to purchase up to 673,901 additional shares of common stock from us as described in Underwriting.
Use of proceeds	<p>The net proceeds from the issuance of our common stock in this offering will be approximately \$82.2 million, or approximately \$100.9 million if the underwriters exercise their option to purchase additional shares in full, based on the public offering price of \$29.25 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We currently estimate that we will use the net proceeds to us from this offering, together with our existing cash and cash equivalents:</p> <ul style="list-style-type: none"> to fund a portion of our share of the global development costs for EPZ-5676, including the costs of the expansion stage of our ongoing Phase 1 clinical trial of EPZ-5676 in MLL-r adult patients and MLL-PTD adult patients and our planned Phase 1b clinical trial of EPZ-5676 in MLL-r pediatric patients; to fund a portion of our share of U.S. development costs for EPZ-6438, including the costs of our planned Phase 2 clinical trial of EPZ-6438 in non-Hodgkin lymphoma patients with EZH2 point mutations as part of our ongoing Phase 1/2 clinical trial of EPZ-6438 and our planned Phase 2 clinical trial of EPZ-6438 in synovial sarcoma patients, to the extent that we exercise our opt-in right to co-develop, co-commercialize and share profits in the United States for this product candidate; to fund research and development to build our product platform and advance our pipeline of preclinical product candidates; and for working capital and general corporate purposes. <p>We will not receive any of the proceeds from the sale of shares by the selling stockholders.</p> <p>See the Use of Proceeds section in this prospectus for a more complete description of the intended use of proceeds from this offering.</p>
Risk Factors	You should read the Risk Factors section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.

Edgar Filing: Epizyme, Inc. - Form 424B4

NASDAQ Global Market symbol

EPZM

Table of Contents

CEIC, which is affiliated with one of our collaborators and is an existing investor, has agreed to purchase 340,000 shares of our common stock in this offering at the public offering price. The underwriters will receive the same underwriting discount on any shares purchased by CEIC as they will on any other shares sold to the public in this offering.

The number of shares of our common stock to be outstanding after this offering is based on 28,494,447 shares of our common stock outstanding as of December 31, 2013, including 5,555 shares of unvested restricted stock, and reflects the exercise by certain selling stockholders of options to purchase 123,500 shares that are being sold in this offering, and excludes:

4,605,003 shares of our common stock issuable upon the exercise of stock options outstanding as of December 31, 2013 at a weighted average exercise price of \$3.16 per share; and

1,594,304 shares of our common stock available for future issuance under our equity compensation plans as of December 31, 2013.

Unless otherwise indicated, all information in this prospectus assumes no exercise by the underwriters of their option to purchase additional shares of our common stock.

In addition, unless otherwise indicated, all information in this prospectus gives effect to a one-for-three reverse stock split of our common stock that was effected on May 13, 2013.

Table of Contents**SUMMARY CONSOLIDATED FINANCIAL DATA**

The following summary consolidated financial data as of and for the years ended December 31, 2011 and 2012 has been derived from our consolidated financial statements as of and for the years ended December 31, 2011 and 2012 included elsewhere in this prospectus. The following summary consolidated statements of operations data for the nine months ended September 30, 2012 and 2013 and the balance sheet data as of September 30, 2013 have been derived from our unaudited consolidated financial statements included elsewhere in this prospectus. The summary consolidated financial data below should be read together with those consolidated financial statements as well as the Selected Consolidated Financial Data and the Management's Discussion and Analysis of Financial Condition and Results of Operations sections in this prospectus. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our interim period results are not necessarily indicative of results to be expected for a full year or any other interim period.

	Year Ended December 31, 2011	Year Ended December 31, 2012	Nine Months Ended September 30, 2012 2013	
	(in thousands, except per share data)			
Consolidated Statements of Operations Data:				
Collaboration revenue	\$ 6,944	\$ 45,222	\$ 36,327	\$ 32,165
Operating expenses:				
Research and development	22,911	38,482	27,385	41,882
General and administrative	5,000	7,508	5,175	9,664
Total operating expenses	27,911	45,990	32,560	51,546
(Loss) income from operations	(20,967)	(768)	3,767	(19,381)
Other income (expense), net	10	67	69	(32)
Income tax expense		1		
Net (loss) income	\$ (20,957)	\$ (702)	\$ 3,836	\$ (19,413)
Less: accretion of redeemable convertible preferred stock to redemption value	45	486	326	264
Less: income allocable to participating securities			3,239	
(Loss) income allocable to common stockholders - basic	(21,002)	(1,188)	271	(19,677)
Undistributed income re-allocated to common stockholders			147	
(Loss) income allocable to common stockholders - diluted	\$ (21,002)	\$ (1,188)	\$ 418	\$ (19,677)
(Loss) earnings per share allocable to common stockholders:				
Basic	\$ (14.65)	\$ (0.72)	\$ 0.17	\$ (1.49)
Diluted	\$ (14.65)	\$ (0.72)	\$ 0.16	\$ (1.49)
Weighted average shares outstanding:				
Basic	1,434	1,645	1,637	13,212
Diluted	1,434	1,645	2,641	13,212
			September 30, 2013	
			Actual	As Adjusted(1)
			(in thousands)	
Consolidated Balance Sheet Data:				
Cash and cash equivalents			\$ 139,575	\$ 222,036
Total assets			147,350	229,811

Edgar Filing: Epizyme, Inc. - Form 424B4

Deferred revenue	50,706	50,706
Total stockholders' equity	87,283	169,744

- (1) The as adjusted consolidated balance sheet data give effect to our issuance of 3,000,000 shares of common stock being sold by us at the public offering price of \$29.25 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, and the exercise by certain selling stockholders of options to purchase 123,500 shares that are being sold in this offering.

Table of Contents

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below together with all of the other information contained in this prospectus, including our financial statements and the related notes appearing at the end of this prospectus and Management's Discussion and Analysis of Financial Condition and Results of Operations, before deciding to invest in our common stock. If any of the following risks actually occur, our business, prospects, operating results and financial condition could suffer materially. In such event, the trading price of our common stock could decline and you might lose all or part of your investment.

Risks Related to Our Financial Position and Need For Additional Capital

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was \$21.0 million for the year ended December 31, 2011, \$0.7 million for the year ended December 31, 2012 and \$19.4 million for the nine months ended September 30, 2013. As of September 30, 2013, we had an accumulated deficit of \$72.0 million. To date, we have financed our operations primarily through our collaborations, our initial public offering and private placements of our preferred stock. All of our revenue to date has been collaboration revenue. We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and, beginning in 2012, clinical trials. We are still in the early stages of development of our product candidates, and we have not completed development of any drugs. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially over the next several years as we:

continue our Phase 1 clinical trial of EPZ-5676, our most advanced product candidate, for treatment of patients with mixed lineage leukemia, or MLL-r, a genetically defined subtype of the two most common forms of acute leukemia, and patients with adult acute myeloid leukemia with a partial tandem duplication in the *MLL* gene, or MLL-PTD;

continue, together with Eisai, the Phase 1/2 clinical trial of EPZ-6438, our second most advanced product candidate, for treatment of patients with a genetically defined subtype of non-Hodgkin lymphoma, and seek to treat additional indications, including INI1-deficient solid tumors, such as synovial sarcoma and malignant rhabdoid tumors;

initiate our planned Phase 1b clinical trial of EPZ-5676 in pediatric patients with MLL-r and our planned Phase 2 clinical trial of EPZ-6438 in patients with synovial sarcoma;

continue the research and development of our other product candidates;

seek to discover and develop additional product candidates;

seek regulatory approvals for any product candidates that successfully complete clinical trials;

Edgar Filing: Epizyme, Inc. - Form 424B4

ultimately establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any products for which we may obtain regulatory approval;

maintain, expand and protect our intellectual property portfolio;

hire additional clinical, quality control and scientific personnel; and

add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

To become and remain profitable, we must succeed in developing, and eventually commercializing, products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including completing preclinical testing and clinical trials of our product

Table of Contents

candidates, discovering additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the United States Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could cause you to lose all or part of your investment.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the Phase 1 clinical trial of EPZ-5676 in MLL-r and MLL-PTD adult patients and the Phase 1/2 clinical trial of EPZ-6438, subject to our opt-in right, initiate our planned Phase 1b clinical trial of EPZ-5676 in pediatric patients with MLL-r, initiate our planned Phase 2 clinical trial of EPZ-6438 in patients with synovial sarcoma, subject to our opt-in right, and continue research and development and initiate additional clinical trials of, and seek regulatory approval for, these product candidates and other product candidates. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on acceptable terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that the net proceeds to us from this offering, together with our existing cash and cash equivalents as of September 30, 2013, accounts receivable for milestones earned in December 2013 and research funding that we expect to receive under our existing collaborations, will enable us to fund our operating expenses and capital expenditure requirements until at least mid-2016, without giving effect to any potential option exercise fees or milestone payments we may receive under our collaboration agreements. Prior to such time, we expect to complete four ongoing and planned proof-of-concept trials in five genetically defined cancer patient groups: MLL-r adult patients, MLL-PTD adult patients, MLL-r pediatric patients, non-Hodgkin lymphoma patients with EZH2 point mutations and synovial sarcoma patients. We have based these expectations on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect. Our future capital requirements will depend on many factors, including:

our collaboration agreements remaining in effect and our ability to obtain research funding and achieve milestones under these agreements;

the progress and results of our ongoing Phase 1 clinical trial of EPZ-5676 and Phase 1/2 clinical trial of EPZ-6438 and our planned expansion trials of EPZ-5676 and EPZ-6438;

the number and development requirements of additional indications for EPZ-5676 and EPZ-6438 and other product candidates that we may pursue, including the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for such product candidates;

the costs, timing and outcome of regulatory review of our product candidates;

Table of Contents

the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution for any of our product candidates for which we receive marketing approval;

the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;

the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims; and

the extent to which we acquire or in-license other products and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans.

Raising additional capital may cause dilution to our stockholders, including purchasers of common stock in this offering, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings and license and development agreements with collaboration partners. We do not have any committed external source of funds other than research funding under our existing collaborations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in early 2008, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and, beginning in 2012, conducting clinical trials. All but two of our product candidates are still in preclinical development. We are conducting a Phase 1 clinical trial of EPZ-5676, our most advanced product candidate, and a Phase 1/2 clinical trial of EPZ-6438, our second most advanced product candidate, but have not completed enrollment in either of these trials. We have not yet demonstrated our ability to successfully complete any

Edgar Filing: Epizyme, Inc. - Form 424B4

clinical trials, obtain regulatory approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Table of Contents

In addition, as a young business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Risks Related to the Discovery and Development of Our Product Candidates

Our research and development is focused on the creation of personalized therapeutics for patients with genetically defined cancers, which is a rapidly evolving area of science, and the approach we are taking to discover and develop drugs is novel and may never lead to marketable products.

The discovery of personalized drug therapeutics for patients with genetically defined cancers is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. Although epigenetic regulation of gene expression plays an essential role in biological function, very few drugs premised on epigenetics have been discovered. Moreover, those drugs based on an epigenetic mechanism that have received marketing approval are in a different target class than HMTs, where our research and development is focused. Although preclinical studies suggest that genetic alterations in HMTs cause them to drive particular human cancers, to date no company has translated these biological observations into systematic drug discovery that has yielded a drug that has received marketing approval. We believe that we are the first company to conduct a clinical trial of an HMT inhibitor. Therefore, we do not know if our approach of inhibiting HMTs to treat patients with genetically defined cancers will be successful.

We are early in our development efforts and have only two product candidates in clinical trials. All of our other product candidates are still in preclinical development. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are very early in our development efforts and have only two product candidates in clinical trials. All of our other product candidates are still in preclinical development. We have invested substantially all of our efforts and financial resources in the identification and preclinical development of HMT inhibitors. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following:

successful completion of preclinical studies and clinical trials;

receipt of marketing approvals from applicable regulatory authorities;

obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;

Edgar Filing: Epizyme, Inc. - Form 424B4

making arrangements with third party manufacturers for, or establishing, commercial manufacturing capabilities;

launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;

acceptance of the products, if and when approved, by patients, the medical community and third party payors;

effectively competing with other therapies;

obtaining and maintaining healthcare coverage and adequate reimbursement;

Table of Contents

protecting our rights in our intellectual property portfolio; and

maintaining a continued acceptable safety profile of the products following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business.

We may not be successful in our efforts to use and expand our product platform to build a pipeline of product candidates.

A key element of our strategy is to use and expand our product platform to build a pipeline of small molecule inhibitors of HMT targets and progress these product candidates through clinical development for the treatment of a variety of different types of cancer. Although our research and development efforts to date have resulted in a pipeline of programs directed at specific HMT targets, we may not be able to develop product candidates that are safe and effective HMT inhibitors. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our technological approach, we will not be able to obtain product revenues in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

Two of our product candidates are in early clinical development, and our remaining product candidates are in preclinical development. The risk of failure for each of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, it is important to note that the objective responses observed in the fourth dose cohort of the dose escalation stage of our Phase 1 clinical trial of EPZ-5676 were observed in only two of the MLL-r patients enrolled in the trial through the fourth cohort, were achieved in an open-label setting, are not statistically significant, and might not be achieved by any other patient treated with EPZ-5676. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

Edgar Filing: Epizyme, Inc. - Form 424B4

we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;

clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

Table of Contents

the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;

our third party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;

regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;

the cost of clinical trials of our product candidates may be greater than we anticipate;

the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and

our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

be delayed in obtaining marketing approval for our product candidates;

not obtain marketing approval at all;

obtain approval for indications or patient populations that are not as broad as intended or desired;

obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;

be subject to additional post-marketing testing requirements; or

have the product removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in clinical testing or in obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to

commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside of the United States. In particular, because we are focused on patients with genetically defined cancers, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. For example, enrollment in our Phase 1 clinical trial of EPZ-5676 was slower than we expected because of delays in establishing trial sites. In addition, some of our competitors have ongoing clinical trials for product candidates that treat the broader patient populations within which our product candidates are being developed for the treatment of a subset of identifiable patients with genetically defined cancers, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors product candidates.

Table of Contents

Patient enrollment is affected by other factors including:

the severity of the disease under investigation;

the eligibility criteria for the trial in question;

the perceived risks and benefits of the product candidate under trial;

the efforts to facilitate timely enrollment in clinical trials;

the patient referral practices of physicians;

the ability to monitor patients adequately during and after treatment; and

the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

Following our general product development strategy, we have designed our ongoing clinical trials of EPZ-5676 and EPZ-6438, and expect to design future trials, to include some patients with the applicable genetic alteration that causes the disease with a view to assessing possible early evidence of potential therapeutic effect. If we are unable to include patients with the applicable genetic alteration, this could compromise our ability to seek participation in FDA expedited review and approval programs, including breakthrough therapy and fast track designation, or otherwise to seek to accelerate clinical development and regulatory timelines.

If serious adverse or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.

If our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. In pharmaceutical development, many compounds that initially show promise in early stage testing for treating cancer are later found to cause side effects that prevent further development of the compound.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Table of Contents

If we are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience significant delays in doing so, we may not achieve marketing approval or realize the full commercial potential of our therapeutic product candidates.

We plan to develop companion diagnostics for our therapeutic product candidates. We expect that, at least in some cases, the FDA and similar regulatory authorities outside of the United States may require the development and regulatory approval of a companion diagnostic as a condition to approving our therapeutic product candidates. We do not have experience or capabilities in developing or commercializing diagnostics and plan to rely in large part on third parties to perform these functions. For example, in December 2012, Eisai and we entered into an agreement with Roche to develop and commercialize a companion diagnostic for use with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations. In February 2013, we entered into a similar agreement with Abbott to develop and commercialize a companion diagnostic for use with EPZ-5676 in MLL-r patients. We may seek to enter into a similar agreement with a third party to create a companion diagnostic for use with EPZ-5676 in MLL-PTD patients. However, the MLL-PTD genetic alteration is not currently identified as part of standard diagnostic care, and as a result, it may be more difficult to enter into an agreement with a diagnostic company to create a companion diagnostic for this potential indication or to obtain comparable diagnostic results from those methods being used by sites enrolling MLL-PTD patients in our ongoing Phase 1 trial of EPZ-5676.

We generally expect to enter into similar agreements for our other therapeutic product candidates and possible expansion indications for EPZ-5676 and EPZ-6438. Companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside of the United States as medical devices and require separate regulatory approval prior to commercialization.

If we, or any third parties that we engage to assist us, are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience delays in doing so:

the development of our therapeutic product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;

our therapeutic product candidates may not receive marketing approval if their safe and effective use depends on a companion diagnostic; and

we may not realize the full commercial potential of any therapeutic product candidates that receive marketing approval if, among other reasons, we are unable to appropriately identify patients with the specific genetic alterations targeted by our therapeutic product candidates.

If any of these events were to occur, our business would be harmed, possibly materially.

Risks Related to the Commercialization of Our Product Candidates

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third party payors and others in the medical community necessary for commercial success.

Edgar Filing: Epizyme, Inc. - Form 424B4

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third party payors and others in the medical community. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and doctors may continue to rely on these treatments. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

the efficacy and potential advantages compared to alternative treatments;

our ability to offer our products for sale at competitive prices;

Table of Contents

the convenience and ease of administration compared to alternative treatments;

the willingness of the patient population to try new therapies and of physicians to prescribe these therapies;

the strength of marketing and distribution support;

the availability of third party coverage and adequate reimbursement;

the prevalence and severity of any side effects; and

any restrictions on the use of our products together with other medications.

If we are unable to establish sales, marketing and distribution capabilities, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales and marketing organization.

In the future, we expect to build a focused sales and marketing infrastructure to market or co-promote some of our product candidates in the United States, if and when they are approved. There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;

the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;

the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and

unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and enter into arrangements with third parties to perform these services, our product revenues and our profitability, if any, are likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will likely face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large

Table of Contents

pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Specifically, there are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. In addition, many companies are developing cancer therapeutics that work by targeting epigenetic mechanisms other than HMTs, and some companies, including Celgene and Eisai, are marketing such treatments. There are also a number of companies that we believe are developing new epigenetic treatments for cancer that target HMTs, including GSK, Novartis AG, Pfizer, Inc. and Genentech, Inc.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third party payors seeking to encourage the use of generic products. Generic products are currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third party reimbursement practices or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Table of Contents

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for any product candidates or products that we may develop;

injury to our reputation and significant negative media attention;

withdrawal of clinical trial participants;

significant costs to defend any related litigation;

substantial monetary awards to trial participants or patients;

loss of revenue;

reduced resources of our management to pursue our business strategy; and

the inability to commercialize any products that we may develop.

Table of Contents

We currently hold \$5.0 million in product liability insurance coverage in the aggregate, with a per incident limit of \$5.0 million, which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Risks Related to Our Dependence on Third Parties

Our existing therapeutic collaborations are important to our business, and future collaborations may also be important to us. If we are unable to maintain any of these collaborations, or if these collaborations are not successful, our business could be adversely affected.

We have limited capabilities for drug development and do not yet have any capability for sales, marketing or distribution. Accordingly, we have entered into therapeutic collaborations with other companies that we believe can provide such capabilities, including our collaboration and license agreements with Celgene, Eisai and GSK. These collaborations also have provided us with important funding for our development programs and product platform and we expect to receive additional funding under these collaborations in the future. Our existing therapeutic collaborations, and any future collaborations we enter into, may pose a number of risks, including the following:

collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;

collaborators may not perform their obligations as expected;

collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators strategic focus or available funding, or external factors, such as an acquisition, that may divert resources or create competing priorities;

collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products and product candidates if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

a collaborator may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;

a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

Edgar Filing: Epizyme, Inc. - Form 424B4

disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

Table of Contents

collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

collaborations may be terminated for the convenience of the collaborator, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our therapeutic collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product platform and product candidates could be delayed and we may need additional resources to develop product candidates and our product platform. All of the risks relating to product development, regulatory approval and commercialization described in this prospectus also apply to the activities of our therapeutic collaborators.

Each of our existing three therapeutic collaborations contains a restriction on our engaging in activities that are the subject of the collaboration with third parties for specified periods of time. In addition, under our collaboration agreement with Celgene, during the option period specified in the agreement, which could extend to July 2016, Celgene has the right to exercise its option to acquire a license to additional targets other than DOT1L until the effectiveness of an investigational new drug application, or IND, for an HMT inhibitor directed to such additional target. This option effectively covers all HMT targets that are not currently subject to our Eisai and GSK collaborations. As a result, our ability to enter into collaboration agreements for additional HMT targets is significantly limited until the end of the option period under the Celgene agreement and may continue to be limited after that time depending on how many targets Celgene elects to license, if any. These restrictions may have the effect of preventing us from undertaking development and other efforts that may appear to be attractive to us.

Additionally, subject to its contractual obligations to us, if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

For some of our product candidates or for some HMT targets, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for development and potential commercialization of therapeutic products. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform and our business may be materially and adversely affected.

Table of Contents

Failure of our third party collaborators to successfully commercialize companion diagnostics developed for use with our therapeutic product candidates could harm our ability to commercialize these product candidates.

We do not plan to develop companion diagnostics internally and, as a result, we are dependent on the efforts of our third party collaborators to successfully commercialize these companion diagnostics. Our collaborators:

may not perform their obligations as expected;

may encounter production difficulties that could constrain the supply of the companion diagnostics;

may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community;

may not pursue commercialization of any therapeutic product candidates that achieve regulatory approval;

may elect not to continue or renew commercialization programs based on changes in the collaborators' strategic focus or available funding, or external factors such as an acquisition, that divert resources or create competing priorities;

may not commit sufficient resources to the marketing and distribution of such product or products; and

may terminate their relationship with us.

If companion diagnostics for use with our therapeutic product candidates fail to gain market acceptance, our ability to derive revenues from sales of our therapeutic product candidates could be harmed. If our collaborators fail to commercialize these companion diagnostics, we may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with our therapeutic product candidates or do so on commercially reasonable terms, which could adversely affect and delay the development or commercialization of our therapeutic product candidates.

We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We currently rely on third party clinical research organizations, or CROs, to conduct our ongoing Phase 1 clinical trial of EPZ-5676 and our ongoing Phase 1/2 clinical trial of EPZ-6438 and do not plan to independently conduct clinical trials of our other product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, our product development activities might be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the

Edgar Filing: Epizyme, Inc. - Form 424B4

general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

Table of Contents

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities or personnel. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We also expect to rely on third party manufacturers or third party collaborators for the manufacture of commercial supply of any other product candidates for which our collaborators or we obtain marketing approval.

We may be unable to establish any agreements with third party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third party manufacturers, reliance on third party manufacturers entails additional risks, including:

reliance on the third party for regulatory compliance and quality assurance;

the possible breach of the manufacturing agreement by the third party

the possible misappropriation of our proprietary information, including our trade secrets and know-how; and

the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside of the United States. Our failure, or the failure of our third party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Edgar Filing: Epizyme, Inc. - Form 424B4

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

Table of Contents

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These changes include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Moreover, we may be subject to a third party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us,

Table of Contents

without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent rights, that are important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we may be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference or derivation

Edgar Filing: Epizyme, Inc. - Form 424B4

proceedings before the U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

Table of Contents

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

We are party to a license agreement and a research agreement that impose, and we may enter into additional licensing and funding arrangements with third parties that may impose, diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. Under our existing licensing and funding agreements, we are obligated to pay royalties on net product sales of product candidates or related technologies to the extent they are covered by the agreement. We also had diligence and development obligations under those agreements that we have satisfied. If we fail to comply with our obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product that is covered by these agreements or may face other penalties under the agreements. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Table of Contents

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside of the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and similar regulatory authorities outside of the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third party CROs to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. New cancer drugs frequently are indicated only for patient populations that have

Table of Contents

not responded to an existing therapy or have relapsed. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

We may not be able to obtain orphan drug exclusivity for our product candidates.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the EMA or the FDA from approving another marketing application for the same drug for that time period. The applicable period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

A fast track designation by the FDA may not actually lead to a faster development or regulatory review or approval process.

We intend to seek fast track designation for some of our product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is

Edgar Filing: Epizyme, Inc. - Form 424B4

eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional

Table of Contents

FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

A breakthrough therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek a breakthrough therapy designation for some of our product candidates. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs and biologics that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for accelerated approval.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. Even if we receive breakthrough therapy designation, the receipt of such designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad.

In order to market and sell our products in the European Union and many other jurisdictions, we or our third party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside of the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside of the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside of the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance

Table of Contents

of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a risk evaluation and mitigation strategy. New cancer drugs frequently are indicated only for patient populations that have not responded to an existing therapy or have relapsed. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers communications regarding off-label use, and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

restrictions on such products, manufacturers or manufacturing processes;

restrictions on the labeling or marketing of a product;

restrictions on product distribution or use;

requirements to conduct post-marketing studies or clinical trials;

warning letters;

withdrawal of the products from the market;

refusal to approve pending applications or supplements to approved applications that we submit;

recall of products;

fines, restitution or disgorgement of profits or revenues;

suspension or withdrawal of marketing approvals;

refusal to permit the import or export of our products;

product seizure; or

injunctions or the imposition of civil or criminal penalties.

Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the European Union's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Our relationships with customers and third party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with

Table of Contents

third party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;

the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or *qui tam* actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

federal law requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals, with data collection beginning in August 2013; and

analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

Table of Contents

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

More recently, in March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively, the PPACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the PPACA of importance to our potential product candidates are the following:

an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;

an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;

expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;

a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;

extension of manufacturers' Medicaid rebate liability;

expansion of eligibility criteria for Medicaid programs;

expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

new requirements to report financial arrangements with physicians and teaching hospitals;

a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and

a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Edgar Filing: Epizyme, Inc. - Form 424B4

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding.

We expect that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products.

Table of Contents

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Governments outside of the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

Edgar Filing: Epizyme, Inc. - Form 424B4

We are highly dependent on the research and development, clinical and business development expertise of Robert J. Gould, Ph.D., our Chief Executive Officer, Jason P. Rhodes, our President, Chief Financial Officer and Treasurer, Robert A. Copeland, Ph.D., our Executive Vice President and Chief Scientific Officer, and Eric E. Hedrick, M.D., our Chief Medical Officer, as well as the other principal members of our management, scientific and clinical team. Although we have entered into employment letter agreements with our executive officers, each

Table of Contents

of them may terminate their employment with us at any time. We do not maintain key person insurance for any of our executives or other employees.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies, universities and research institutions for similar personnel. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to Our Common Stock and This Offering

After this offering, our executive officers and directors and their affiliates, if they choose to act together, will continue to have the ability to control or significantly influence all matters submitted to stockholders for approval.

Our executive officers and directors and their affiliates beneficially own, in the aggregate, shares representing approximately 76.3% of our common stock before this offering. Upon the closing of this offering our executive officers and directors and their affiliates will own, in the aggregate, shares representing approximately 66.1% of our common stock, assuming no exercise by the underwriters of their option to purchase additional shares and no exercise of options outstanding as of December 31, 2013 other than the options to purchase 123,500 shares being exercised in connection with this offering. As a result, following this offering, if these stockholders were to choose to act together, they would be able to control or significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control or significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership control may:

delay, defer or prevent a change in control;

Table of Contents

entrench our management and board of directors; or

impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Provisions in our corporate charter documents, under Delaware law and in our collaboration agreements could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

establish a classified board of directors such that only one of three classes of directors is elected each year;

allow the authorized number of our directors to be changed only by resolution of our board of directors;

limit the manner in which stockholders can remove directors from our board of directors;

establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

limit who may call stockholder meetings;

authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a poison pill that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and

require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our certificate of incorporation or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Some provisions in our collaboration agreements with Celgene and Eisai could deter potential buyers of our company from proposing an acquisition and could make us a less attractive target for them. These provisions include the following:

We granted Celgene an exclusive license, for all countries other than the United States, to HMT inhibitors directed to DOT1L and an option, on a target-by-target basis, to exclusively license, for all countries of the world other than the United States, rights to HMT inhibitors directed to any other HMT targets during the option period, excluding targets covered by our two other existing therapeutic collaborations. During the option period specified in the agreement, which could extend until July 2016, Celgene has the right to exercise its option to license non-U.S. rights to additional targets other than DOT1L until the effectiveness of an IND for an HMT inhibitor directed to such additional target. This option effectively covers all HMT targets that are not currently subject to our Eisai and GSK collaborations. The decision to exercise the options for available targets is in Celgene's sole discretion.

Table of Contents

Under our collaboration agreement with Celgene, we granted to Celgene a right of first negotiation with respect to business combination transactions that we may desire to pursue with third parties during the option period, including any extension of this period. During the option period, we are required to notify Celgene if we desire to pursue a specified business combination transaction with a third party prior to negotiating terms with the third party, and after so notifying Celgene, we have agreed not to, directly or indirectly, solicit, initiate or encourage proposals from, discuss or negotiate with, or provide any information to, any third party related to the proposed transaction for a specified period from the date we first notify Celgene of such proposed transaction, or the Celgene negotiation period. If Celgene notifies us that it is interested in entering into the proposed transaction, we have agreed to negotiate in good faith with Celgene during the Celgene negotiation period. Following the Celgene negotiation period, if we have not entered into the proposed transaction with Celgene, or if Celgene does not notify us that it is interested in entering into the proposed transaction, we are free to enter into the proposed transaction with a third party for a period of 225 days following the expiration of the Celgene negotiation period, but we are obligated to re-offer the proposed transaction to Celgene if, during the option term, we propose to enter into the proposed transaction with a third party on terms that, in specified respects, are less favorable to us than the terms last offered by Celgene.

Under our collaboration agreement with Eisai, if we undergo a specified change of control event in which we are acquired by or combine with an entity with a specified competing business, or if following a change of control event we materially breach the agreement, Eisai will have the right to terminate our co-development, co-commercialization and profit sharing option and, if we have previously exercised our option, our co-development, co-commercialization and profit sharing rights.

If you purchase shares of common stock in this offering, you will suffer immediate dilution of your investment.

The price of our common stock in this offering is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering. To the extent outstanding options are exercised, you will incur further dilution. Based on the public offering price of \$29.25 per share, you will experience immediate dilution of \$23.87 per share, representing the difference between our as adjusted net tangible book value per share after giving effect to this offering and the public offering price.

An active trading market for our common stock may not be sustained following this offering.

Although our common stock is listed on The NASDAQ Global Market, an active trading market for our shares may not be sustained following this offering. If an active market for our common stock does not continue, it may be difficult for you to sell your shares, including shares you may purchase in this offering, without depressing the market price for the shares or to sell your shares at all. Any inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

The price of our common stock has been and may in the future be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock in this offering.

Our stock price has been and may in the future be volatile. From May 31, 2013 to February 4, 2014, the sale price of our common stock as reported on the NASDAQ Global Market ranged from a high of \$45.72 per share to a low of \$18.10 per share. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell the shares of

Table of Contents

common stock you acquire in this offering at or above the price paid by you in this offering. The market price for our common stock may be influenced by many factors, including:

the success of competitive products or technologies;

results of clinical trials of our product candidates or those of our competitors;

regulatory or legal developments in the United States and other countries;

developments or disputes concerning patent applications, issued patents or other proprietary rights;

the recruitment or departure of key personnel;

the level of expenses related to any of our product candidates or clinical development programs;

the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;

actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;

variations in our financial results or the financial results of companies that are perceived to be similar to us;

changes in the structure of healthcare payment systems;

market conditions in the pharmaceutical and biotechnology sectors;

general economic, industry and market conditions; and

the other factors described in this *Risk Factors* section.

We have broad discretion over the use of our cash and cash equivalents, including the net proceeds we receive in this offering and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents, including the net proceeds we receive in this offering, to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use to fund

operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

A significant portion of our total outstanding shares are eligible to be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Upon completion of this offering, based on our shares outstanding as of December 31, 2013 and reflecting the exercise by certain selling stockholders of options to purchase 123,500 shares that are being sold in this offering, we will have 31,617,947 shares of common stock outstanding, assuming no exercise of the underwriters' option to purchase additional shares of common stock. Of these shares, 20,199,673 are currently restricted as a result of securities laws or lock-up agreements entered into in connection with this offering but will be able to be sold after this offering as described in the "Shares Eligible for Future Sale" section of this prospectus. The remaining 11,418,274 shares, including any shares purchased in this offering, may be resold into the public market immediately without restriction, unless owned or purchased by our affiliates. Moreover, after this offering, holders of an aggregate of 18,462,333 shares of our common stock will have the right, subject to specified conditions, to require us to file registration statements covering their shares or, along with holders of an additional 178,331 shares of our common stock, to include their shares in registration statements that we may file for ourselves or other stockholders.

Table of Contents

As of December 31, 2013, there were 6,322,807 shares subject to outstanding options or that are otherwise issuable under our equity compensation plans. In June 2013, we registered all of these shares under the Securities Act of 1933, as amended, on a registration statement on Form S-8. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the Underwriting section of this prospectus.

We are an emerging growth company, and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company through 2018. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced Management's Discussion and Analysis of Financial Condition and Results of Operations disclosure;

not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;

not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;

reduced disclosure obligations regarding executive compensation; and

exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive, as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We will continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an emerging growth company, we will continue to incur significant legal, accounting and other expenses. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing

Edgar Filing: Epizyme, Inc. - Form 424B4

requirements of The NASDAQ Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and make some activities more time-consuming and costly.

We cannot predict or estimate the amount of additional costs we may incur to continue to operate as a public company, nor can we predict the timing of such costs. These rules and regulations are often subject to varying

Table of Contents

interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies which could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we are not required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

If securities or industry analysts do not continue to publish research, or publish inaccurate or unfavorable research, about our business, our share price and trading volume could decline.

The trading market for our common stock may be impacted, in part, by the research and reports that securities or industry analysts publish about us or our business. There can be no assurance that analysts will cover us, continue to cover us or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price may decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This prospectus contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this prospectus, 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, predict, project, target, potential, will, would, could, should, continue, and similar words are used to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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

our plans to develop and commercialize personalized therapeutics for patients with genetically defined cancers;

our ongoing and planned clinical trials, including the timing of anticipated results;

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 position;

our ability to identify additional products or product candidates with significant commercial potential that are consistent with our commercial objectives; 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, 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.

Edgar Filing: Epizyme, Inc. - Form 424B4

You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement of which this prospectus is a part 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.

This prospectus includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third party research, surveys and studies are reliable, we have not independently verified such data.

Table of Contents

USE OF PROCEEDS

We estimate that the net proceeds to us from our issuance and sale of shares of our common stock in this offering will be approximately \$82.2 million, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that our net proceeds from this offering will be approximately \$100.9 million.

We will not receive any of the proceeds from the sale of shares in this offering by the selling stockholders.

As of September 30, 2013, we had cash and cash equivalents of \$139.6 million. We currently estimate that we will use our net proceeds from this offering, together with our existing cash and cash equivalents, as follows:

approximately \$66.0 million to fund our share of the global development costs of clinical development of EPZ-5676, including the costs of the expansion stage of our ongoing Phase 1 clinical trial of EPZ-5676 in MLL-r adult patients and MLL-PTD adult patients and our planned Phase 1b clinical trial of EPZ-5676 in MLL-r pediatric patients;

if we exercise our opt-in right to co-develop, co-commercialize and share profits in the United States for EPZ-6438, approximately \$28.0 million to fund a portion of our share of U.S. development costs of EPZ-6438, including the costs of our planned Phase 2 clinical trial of EPZ-6438 in non-Hodgkin lymphoma patients with EZH2 point mutations as part of our ongoing Phase 1/2 clinical trial of EPZ-6438 and our planned Phase 2 clinical trial of EPZ-6438 in synovial sarcoma patients;

approximately \$76.0 million to fund research and development to build our product platform and advance our pipeline of preclinical product candidates; and

the remainder for working capital and general corporate purposes.

This expected use of our net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Based on our planned use of our net proceeds from this offering described above, we estimate that such funds, together with our existing cash and cash equivalents as of September 30, 2013, accounts receivable for milestones earned in December 2013 and research funding that we expect to receive under our existing collaborations, will enable us to fund our operations and capital expenditure requirements until at least mid-2016, without giving effect to any potential option exercise fees or milestone payments we may receive under our collaboration agreements. Prior to such time, we expect to complete four ongoing and planned proof-of-concept trials in five genetically defined cancer patient groups: MLL-r adult patients, MLL-PTD adult patients, MLL-r pediatric patients, non-Hodgkin lymphoma patients with EZH2 point mutations and synovial sarcoma patients.

Edgar Filing: Epizyme, Inc. - Form 424B4

Pending our use of our net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities.

Table of Contents**PRICE RANGE OF COMMON STOCK**

Our common stock began trading on The NASDAQ Global Market under the symbol EPZM on May 31, 2013. Prior to that time, there was no public market for our common stock. The following table sets forth the high and low sale prices per share of our common stock, as reported on The NASDAQ Global Market, for the periods indicated.

	High	Low
Year Ended December 31, 2013		
Second quarter (from May 31, 2013)	\$ 30.86	\$ 18.60
Third quarter	\$ 45.72	\$ 26.06
Fourth quarter	\$ 42.71	\$ 18.10
Year Ending December 31, 2014		
First quarter (through February 4, 2014)	\$ 41.23	\$ 19.76

On February 4, 2014, the last reported sale price of our common stock as reported on The NASDAQ Global Market was \$30.00 per share. As of the date of this prospectus, we had approximately 32 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. We intend to retain all of our future earnings, if any, to finance the growth and development of our business. We do not intend to pay cash dividends to our stockholders in the foreseeable future.

Table of Contents**CAPITALIZATION**

The following table sets forth our cash and cash equivalents and capitalization as of September 30, 2013:

on an actual basis; and

on an as adjusted basis to give effect to our issuance and sale of 3,000,000 shares of our common stock in this offering at the public offering price of \$29.25 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, and reflects the exercise by certain selling stockholders of options to purchase 123,500 shares that are being sold by them in this offering.

You should read this table in conjunction with the Management's Discussion and Analysis of Financial Condition and Results of Operations section of this prospectus and with our consolidated financial statements and the notes thereto included elsewhere in this prospectus.

	As of September 30, 2013	
	Actual	As Adjusted
	(in thousands)	
Cash and cash equivalents	\$ 139,575	\$ 222,036
Stockholders' equity:		
Common stock, \$0.0001 par value; 125,000,000 shares authorized, 28,418,420 shares issued and 28,408,698 shares outstanding, actual; and 125,000,000 shares authorized, 31,541,920 shares issued and 31,532,198 shares outstanding, as adjusted	\$ 3	\$ 3
Additional paid-in capital	159,290	241,751
Accumulated deficit	(72,010)	(72,010)
Total stockholders' equity	87,283	169,744
Total capitalization	\$ 87,283	\$ 169,744

The table above does not include:

4,649,530 shares of our common stock issuable upon the exercise of stock options outstanding as of September 30, 2013 at a weighted average exercise price of \$2.97 per share; and

1,625,804 shares of our common stock available for future issuance under our equity compensation plans as of September 30, 2013.

Table of Contents**DILUTION**

If you invest in our common stock in this offering, your ownership interest will be diluted immediately to the extent of the difference between the public offering price per share of our common stock and the as adjusted net tangible book value per share of our common stock after this offering.

Our historical net tangible book value as of September 30, 2013 was \$87.3 million, or \$3.07 per share of our common stock. Historical net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding as of September 30, 2013, which includes 9,722 shares of unvested restricted stock.

After giving effect to our issuance and sale of 3,000,000 shares of our common stock in this offering at the public offering price of \$29.25 per share, as well as the exercise by certain selling stockholders of options to purchase 123,500 shares that are being sold by them in this offering, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2013 would have been \$169.7 million, or \$5.38 per share. This represents an immediate increase in as adjusted net tangible book value per share of \$2.31 to existing stockholders and immediate dilution of \$23.87 in as adjusted net tangible book value per share to new investors purchasing common stock in this offering. Dilution per share to new investors is determined by subtracting as adjusted net tangible book value per share after this offering from the public offering price per share paid by new investors. The following table illustrates this dilution on a per share basis:

Public offering price per share		\$ 29.25
Historical net tangible book value per share as of September 30, 2013	\$ 3.07	
Increase in net tangible book value per share attributable to new investors	2.31	
As adjusted net tangible book value per share after this offering		5.38
Dilution per share to new investors		\$ 23.87

If the underwriters exercise their option to purchase additional shares or if any additional shares are issued in connection with the exercise of options, you will experience further dilution.

CEIC, which is affiliated with one of our collaborators and is an existing investor, has agreed to purchase 340,000 shares of our common stock in this offering at the public offering price. The underwriters will receive the same underwriting discount on any shares purchased by CEIC as they will on any other shares sold to the public in this offering.

Table of Contents**SELECTED CONSOLIDATED FINANCIAL DATA**

The following selected consolidated financial data as of and for the years ended December 31, 2011 and 2012 has been derived from our audited consolidated financial statements as of December 31, 2011 and 2012 and for the years then ended included elsewhere in this prospectus. The following selected consolidated statements of operations data for the nine months ended September 30, 2012 and 2013 and the balance sheet data as of September 30, 2013 have been derived from our unaudited consolidated financial statements included elsewhere in this prospectus. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our interim period results are not necessarily indicative of results to be expected for a full year or any other interim period.

The information set forth below should be read in conjunction with the Management's Discussion and Analysis of Financial Condition and Results of Operations section of this prospectus and with our consolidated financial statements and notes thereto included elsewhere in this prospectus.

	Year Ended December 31,		Nine Months Ended September 30,	
	2011	2012	2012	2013
	(in thousands, except per share data)			
Consolidated Statements of Operations Data:				
Collaboration revenue	\$ 6,944	\$ 45,222	\$ 36,327	\$ 32,165
Operating expenses:				
Research and development	22,911	38,482	27,385	41,882
General and administrative	5,000	7,508	5,175	9,664
Total operating expenses	27,911	45,990	32,560	51,546
(Loss) income from operations	(20,967)	(768)	3,767	(19,381)
Other income (expense), net	10	67	69	(32)
Income tax expense		1		
Net (loss) income	\$ (20,957)	\$ (702)	\$ 3,836	\$ (19,413)
Less: accretion of redeemable convertible preferred stock to redemption value	45	486	326	264
Less: income allocable to participating securities			3,239	
(Loss) income allocable to common stockholders - basic	(21,002)	(1,188)	271	(19,677)
Undistributed income re-allocated to common stockholders			147	
(Loss) income allocable to common stockholders - diluted	\$ (21,002)	\$ (1,188)	\$ 418	\$ (19,677)
(Loss) earnings per share allocable to common stockholders:				
Basic	\$ (14.65)	\$ (0.72)	\$ 0.17	\$ (1.49)
Diluted	\$ (14.65)	\$ (0.72)	\$ 0.16	\$ (1.49)
Weighted average shares outstanding:				
Basic	1,434	1,645	1,637	13,212
Diluted	1,434	1,645	2,641	13,212

As of December 31,
2011 2012 As of
September 30,

Edgar Filing: Epizyme, Inc. - Form 424B4

			2013
			(in thousands)
Consolidated Balance Sheet Data:			
Cash and cash equivalents	\$ 33,341	\$ 97,981	\$ 139,575
Total assets	37,360	103,511	147,350
Deferred revenue	29,817	69,445	50,706
Redeemable convertible preferred stock	53,747	76,156	
Total stockholders (deficit) equity	(50,644)	(51,126)	87,283

Table of Contents

**MANAGEMENT'S DISCUSSION AND ANALYSIS OF
FINANCIAL CONDITION AND RESULTS OF OPERATIONS**

You should read the following discussion and analysis of our financial condition and results of operations in conjunction with our consolidated financial statements and notes thereto included elsewhere in this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the Risk Factors section of this prospectus, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize innovative personalized therapeutics for patients with genetically defined cancers. 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. Genetic alterations can result in changes to the activity of HMTs, making them oncogenic. Our therapeutic strategy is to inhibit oncogenic HMTs to treat the underlying causes of the associated genetically defined cancers.

We are a leader in the translation of the science of epigenetics into first-in-class personalized therapeutics for patients with genetically defined cancers and currently have two HMT inhibitors in clinical development for the treatment of patients with genetically defined cancers. We believe we are the first company to conduct a clinical trial of an HMT inhibitor. We are conducting a Phase 1 clinical trial of our most advanced product candidate, EPZ-5676, an inhibitor targeting the DOT1L HMT, being developed for the treatment of acute leukemias with genetic alterations of the *MLL* gene, referred to as MLL-r and MLL-PTD. We are also conducting a Phase 1/2 clinical trial of our second most advanced product candidate, EPZ-6438, an inhibitor targeting the EZH2 HMT, being developed for the treatment of a genetically defined subtype of non-Hodgkin lymphoma and solid tumors including INI1-deficient tumors such as synovial sarcoma and malignant rhabdoid tumors, or MRT.

In 2014, we plan to have four clinical trials ongoing that are intended to assess the proof of concept of our product candidates in five genetically defined cancer patient groups:

The expansion stage of our ongoing Phase 1 clinical trial of EPZ-5676 in MLL-r adult patients and MLL-PTD adult patients;

Our planned Phase 1b clinical trial of EPZ-5676 in MLL-r pediatric patients;

Our planned Phase 2 clinical trial of EPZ-6438 in non-Hodgkin lymphoma patients with EZH2 point mutations as part of our ongoing Phase 1/2 clinical trial of EPZ-6438; and

Our planned Phase 2 clinical trial of EPZ-6438 in synovial sarcoma patients.

Edgar Filing: Epizyme, Inc. - Form 424B4

The initiation of our proof-of-concept trials of EPZ-6438 is subject to our review of the data from the Phase 1 clinical trial of EPZ-6438 that we are conducting as part of our ongoing Phase 1/2 clinical trial of EPZ-6438.

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 genetically defined cancers, both hematological and solid tumors.

We have entered into three therapeutic collaborations that have provided us with \$133.3 million in non-equity funding as of September 30, 2013. We retain commercialization or co-commercialization rights in the United States under two of these collaborations. On January 6, 2014, we announced that we had earned a \$25.0 million proof-of-concept milestone in our collaboration with Celgene Corporation and Celgene International Sàrl, collectively referred to as Celgene, in December 2013 by achieving objective responses in two MLL-r

Table of Contents

patients enrolled in the dose escalation stage of our Phase 1 trial of EPZ-5676 and a \$4.0 million milestone in our collaboration with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK, by achieving a development candidate milestone.

The clinical development plan for each of our therapeutic product candidates is directed towards patients with a particular genetically defined cancer. For many of our therapeutic product candidates, we plan to develop a companion diagnostic for the identification of patients with the genetically defined cancers that we seek to treat with our therapeutic product candidates. We plan to include patients with the particular genetically defined cancer in our clinical trials beginning in Phase 1 with a view to assessing possible early evidence of potential therapeutic effect. As we are tailoring our personalized therapeutics for discrete patient populations with genetically defined cancers, we believe that many of our products may qualify for orphan drug designation in the United States, the European Union and other regions.

In addition to the therapeutic programs listed above, we are actively working with GSK on the development of three specified HMT inhibitors that are in preclinical development and for which GSK holds commercial rights. We also have active drug discovery programs for other HMTs that we have prioritized.

We design, manage and evaluate the results of all of our research and development plans centrally and have engaged a multinational network of clinical research organizations, or CROs, to execute on specific phases of our research and development programs. By employing this network of CROs, we seek to manage multiple development programs while maintaining flexibility in our cost structure.

We commenced active operations in early 2008, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies and, beginning in 2012, conducting clinical trials. To date, we have financed our operations primarily through our initial public offering, private placements of our preferred stock and funding received from collaboration and license agreements. All of our revenue to date has been collaboration revenue. Since our inception and through September 30, 2013, we have raised an aggregate of \$291.8 million to fund our operations, of which \$133.3 million was non-equity funding through our collaboration agreements, \$82.5 million was from our initial public offering and \$76.0 million was from the sale of preferred stock. Further, in December 2013, we earned an additional \$29.0 million in milestones from Celgene and GSK.

Since inception, we have incurred significant operating losses. Our net loss was \$21.0 million for the year ended December 31, 2011, \$0.7 million for the year ended December 31, 2012 and \$19.4 million for the nine months ended September 30, 2013. As of September 30, 2013, we had an accumulated deficit of \$72.0 million. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we continue our Phase 1 clinical trial of EPZ-5676 in MLL-r and MLL-PTD adult patients; initiate our planned Phase 1b clinical trial of EPZ-5676 in pediatric patients with MLL-r; continue our Phase 1/2 clinical trial of EPZ-6438, subject to our opt-in right; initiate our planned Phase 2 clinical trial of EPZ-6438 in patients with synovial sarcoma, subject to our opt-in right; continue the research and development of our other product candidates; seek to discover and develop additional product candidates; seek regulatory approvals for our product candidates that successfully complete clinical trials; establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any products for which we may obtain regulatory approval; maintain, expand and protect our intellectual property portfolio; hire additional clinical, quality control and scientific personnel; and add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

Collaborations

Edgar Filing: Epizyme, Inc. - Form 424B4

We have entered into a number of strategic collaborations for our therapeutic programs and corresponding companion diagnostics. Our therapeutic collaborations provide us with significant funding for both our specific

Table of Contents

development programs and our product platform. They also provide us with access to the considerable scientific, development, regulatory and commercial capabilities of our collaborators. We believe that our collaborations have contributed to our ability to rapidly progress our most advanced product candidates, build our product platform and concurrently progress a wide range of development programs. We have established the following key collaborations:

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 for patients with genetically defined cancers, excluding targets covered by our two other existing therapeutic collaborations, which we refer to as the available targets.

Agreement Structure

Under the terms of the agreement, through September 30, 2013, we received a \$65.0 million upfront payment and \$25.0 million from the sale of our series C preferred stock to an affiliate of Celgene, of which \$3.0 million was considered a premium and included as collaboration arrangement consideration for a total upfront payment of \$68.0 million, and in December 2013, we earned a \$25.0 million clinical development milestone. In addition, we are eligible to earn up to \$35.0 million in clinical development milestone payments and up to \$100.0 million in regulatory milestone payments related to DOT1L. We are also eligible to earn up to \$65.0 million in payments, including a combination of clinical development milestone payments and an option exercise fee, and up to \$100.0 million in regulatory milestone payments for each available target as to which Celgene exercises its option during an initial option period ending in July 2015. Celgene has the right to extend the option period until July 2016 by making a significant option extension payment. As to DOT1L and each available target as to which Celgene may exercise its option, we retain all product rights in the United States and are eligible to receive royalties for each target at defined percentages ranging from the mid-single digits to the mid-teens on net product sales outside of the United States, subject to reductions in specified circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with pharmaceutical development, we may not receive any milestone or royalty payments from Celgene. The next potential milestone payment that we might be entitled to receive under this agreement is \$35.0 million for the initiation of a pivotal clinical trial, as defined in the agreement, for our DOT1L inhibitor.

We are obligated to conduct and solely fund research and development costs of the Phase 1 clinical trials for EPZ-5676 and through the effectiveness of the first investigational new drug application for an HMT inhibitor directed to each available target selected by Celgene, after which Celgene and we will equally co-fund global development and each party will solely fund territory-specific development costs for its territory. In the third quarter of 2013, we recorded accounts receivable of \$0.7 million related to non-Phase 1 global development costs subject to the co-funding provisions of this agreement. Global development co-funding from Celgene is recorded as a reduction to research and development expense.

Collaboration Revenue

Through September 30, 2013, in addition to amounts allocated to Celgene's purchase of shares of our series C preferred stock, we had received a total of \$68.0 million in upfront payments under the Celgene agreement, including a \$3.0 million implied premium on Celgene's purchase of our series C preferred stock. Through September 30, 2013, we have recognized \$34.7 million of collaboration revenue in the consolidated statements of operations and comprehensive (loss) income related to this agreement, including \$23.9 million in the year ended December 31, 2012 and \$20.3 million and \$10.8 million in the nine months ended September 30, 2012 and 2013, respectively. As of December 31, 2012 and

Edgar Filing: Epizyme, Inc. - Form 424B4

September 30, 2013, we had deferred revenue of \$44.1 million and \$33.3 million, respectively, related to this agreement.

Table of Contents

Eisai

In April 2011, we entered into a collaboration and license agreement with Eisai under which we granted Eisai an exclusive worldwide license to our small molecule HMT inhibitors directed to EZH2, 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. Additionally, as part of the research collaboration, we agreed to provide research and development services related to the licensed compounds through December 31, 2014.

Agreement Structure

Under the terms of the agreement, we have recorded a \$3.0 million upfront payment, \$7.0 million in preclinical research and development milestone payments, a \$6.0 million clinical development milestone payment and cash payments and accounts receivable of an aggregate of \$16.5 million for research and development services through September 30, 2013. We are eligible to earn up to \$25.0 million in additional clinical development milestone payments, up to \$55.0 million in regulatory milestone payments and up to \$115.0 million in sales-based milestone payments. We are also eligible to receive royalties at a percentage in the mid-single digits on any net product sales outside the United States and at a percentage from the mid-single digits to low double-digits on any net product sales in the United States, subject to reduction in specified circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with pharmaceutical development, we may not receive any additional milestone payments or royalty or profit share payments from Eisai. The next potential milestone payment that we might be entitled to receive under this agreement is \$10.0 million for the initiation of the Phase 2 portion of the Phase 1/2 clinical trial.

Eisai solely funds all research, development and commercialization costs for licensed compounds, except for the cost obligations that we will undertake if we exercise our opt-in right to co-develop, co-commercialize and share profits with Eisai as to licensed products in the United States. If we exercise our opt-in right as to a licensed compound, the licensed compound would become a shared product as to which Eisai's obligation to pay royalties to us as to such shared product in the United States will terminate; Eisai and we will share in net profits or losses with respect to such shared product in the United States; 25.0% of specified past development costs will become creditable by Eisai against future milestones or royalties due to us, subject to specified limitations; Eisai and we will share equally in subsequent development costs allocated to the United States; and all subsequent milestone payments that become payable by Eisai to us based on the shared product will be decreased by 50.0%.

Collaboration Revenue

Through September 30, 2013, we have recorded a total of \$32.5 million in cash and accounts receivable and have recognized \$30.5 million of collaboration revenue in the consolidated statements of operations and comprehensive (loss) income related to this agreement, including \$6.6 million and \$11.5 million in the years ended December 31, 2011 and 2012, respectively, and \$9.3 million and \$12.4 million in the nine months ended September 30, 2012 and 2013, respectively, with a \$4.0 million preclinical research and development milestone achieved and recognized as collaboration revenue in the nine months ended September 30, 2012 and a \$6.0 million clinical development milestone achieved and recognized as collaboration revenue in the nine months ended September 30, 2013. As of December 31, 2012 and September 30, 2013, we had deferred revenue of \$3.2 million and \$2.0 million, respectively, related to this agreement.

GSK

Edgar Filing: Epizyme, Inc. - Form 424B4

In January 2011, we entered into a collaboration and license agreement with GSK to discover, develop and commercialize novel small molecule HMT inhibitors directed to available targets from our product platform. Under the terms of the agreement, we granted GSK exclusive worldwide license rights to HMT inhibitors directed to three targets. Additionally, as part of the research collaboration provided for in the agreement, we agreed to provide research and development services related to the licensed targets pursuant to agreed upon research plans during a research term that ends January 8, 2015.

Table of Contents*Agreement Structure*

Under the agreement, we had received a \$20.0 million upfront payment, \$8.0 million in preclinical research and development milestone payments and \$6.0 million of fixed research funding through September 30, 2013 and in December 2013, we earned a \$4.0 million preclinical research and development milestone. We are eligible to receive up to \$17.0 million in additional preclinical research and development milestone payments, up to \$99.0 million in clinical development milestone payments, up to \$240.0 million in regulatory milestone payments and up to \$270.0 million in sales-based milestone payments. In addition, GSK is required to pay us royalties at percentages from the mid-single digits to the low double-digits, on a licensed product-by-licensed product basis, on worldwide net product sales, subject to reductions in specified circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with pharmaceutical development, we may not receive any additional milestone payments or royalty payments from GSK. The next potential milestone payment that we might be entitled to receive under this agreement is a preclinical research and development milestone. However, due to the varying stages of development of each licensed target, we are not able to determine the next milestone that might be achieved, if any.

For each selected target in the collaboration, we are primarily responsible for research until the selection of the development candidate, and GSK is solely responsible for subsequent development and commercialization. GSK provided a fixed amount of research funding during the second and third years of the research term and is obligated to provide research funding equal to 100.0% of research and development costs, subject to specified limitations, for any research activities we conduct in the fourth year of the research term.

Collaboration Revenue

Through September 30, 2013, we had received a total of \$34.0 million in payments under the GSK agreement and have recognized \$18.7 million of collaboration revenue in the consolidated statements of operations and comprehensive (loss) income related to this agreement, including \$9.7 million in the year ended December 31, 2012 and \$6.7 million and \$9.0 million in the nine months ended September 30, 2012 and 2013, respectively, with \$4.0 million in preclinical research and development milestones achieved and recognized as collaboration revenue in the nine months ended September 30, 2012. As of December 31, 2012 and September 30, 2013, we had deferred revenue of \$22.0 million and \$15.3 million, respectively, related to this agreement.

Companion Diagnostic Collaborations. In collaboration with established diagnostic companies, we are developing companion diagnostics to identify patients who have the specific genetically defined cancer targeted by our product candidate. In December 2012, Eisai and we entered into an agreement with Roche Molecular Systems, Inc., or Roche, to develop and to commercialize a companion diagnostic for use with our EPZ-6438 product candidate for non-Hodgkin lymphoma patients with EZH2 point mutations. The development costs under the agreement with Roche will be the responsibility of Eisai until such time as we may exercise our opt-in right under the collaboration with Eisai. If we exercise our opt-in right under the Eisai agreement, the costs under the Roche agreement will be shared by us and Eisai as determined under the profit share and co-commercialization components of the Eisai collaboration agreement.

In February 2013, we entered into an agreement with Abbott under which we agreed to fund Abbott's development of a companion diagnostic to identify patients with the MLL-r genetic alteration targeted by EPZ-5676. Under the terms of the agreement, we paid Abbott an upfront payment of \$0.9 million upon the execution of the agreement, are obligated to make aggregate milestone-based development payments of up to \$6.0 million and are obligated to reimburse Abbott specified costs expected to be incurred in connection with Abbott conducting clinical trials to obtain the necessary regulatory approvals for the companion diagnostic which are not to exceed \$0.9 million unless agreed to in advance.

Table of Contents

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of financial condition and results of operations is based upon our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States of America. The preparation of these consolidated financial statements requires us to make estimates, judgments and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities as of the date of the balance sheets and the reported amounts of collaboration revenue and expenses during the reporting periods. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances at the time such estimates are made. Actual results and outcomes may differ materially from our estimates, judgments and assumptions. We periodically review our estimates in light of changes in circumstances, facts and experience. The effects of material revisions in estimates are reflected in the consolidated financial statements prospectively from the date of the change in estimate.

We define our critical accounting policies as those accounting principles generally accepted in the United States of America that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations as well as the specific manner in which we apply those principles. We believe the critical accounting policies used in the preparation of our financial statements which require significant estimates and judgments are as follows:

Revenue Recognition

We recognize revenue when all of the following criteria are met: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; our price to the customer is fixed or determinable and collectability is reasonably assured. The terms of our collaboration and license agreements typically contain multiple deliverables, which may include licenses, or options to obtain licenses, to compounds directed to specific HMT targets, referred to as exclusive licenses, as well as research and development activities to be performed by us on behalf of the collaboration partner related to the licensed HMT targets. Payments that we may receive under these agreements include non-refundable license fees, option fees, extension fees, payments for research activities, payments based upon the achievement of specified milestones and royalties on any resulting net product sales.

Multiple-Element Revenue Arrangements. Our collaborations primarily represent multiple-element revenue arrangements. To account for these transactions, we determine the elements, or deliverables, included in the arrangement and allocate arrangement consideration to the various elements based on each element's relative selling price. The identification of individual elements in a multiple-element arrangement and the estimation of the selling price of each element involve significant judgment, including consideration as to whether each delivered element has standalone value to the collaborator. We determine the estimated selling price for deliverables within each agreement using vendor-specific objective evidence of selling price, if available, or third party evidence of selling price if vendor-specific objective evidence is not available, or our best estimate of selling price, if neither vendor-specific objective evidence nor third party evidence is available. Determining the best estimate of selling price for a deliverable requires significant judgment. We typically use our best estimate of selling price to estimate the selling price for licenses to our proprietary technology, since we do not have vendor-specific objective evidence or third party evidence of selling price for these deliverables. In those circumstances where we apply our best estimate of selling price to determine the estimated selling price of a license to our proprietary technology, we consider market conditions as well as entity-specific factors, including those factors contemplated in negotiating the agreements as well as internally developed estimates that include assumptions related to the market opportunity, estimated development costs, probability of success and the time needed to commercialize a product candidate pursuant to the license. In validating our best estimate of selling price, we evaluate whether changes in the key assumptions used to determine our best estimate of selling price will have a significant effect on the allocation of arrangement consideration between deliverables. We recognize consideration allocated to an individual element when all other revenue recognition criteria are met for that element.

Table of Contents

Our multiple-element revenue arrangements generally include the following:

Exclusive Licenses. The deliverables under our collaboration agreements generally include exclusive licenses to discover, develop, manufacture and commercialize compounds with respect to one or more specified HMT targets. To account for this element of the arrangement, we evaluate whether the exclusive license has standalone value from the undelivered elements to the collaboration partner based on the consideration of the relevant facts and circumstances of each arrangement, including the research and development capabilities of the collaboration partner and other market participants. Arrangement consideration allocated to licenses may be recognized upon delivery of the license if facts and circumstances indicate that the license has standalone value apart from the undelivered elements, which generally include research and development services. Arrangement consideration allocated to licenses is deferred if facts and circumstances indicate that the delivered license does not have standalone value from the undelivered elements.

We have determined that some of our exclusive licenses lack standalone value apart from the related research and development services, and in those circumstances we recognize collaboration revenue from non-refundable exclusive license fees on a straight-line basis over the contracted or estimated period of performance, which is generally the period over which the research and development services are to be provided.

Research and Development Services. The deliverables under our collaboration and license agreements generally include deliverables related to research and development services to be performed on behalf of the collaboration partner. As the provision of research and development services is a part of our central operations, when we are principally responsible for the performance of these services under the agreements, we recognize revenue on a gross basis for research and development services as those services are performed.

Option Arrangements. Our arrangements may provide a collaborator with the right to select a target for licensing either at the inception of the arrangement or within an initial pre-defined selection period, which may, in certain cases, include the right of the collaborator to extend the selection period. Under these agreements, fees may be due to us at the inception of the arrangement as an upfront fee or payment, upon the exercise of an option to acquire a license or upon extending the selection period as an extension fee or payment.

The accounting for option arrangements is dependent on the nature of the options granted to the collaboration partner. Options are considered substantive if, at the inception of the arrangement, we are at risk as to whether the collaboration partner will choose to exercise the options to secure exclusive licenses. Factors that are considered in evaluating whether options are substantive include the overall objective of the arrangement, the benefit the collaborator might obtain from the arrangement without exercising the options, the cost to exercise the options relative to the total upfront consideration and the additional financial commitments or economic penalties imposed on the collaborator as a result of exercising the options. For arrangements under which the option to secure licenses is considered substantive, we do not consider the licenses to be deliverables at the inception of the arrangement. For arrangements where the option to secure licenses is not considered substantive, we consider the license to be a deliverable at the inception of the arrangement and, upon delivery of the license, would apply the multiple-element revenue arrangement criteria to the license and any other deliverables to determine the appropriate revenue recognition. None of the options to secure exclusive licenses included in our collaborative arrangements have been determined to be substantive.

Milestone Revenue. Our collaboration and license agreements generally include contingent milestone payments related to specified preclinical research and development milestones, clinical development milestones, regulatory milestones and sales-based milestones. Preclinical research and development milestones are typically payable upon the selection of a compound candidate for the next stage of research and development. Clinical development milestones are typically payable when a product candidate initiates or advances in clinical trial phases or achieves defined clinical events, such as proof-of-concept. Regulatory milestones are typically payable

Table of Contents

upon submission for marketing approval with regulatory authorities, upon receipt of actual marketing approvals for a compound or for additional indications or upon the first commercial sale. Sales-based milestones are typically payable when annual sales reach specified levels.

At the inception of each arrangement that includes milestone payments, we evaluate whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether:

the consideration is commensurate with either the entity's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone;

the consideration relates solely to past performance; and

the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement.

We evaluate factors such as the scientific, regulatory, commercial and other risks that must be overcome to achieve the respective milestone, the level of effort and investment required to achieve the respective milestone and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement in making this assessment.

Non-refundable preclinical research and development, clinical development and regulatory milestones that are expected to be achieved as a result of our efforts during the period of our performance obligations under the collaboration and license agreements are generally considered to be substantive and are recognized as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. If not considered to be substantive, revenue from achievement of milestones is initially deferred and recognized over the remaining term of our performance obligations. Milestones that are not considered substantive because we do not contribute effort to their achievement are recognized as revenue upon achievement, assuming all other revenue recognition criteria are met, as there are no undelivered elements remaining and no continuing performance obligations on our part.

Stock-Based Compensation

We issue stock-based compensation awards to employees, including stock options and restricted stock, and offer an employee stock purchase plan. We measure stock-based compensation expense related to these awards based on the fair value of the award on the date of grant and recognize stock-based compensation expense, less estimated forfeitures, on a straight-line basis over the requisite service period of the awards, which generally equals the vesting period. We have selected the Black-Scholes option pricing model to determine the fair value of stock option awards which requires the input of various assumptions that require management to apply judgment and make assumptions and estimates, including:

the expected life of the stock option award, which we calculate using the simplified method as we have insufficient historical information regarding our stock options to provide a basis for estimate;

the expected volatility of the underlying common stock, which we estimate based on the historical volatility of a peer group of comparable publicly traded companies with product candidates in similar stages of development; and

Edgar Filing: Epizyme, Inc. - Form 424B4

historically, the fair value of our common stock determined on the date of grant.

Compensation expense for restricted stock is based on the estimated fair value of our common stock on the date of grant. Our assumptions may differ from those used in prior periods, and changes in the assumptions may have a significant impact on the fair value of future equity awards, which could have a material impact on our consolidated financial statements. We grant stock options with exercise prices equal to the estimated fair value of our common stock on the date of grant.

Table of Contents

The amount of stock-based compensation expense recognized during a period is based on the value of the portion of the awards that are ultimately expected to vest. We estimate forfeitures for employee grants at the time of grant, and revise the estimates, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Ultimately, the actual expense recognized over the vesting period will only represent those options that vest.

The following table summarizes by grant date the number of shares of common stock underlying stock options granted from January 1, 2012 through May 30, 2013, the last day prior to the commencement of trading of our common stock on the NASDAQ Global Market, as well as the associated per share exercise price, the estimated fair value per share of our common stock on the grant date and, for awards granted in January, February and April 2013, the retrospective fair value per share on the grant date:

Grant date	Number of common shares underlying options granted	Option exercise price	Estimated fair value per common share on grant date	Retrospective fair value per share on grant date
June 7, 2012	340,164	2.19	2.19	n/a
October 3, 2012	346,469	2.19	2.19	n/a
December 13, 2012	79,664	3.54	3.54	n/a
January 25, 2013	1,212,983	3.54	3.54	\$ 5.13(1)
February 14, 2013	13,333	3.54	3.54	5.13(1)
April 18, 2013	20,999	6.30	6.30	11.73(1)

- (1) The fair value of common stock at the grant date was adjusted in connection with a retrospective fair value assessment for financial reporting purposes, as described below.

Since our initial public offering, the exercise price per share of all option grants has been set at the closing price of our common stock on The NASDAQ Global Market on the applicable date of grant, which we believe represents the fair value of our common stock.

Determination of the Fair Value of Common Stock on Grant Dates. Prior to our initial public offering, we were a private company with no active public market for our common stock. Therefore, we periodically determined for financial reporting purposes the estimated per share fair value of our common stock at various dates using contemporaneous valuations performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, also known as the Practice Aid. We performed these contemporaneous valuations as of April 30, 2012, November 30, 2012, February 28, 2013, April 18, 2013 and April 30, 2013. In conducting the contemporaneous valuations, we considered all objective and subjective factors that we believed to be relevant for each valuation conducted, including our best estimate of our business condition, prospects and operating performance at each valuation date. Within the contemporaneous valuations performed, a range of factors, assumptions and methodologies were used. The significant factors included:

the prices of our preferred stock sold to or exchanged between outside investors in arm's length transactions, and the rights, preferences and privileges of our preferred stock as compared to those of our common stock, including the liquidation preferences of our preferred stock;

our results of operations, financial position and the status of research and development efforts;

Edgar Filing: Epizyme, Inc. - Form 424B4

the composition of, and changes to, our management team and board of directors;

the lack of liquidity of our common stock as a private company;

our stage of development and business strategy and the material risks related to our business and industry;

the achievement of enterprise milestones, including entering into collaboration and license agreements;

Table of Contents

the valuation of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed mergers and acquisitions of peer companies;

any external market conditions affecting the life sciences and biotechnology industry sectors;

the likelihood of achieving a liquidity event for the holders of our common stock and stock options, such as an initial public offering, or IPO, or a sale of our company, given prevailing market conditions;

the state of the IPO market for similarly situated privately held biotechnology companies; and

any recent contemporaneous valuations prepared in accordance with methodologies outlined in the Practice Aid.

The dates of our contemporaneous valuations did not always coincide with the dates of our stock-based compensation grants. In determining the exercise prices of the options set forth in the table above, our board of directors considered, among other things, the most recent contemporaneous valuations of our common stock and our assessment of additional objective and subjective factors we believed were relevant as of the grant date. The additional factors considered when determining any changes in fair value between the most recent contemporaneous valuation and the grant dates included, when available, the prices paid in recent transactions involving our equity securities, as well as our stage of development, our operating and financial performance and current business conditions.

There were significant judgments and estimates inherent in the determination of fair value of our common stock, including the contemporaneous valuations. These judgments and estimates included assumptions regarding our future operating performance, the time to completing an IPO or other liquidity event and the determinations of the appropriate valuation methods. If we had made different assumptions, our stock-based compensation expense, net loss and net loss per common share could have been significantly different.

Since our initial public offering, we have determined the fair value of our common stock based on the closing price of our common stock on The NASDAQ Global Market on the applicable date of such grant.

Common Stock Valuation Methodologies. Prior to our initial public offering, our contemporaneous valuations were prepared in accordance with the guidelines in the Practice Aid, which prescribes several valuation approaches for setting the value of an enterprise, such as the cost, market and income approaches, and various methodologies for allocating the value of an enterprise to its common stock. We generally used the market approach, in particular the guideline company and precedent transaction methodologies, based on inputs from comparable public companies' equity valuations and comparable acquisition transactions, to estimate the enterprise value of our company.

Methods Used to Allocate Our Enterprise Value to Classes of Securities. In accordance with the Practice Aid, we considered the various methods for allocating the enterprise value across our classes and series of capital stock to determine the fair value of our common stock at each valuation date. The methods we considered consisted of the following:

Current Value Method. Under the current value method, once the fair value of the enterprise is established, the value is allocated to the various series of preferred and common stock based on their respective seniority, liquidation preferences or conversion values, whichever is greatest.

Edgar Filing: Epizyme, Inc. - Form 424B4

Option Pricing Method. Under the option pricing method, shares are valued by creating a series of call options with exercise prices based on the liquidation preferences and conversion terms of each equity class. The values of the preferred and common stock are inferred by analyzing these options.

Probability-Weighted Expected Return Method, or PWERM. The PWERM is a scenario-based analysis that estimates the value per share based on the probability-weighted present value of expected future investment returns, considering each of the possible outcomes available to us, as well as the economic and control rights of each share class.

Table of Contents

For each of the contemporaneous valuations described below, we used the PWERM to determine the estimated fair value of our common stock.

April 2012 Valuation

In April 2012, we entered into our collaboration with Celgene and, in light of the significance of that transaction, we deemed it appropriate to obtain a contemporaneous valuation of our common stock as of April 30, 2012. This valuation contemplated the collaboration with Celgene as well as the likelihood of achieving effectiveness of our investigational new drug application, or IND, for EPZ-5676, which later occurred in July 2012. The April 2012 valuation utilized the PWERM to determine the equity value of the company, using the following probability-weighted scenarios:

Exit Scenario	Weighting
Merger or Sale	20%
IPO	30
Liquidation	10
No Value to Common	40
Total	100%

For each future exit scenario, the rights and preferences of each class of our capital stock were considered in order to determine the appropriate allocation of our future exit value to the shares of common stock. In the merger or sale scenario, we contemplated estimated high and low sale prices resulting from possible future outcomes of research and development for our two most advanced product candidates, EPZ-5676 and EPZ-6438, with merger or sale exit values estimated based on comparable sales of guideline companies. In this valuation, we incorporated an IPO scenario, as this exit was then considered a possibility based on our stage of development. In the IPO scenario, we contemplated an estimated future public offering of our common stock, with the IPO exit value estimated based on comparable transactions of guideline companies. In the liquidation scenario, we contemplated both early and late liquidations resulting from possible future outcomes of our efforts to raise additional funding, with liquidation exit values estimated based on projected remaining assets at the time of liquidation. In the no value to common scenario, we contemplated circumstances resulting from a possible future inability to raise additional funding, with the no value to common exit value estimated based on projections that holders of our preferred stock would recover their original investment through a sale of the company's assets but no value remained available for common stock holders. At the time of the April 2012 valuation, we considered the possibility of a potential IPO scenario. However, there continued to be a reasonable likelihood that proof-of-concept would not be achieved for either EPZ-5676 or EPZ-6438 or that we would be unable to raise additional capital in order to sustain operations. Accordingly, we assigned a 40% probability to the no value to common scenario. For this valuation, we discounted our common stock value under each of the scenarios using an assumed cost of capital of 19% and applied a discount for lack of marketability, or DLOM, of 40%. The cost of capital utilized for the PWERM scenarios is a risk-adjusted cost of capital, indicating that at the time of an exit event, the risk associated with a company is anticipated to decrease commensurate with its progress toward commercialization. The cost of capital of 19% was calculated based on an industry weighted average cost of capital for newly public biotech companies based on publicly available information. The computations used a size-adjusted capital asset pricing model, or CAPM, assuming a risk-free rate of 4.0%, a market risk premium of 5.2% and a size adjustment of 3.1%. Betas were sourced by selecting all companies in the industry segment with a market capitalization less than or equal to \$250.0 million. We concluded that our common stock had a fair value of \$2.19 per share as of April 30, 2012.

Stock Option Grants in June 2012 and October 2012

Our board of directors granted options to purchase common stock on June 7, 2012 and October 3, 2012, with each option having an exercise price of \$2.19 per share. In establishing this exercise price, our board of

Table of Contents

directors considered input from management, including the valuation we conducted of our common stock as of April 30, 2012, as well as the objective and subjective factors outlined above. At each such date, our board of directors considered the events and circumstances most likely to affect the value of our common stock that occurred between April 2012 and the grant date, including achieving effectiveness of our IND application for EPZ-5676 in July 2012. Our board of directors determined that, other than achieving IND effectiveness for EPZ-5676, which had been contemplated in the assumptions used for the April 2012 valuation, there were no other events that occurred between April 2012 and October 2012 that were indicative of a significant change in the fair value of our common stock since April 2012. Moreover, between the April 2012 valuation and the date of the October 2012 awards, we did not believe that an IPO had become more likely. This belief was based in part on the assessment that we should not pursue an IPO until we had commenced our Phase 1 clinical trial of EPZ-5676 and obtained data for an MLL-r patient treated in the EPZ-5676 clinical trial. In addition, during the period from April 2012 to the date of the October 2012 awards, overall market conditions, and particularly the market for biopharmaceutical initial public offerings, were not promising. Based on these factors, our board of directors determined that the fair value of our common stock at June 7, 2012 and October 3, 2012 was \$2.19 per share.

November 2012 Valuation

In November 2012, we enrolled our first patient in our Phase 1 clinical trial of EPZ-5676, and we filed a clinical trial application, or CTA, with respect to a clinical trial for EPZ-6438. We determined that these events demonstrated our ability to continue to execute successfully against our development plans and, therefore, had increased the possibility of an IPO scenario. Accordingly, we deemed it appropriate to obtain a contemporaneous valuation of our common stock as of November 30, 2012. The November 2012 valuation utilized the same methodology as was used in the prior valuations, except that the probability-weighted scenarios were updated as follows:

Exit Scenario	Weighting
Merger or Sale	10%
IPO Early (mid-2013)	30
IPO Late (mid-2014)	15
Liquidation	10
No Value to Common	35
Total	100%

In this valuation, we increased the probability assigned to an IPO scenario, as this exit scenario was becoming more likely based on our stage of development and our execution against our plan. In addition, we bifurcated the IPO scenario into an early IPO scenario, which assumed an IPO in mid-2013, and a late IPO scenario, which assumed an IPO in mid-2014. Based on the continued execution of our clinical and preclinical development plans for EPZ-5676 and EPZ-6438, we reduced the probability assigned to the no value to common scenario from 40% to 35%. For this valuation, we discounted the common stock value under each of the scenarios using an assumed cost of capital of 19% and a DLOM of 30%. We changed the DLOM from 40% to 30% because we believed that we were moving closer to a potential exit event. Using this methodology, we concluded that our common stock had a fair value of \$3.54 per share as of November 30, 2012.

Stock Option Grants in December 2012

Our board of directors granted options to purchase common stock on December 13, 2012, with each option having an exercise price of \$3.54 per share. In establishing this exercise price, our board of directors considered input from management, including the valuation we conducted of our common stock as of November 30, 2012, as well as the objective and subjective factors outlined above. Our board of directors considered the events and circumstances that occurred between November 30, 2012 and December 13, 2012 that would likely impact the previously determined exit scenarios. Our board of directors recognized that the enrollment of the first patient in

Table of Contents

our Phase 1 clinical trial of EPZ-5676 and the filing of the CTA with respect to a clinical trial of EPZ-6438 demonstrated our ability to continue to execute successfully against our development plans, which increased the possibility of an IPO, as reflected in the November 2012 valuation. However, our board of directors also considered our expectations that we would not obtain data for an MLL-r patient treated in the EPZ-5676 clinical trial until 2013 and that the CTA for EPZ-6438 would not be effective until 2013, as well as overall conditions in the capital markets and the market for biopharmaceutical initial public offerings in December 2012, including the generally depressed stock prices for biopharmaceutical companies and the valuations for biopharmaceutical companies that had recently gone public. In particular, the NASDAQ Biotechnology Index declined by 5% from the beginning of October 2012 through the end of November 2012. Although the board of directors considered in December 2012 whether it was appropriate for us to commence the process for a confidential submission of a draft registration statement for an IPO in December 2012, in light of the market conditions and the potential valuation of our company absent patient data supporting our scientific hypothesis for HMT inhibitors, the board of directors determined that it was too early to pursue an IPO. Our board of directors also determined that no events had occurred between November 2012 and December 13, 2012 that were indicative of a significant change in the fair value of our common stock since November 30, 2012. Therefore, our board of directors determined that the fair value of our common stock as of December 13, 2012 was \$3.54 per share.

Stock Option Grants in January 2013 and February 2013

Our board of directors granted options to purchase common stock on January 25, 2013 and February 14, 2013, with each option having an exercise price of \$3.54 per share.

Retrospective Valuation January 2013 and February 2013

In late January 2013, based on the board of directors' review of overall market conditions, the improving market for biopharmaceutical initial public offerings and the progress of the EPZ-5676 clinical trial, including the expectation that data with respect to the first MLL-r patient dosed in our clinical trial of EPZ-5676 would become available in the near term, our board of directors determined that a significant shift was occurring with respect to the valuation we could achieve in an IPO and authorized the preparation and submission of a confidential draft registration statement for an IPO. Additionally, in January 2013 our CTA for a Phase 1/2 clinical trial in France for EPZ-6438 became effective. We selected underwriters and held an organizational meeting in mid-February 2013. In February 2013 we continued the dose escalation phase of our Phase 1 clinical trial for EPZ-5676 and received data for the MLL-r patient dosed in this clinical trial which indicated that we were closer to achieving proof-of-concept for one of our HMT inhibitors. We believe these events increased the probability of an early IPO scenario and therefore we performed a valuation for our common stock as of February 28, 2013. The February 2013 retrospective valuation utilized the PWERM to determine the equity value of the company, using the following probability-weighted scenarios:

Exit Scenario	Weighting
Merger or Sale	10%
IPO Early (mid-2013)	50
IPO Late (mid-2014)	10
Liquidation	5
No Value to Common	25
Total	100%

In this valuation, we increased the probability of an early IPO to 50%, reflecting our progress in preparing a confidential draft registration statement, the advancement of our Phase 1 clinical trial for EPZ-5676 and our other development programs and improving market conditions. Based on the continued execution of our clinical and preclinical development plans for EPZ-5676 and EPZ-6438, we reduced the probability

assigned to the no value

Table of Contents

to common scenario from 35% to 25%. For this valuation, we discounted the common stock using an assumed cost of capital of 19% and a DLOM of 20%. We reduced the DLOM from 30% to 20% because we believed that we were moving closer to a potential exit event. However, at the time this retrospective valuation was undertaken, our underwriters had not yet communicated to us a definitive proposed valuation and our board of directors had not authorized the filing of a public registration statement. Based on these factors, we concluded that our common stock had a fair value of \$5.13 per share as of February 28, 2013. For financial reporting purposes, this value has been applied retrospectively to our January 25, 2013 and February 14, 2013 option grants.

April 2013 Valuation

Overall market conditions and the market for biopharmaceutical initial public offerings continued to improve during 2013 and on March 22, 2013, we submitted to the SEC a confidential draft registration statement for an IPO. We believe that this submission increased the probability of an early IPO scenario, and therefore we performed a valuation of our common stock as of April 18, 2013. The April 2013 valuation utilized the same methodology as was used in the prior valuations, except that the probability-weighted scenarios were updated as follows:

Exit Scenario	Weighting
Merger or Sale	10%
IPO Early (mid-2013)	65
IPO Late (mid-2014)	5
Liquidation	5
No Value to Common	15
Total	100%

In this valuation, we increased the probability of an early IPO to 65%, reflecting the submission of the confidential draft registration statement and the continuing improvement in overall market conditions and the market for biopharmaceutical initial public offerings. We reduced the probability assigned to the no value to common scenario from 25% to 15% as the likelihood of an early IPO was increasing. For this valuation, we discounted the common stock value under each of the scenarios using an assumed cost of capital of 19% and a DLOM of 15%. We reduced the DLOM from 20% to 15% because we believed that we were moving closer to a potential exit event. Additionally, at the time this valuation was undertaken, our underwriters had not yet communicated to us a definitive proposed valuation. Using this methodology, we concluded that our common stock had a fair value of \$6.30 per share as of April 18, 2013.

Stock Option Grants in April 2013

Our board of directors granted options to purchase common stock on April 18, 2013, with each option having an exercise price of \$6.30 per share. In establishing this exercise price, our board of directors considered input from management, including the valuation we conducted of our common stock as of April 18, 2013. Based on these factors, our board of directors determined that the fair value of our common stock as of April 18, 2013 was \$6.30 per share.

Retrospective Valuation April 2013

Edgar Filing: Epizyme, Inc. - Form 424B4

In late April 2013, after the filing of a public registration statement, our underwriters provided us with their perceptions of increased optimism regarding overall market conditions and the market for initial public offerings, particularly for biopharmaceutical companies, and reiterated their prior expectation that we would be able to complete our initial public offering by the end of the second quarter of 2013. For example, market data indicated that in the first four months of 2013, the Nasdaq Biotechnology Index increased approximately 26% and

Table of Contents

increased over 15% between March 1, 2013 and April 30, 2013. As a result, since our organizational meeting for our initial public offering on February 19, 2013, valuations for companies comparable to us had increased significantly. Additionally, our underwriters confirmed that the market for oncology-focused biopharmaceutical companies was particularly strong. In light of this information, we accelerated preparations for a road show. Therefore, we performed a valuation of our common stock as of April 30, 2013. The April 2013 retrospective valuation utilized the PWERM to determine the equity value of the company, using the following probability-weighted scenarios:

Exit Scenario	Weighting
IPO Early (mid-2013)	90%
No Value to Common	10
Total	100%

In this valuation, we increased the probability of an early IPO to 90% and correspondingly reduced the probability of the no value to common scenario to 10%, reflecting current market conditions and our progress in preparing to launch a road show for this offering. For this valuation, we discounted the common stock using an assumed cost of capital of 19% and a DLOM of 5%. We reduced the DLOM from 15% to 5% because we believed that we were moving closer to the launch of this offering, which could lead to a potential exit event. Based on these factors, we concluded that our common stock had a fair value of \$11.73 per share as of April 30, 2013. For financial reporting purposes, this value has been applied retrospectively to our April 18, 2013 option grants.

Recent Accounting Pronouncements

In July 2013, the Financial Accounting Standards Board issued Accounting Standards Update, or ASU, No. 2013-11, *Presentation of an Unrecognized Tax Benefit When a Net Operating Loss Carryforward, a Similar Tax Loss, or a Tax Credit Carryforward Exists*. ASU 2013-11 amends Accounting Standards Codification, or ASC, 740, *Income Taxes*, by providing guidance on the financial statement presentation of an unrecognized benefit when a net operating loss carryforward, a similar tax loss, or a tax credit carryforward exists. The ASU does not affect the recognition or measurement of uncertain tax positions under ASC 740. ASU 2013-11 will be effective for us for interim and annual periods beginning after December 15, 2013, with early adoption permitted. We do not expect the adoption of this ASU to have any impact on our consolidated financial statements.

Financial Overview**Collaboration Revenue**

Our revenue consists of collaboration revenue, including amounts recognized related to upfront payments for licenses or options to obtain licenses in the future, research and development funding and milestone payments earned under collaboration and license agreements with our collaboration partners, including Celgene, Eisai and GSK.

Research and Development

Edgar Filing: Epizyme, Inc. - Form 424B4

Research and development expenses consist of expenses incurred in performing research and development activities, including compensation and benefits for full-time research and development employees, facilities expenses, overhead expenses, clinical trial and related clinical manufacturing expenses, fees paid to CROs and other outside expenses. As we advance our product platform, we are conducting research on several prioritized HMT targets. Our research and development team is organized such that the design, management and evaluation of results of all of our research and development plans is accomplished internally, while some of our research and development activities are executed using our multinational network of CROs. In the early phases of development, our research and development costs are often devoted to expanding our product platform and are

Table of Contents

not necessarily allocable to specific targets. In circumstances where our collaboration and license agreements provide for equally co-funded global development, amounts received from collaboration partners for such co-funding are recorded as a reduction to research and development expense.

Most of our research and development costs have been external costs, which we began tracking on a program-by-program basis in the first quarter of 2010. Our internal research and development costs are primarily compensation expenses for our full-time research and development employees. We do not track internal research and development costs on a program-by-program basis. However, by employing a multinational network of CROs, our employees are able to dedicate significant amounts of their time to the expansion and development of our product platform while managing the research performed by our CROs.

General and Administrative

General and administrative expenses consist primarily of salaries and related benefits, including stock-based compensation, related to our executive, finance, intellectual property, business development and support functions. Other general and administrative expenses include allocated facility-related costs not otherwise included in research and development expenses, travel expenses and professional fees for auditing, tax and legal services, including intellectual property-related legal services.

Other Income (Expense), Net

Other income (expense), net consists of interest income earned on our cash equivalents, offset by interest and other expense.

Accretion of Preferred Stock

Our preferred stock automatically converted into common stock upon the closing of our initial public offering in June 2013. Our preferred stock was redeemable beginning in 2017 at its original issue prices per share plus any declared but unpaid dividends upon a specified vote of the preferred stockholders. Accretion of preferred stock reflects the periodic accretion of issuance costs and premiums on each series of preferred stock, where applicable, to their respective redemption values. As a result of the conversion, we do not have any preferred stock outstanding and will not record any additional accretion of preferred stock related to the shares of preferred stock previously issued.

Results of Operations for the Nine Months Ended September 30, 2012 and 2013

Collaboration Revenue

The following is a comparison of collaboration revenue for the nine months ended September 30, 2012 and 2013:

Edgar Filing: Epizyme, Inc. - Form 424B4

	Nine Months Ended September 30,		Decrease	
	2012	2013		
	(dollars in millions)			
Collaboration revenue	\$ 36.3	\$ 32.2	(\$ 4.1)	(11.3%)

During the nine months ended September 30, 2013, collaboration revenue consisted of \$19.2 million recognized from deferred revenue related to upfront payments for licenses, \$6.0 million in milestone revenue and \$7.0 million in research and development funding. This revenue compares to \$23.7 million recognized from deferred revenue related to upfront payments for licenses, \$8.0 million in milestone revenue and \$4.6 million in research and development funding recognized in the nine months ended September 30, 2012.

Table of Contents

Collaboration revenue recognized from deferred revenue in the nine months ended September 30, 2013 comprised \$10.8 million under our Celgene agreement, \$1.2 million under our Eisai agreement and \$7.2 million under our GSK agreement, as compared to \$20.3 million under our Celgene agreement and \$1.2 million under our Eisai agreement and \$2.2 million under our GSK agreement in the same period of the prior year. Milestone revenue in the nine months ended September 30, 2013 represents a \$6.0 million clinical development milestone achieved under our Eisai agreement, as compared to a \$4.0 million preclinical research and development milestone achieved under Eisai agreement and \$4.0 million in preclinical research and development milestones achieved under our GSK agreement in the same period of the prior year. Collaboration revenue recognized for research and development services in the nine months ended September 30, 2013 comprised \$5.2 million under our Eisai agreement and \$1.8 million under our GSK agreement, as compared to \$4.1 million under our Eisai agreement and \$0.5 million under our GSK agreement in the same period of the prior year.

Research and Development

The following is a comparison of research and development expenses for the nine months ended September 30, 2012 and 2013:

	Nine Months Ended September 30,		Increase
	2012	2013	
	(dollars in millions)		
Research and development	\$ 27.4	\$ 41.9	\$ 14.5 52.9%

The following table illustrates the components of our research and development expenses:

Product Program (Phase as of the latest period end)	Nine Months Ended September 30,	
	2012	2013
	(in millions)	
External research and development expenses:		
EPZ-5676 (Phase 1) and related DOT1L programs	\$ 6.5	\$ 9.4
EPZ-6438 (Phase 1/2) and related EZH2 programs	2.4	3.1
Discovery and preclinical stage product programs, collectively	9.9	16.0
Internal research and development expenses	8.6	13.4
Total research and development expenses	\$ 27.4	\$ 41.9

During the nine months ended September 30, 2013, our total research and development expenses increased by \$14.5 million compared to the same period of 2012, primarily due to the expansion of our product platform and the advancement of our research and development on specific targets, principally, DOT1L, EZH2 and the three target programs partnered with GSK. Our internal research and development expenses increased by \$4.8 million in the nine months ended September 30, 2013 compared to the same period of the prior year as the number of our research and development employees grew from 42 employees as of September 30, 2012 to 54 employees as of September 30, 2013. Research and development expenses for EPZ-5676 and related DOT1L programs for the nine months ended September 30, 2013 are net of \$0.7 million of global development co-funding receivable from Celgene.

Edgar Filing: Epizyme, Inc. - Form 424B4

External research and development spending for DOT1L focused on the advancement of the EPZ-5676 Phase 1 clinical trial, with expenses increasing from \$6.5 million in the nine months ended September 30, 2012 to \$9.4 million in the nine months ended September 30, 2013.

External research and development spending for EZH2 focused on the EPZ-6438 Phase 1/2 clinical trial and increased from \$2.4 million in the nine months ended

Our preferred stock automatically converted into common stock upon the closing of our initial public offering in June 2013. We recorded \$0.3 million of accretion in the nine months ended September 30, 2012 and \$0.3 million of accretion in the nine months ended September 30, 2013, until the conversion into common stock. As a result of this conversion, as of September 30, 2013, we do not have any preferred stock outstanding and will not record any additional accretion of preferred stock related to the shares of preferred stock previously issued.

Table of Contents**Results of Operations for the Years Ended December 31, 2011 and 2012*****Collaboration Revenue***

The following is a comparison of collaboration revenue for the years ended December 31, 2011 and 2012:

	Year Ended December 31,		Increase	
	2011	2012		
Collaboration revenue	\$ 6.9	\$ 45.2	\$ 38.3	555.1%

The increase in collaboration revenue in 2012 compared to 2011 was primarily due to the recognition of \$23.9 million of revenue in connection with our collaboration with Celgene, which was entered into in April 2012, the recognition of \$9.7 million of revenue in 2012 in connection with our collaboration with GSK, as compared to none during 2011, and an increase in revenue recognized from our collaboration with Eisai from \$6.6 million in 2011 to \$11.5 million in 2012.

Collaboration revenue recognized under the Celgene agreement during 2012 reflects amounts earned related to:

the delivery of the DOT1L license and the provision of related research services, both prior to and subsequent to IND effectiveness for EPZ-5676 in July 2012; and

the provision of research services related to other potential DOT1L product candidates.

Collaboration revenue recognized under the Eisai agreement reflects amounts earned related to the EZH2 license and research services, including \$4.0 million that we received upon the achievement of a substantive milestone related to the selection of a development candidate in 2012.

Collaboration revenue recognized under the GSK agreement reflects amounts earned for research services related to all three HMT targets licensed by GSK as of July 2012, the end of the target selection term under this agreement, as well as \$4.0 million related to preclinical research and development milestones that were achieved in 2012 after the end of the selection term. Prior to the end of the selection term, we did not recognize any collaboration revenue under this agreement, as none of the delivered elements were deemed to have standalone value apart from the undelivered elements of the arrangement.

Research and Development

The following is a comparison of research and development expenses for the years ended December 31, 2011 and 2012:

Edgar Filing: Epizyme, Inc. - Form 424B4

	Year Ended December 31,		
	2011	2012	Increase
	(dollars in millions)		
Research and development	\$ 22.9	\$ 38.5	\$ 15.6 68.1%

Table of Contents

The following table illustrates the components of our research and development expenses:

Product Program (Phase as of the latest period end)	Year Ended December 31,	
	2011	2012
	(in millions)	
External research and development expenses:		
EPZ-5676 (Phase 1) and related DOT1L programs	\$ 5.8	\$ 8.0
EPZ-6438 (Preclinical) and related EZH2 programs	3.8	3.5
Discovery and preclinical stage product programs, collectively	5.3	12.9
Internal research and development expenses	8.0	14.1
Total research and development expenses	\$ 22.9	\$ 38.5

During the year ended December 31, 2012, our total research and development expenses increased by \$15.6 million, or 68.1%, compared to the prior year, primarily due to the expansion of our product platform and the advancement of our research and development on specific targets, principally DOT1L and EZH2. Our internal research and development expenses increased by \$6.1 million in 2012 as compared to 2011 as the number of our research and development employees grew from 33 employees as of December 31, 2011 to 47 employees as of December 31, 2012.

External research and development spending for DOT1L focused on the advancement of EPZ-5676, with expenses increasing from \$5.8 million for the year ended December 31, 2011 to \$8.0 million for the year ended December 31, 2012, principally due to spending on preclinical studies. External research and development spending for EZH2 focused on progressing our EPZ-6438 product candidate into preclinical phases and decreased slightly, from \$3.8 million in 2011 to \$3.5 million in 2012, as some phases of development shifted to Eisai. External research and development spending for research stage product programs increased from \$5.3 million for the year ended December 31, 2011 to \$12.9 million for the year ended December 31, 2012 as we advanced the research and development of these programs.

External research and development spending from January 1, 2010 through December 31, 2012 was \$19.2 million for EPZ-5676 and related DOT1L programs and \$8.9 million for EPZ-6438 and related EZH2 programs. We did not maintain program-specific external cost information prior to January 1, 2010.

General and Administrative

The following is a comparison of general and administrative expenses for the years ended December 31, 2011 and 2012:

	Year Ended December 31,			Increase
	2011	2012		
	(dollars in millions)			
General and administrative	\$ 5.0	\$ 7.5	\$ 2.5	50.0%

Edgar Filing: Epizyme, Inc. - Form 424B4

For the year ended December 31, 2012, our general and administrative expenses increased by \$2.5 million, or 50.0%, primarily related to increased compensation expenses, as we grew from nine general and administrative employees as of December 31, 2011 to 15 general and administrative employees as of December 31, 2012, and increased legal expenses for the maintenance, expansion and protection of our intellectual property portfolio.

Table of Contents***Other Income, Net***

The increase in other income, net to \$0.1 million for 2012 from \$10,000 for 2011 reflects the increase in our interest-bearing cash equivalents, which resulted in higher interest income year-over-year.

Income Tax Expense

Income tax expense for the year ended December 31, 2012 consisted solely of current state tax expense, as we were able to utilize federal net operating loss carryforwards to fully offset federal taxable income for the year. For all years prior to 2012, we incurred taxable losses and accumulated significant federal and state net operating losses as well as research and development tax credits. Our ability to use our operating loss carryforwards and tax credits to offset future taxable income may become subject to restrictions under Section 382 of the United States Internal Revenue Code.

Accretion of Preferred Stock

We recorded \$45,000 of accretion for the year ended December 31, 2011 and \$0.5 million of accretion for the year ended December 31, 2012.

Quarterly Results of Operations Data

The following tables set forth our unaudited quarterly consolidated statements of operations data for each of the eleven quarters in the period from January 1, 2011 through September 30, 2013. This information is derived from our unaudited interim financial statements. We have prepared the quarterly data on the same basis as our audited consolidated financial statements. In the opinion of management, the quarterly data contains all adjustments which are necessary to present fairly our financial position and results of operations for such dates. Such adjustments are of a normal and recurring nature. The results of historical periods and any current quarterly period are not necessarily indicative of the results of operations for a full year or any future period. The information set forth below should be read in conjunction with our consolidated financial statements and notes thereto included elsewhere in this prospectus.

	Three Months Ended											
	March 31, 2011	June 30, 2011	September 30, 2011	December 31, 2011	March 31, 2012	June 30, 2012	September 30, 2012	December 31, 2012	March 31, 2013	June 30, 2013	September 30, 2013	December 31, 2013
	(in thousands, except per share data)											
Collaboration revenue	\$	\$ 2,028	\$ 2,444	\$ 2,472	\$ 5,654	\$ 15,342	\$ 15,331	\$ 8,895	\$ 8,882	\$ 14,839	\$ 8,444	
Operating expenses:												
Research and development		4,211	5,385	7,437	9,228	8,899	9,258	11,097	13,361	13,937	14,584	
General and administrative		1,426	1,173	1,265	1,907	1,638	1,630	2,333	2,998	3,079	3,587	
Total operating expenses		5,637	6,558	8,573	11,135	10,537	10,888	13,430	16,359	17,016	18,171	

Edgar Filing: Epizyme, Inc. - Form 424B4

(Loss) income from operations	(5,637)	(4,530)	(4,699)	(6,101)	(5,481)	4,805	4,443	(4,535)	(7,477)	(2,177)	(9,727)
Other income (expense):											
Interest income	7	11	2	13	13	51	44	37	19	15	20
Other income (expense), net			(23)				(39)	(39)	(39)	(50)	3
Other income (expense), net	7	11	(21)	13	13	51	5	(2)	(20)	(35)	23
(Loss) income before taxes	(5,630)	(4,519)	(4,720)	(6,088)	(5,468)	4,856	4,448	(4,537)	(7,497)	(2,212)	(9,704)
Income tax expense								1			
Net (loss) income	\$ (5,630)	\$ (4,519)	\$ (4,720)	\$ (6,088)	\$ (5,468)	\$ 4,856	\$ 4,448	\$ (4,538)	\$ (7,497)	\$ (2,212)	\$ (9,704)

Table of Contents

	Three Months Ended										
	March 31, 2011	June 30, 2011	September 30, 2011	December 31, 2011	March 31, 2012	June 30, 2012	September 30, 2012	December 31, 2012	March 31, 2013	June 30, 2013	September 30, 2013
	(in thousands, except per share data)										
Less: accretion of redeemable convertible preferred stock to redemption value	11	11	11	12	11	156	159	160	157	107	
Less: income allocable to participating securities						4,354	3,972				
(Loss) income allocable to common stockholders basic	(5,641)	(4,530)	(4,731)	(6,100)	(5,479)	346	317	(4,698)	(7,654)	(2,319)	(9,704)
Undistributed income re-allocated to common stockholders						236	229				
(Loss) income allocable to common stockholders diluted	\$ (5,641)	\$ (4,530)	\$ (4,731)	\$ (6,100)	\$ (5,479)	\$ 582	\$ 546	\$ (4,698)	\$ (7,654)	\$ (2,319)	\$ (9,704)
(Loss) earnings per share allocable to common stockholders:											
Basic	\$ (4.47)	\$ (3.44)	\$ (3.04)	\$ (3.81)	\$ (3.38)	\$ 0.21	\$ 0.19	\$ (2.81)	\$ (4.27)	\$ (0.25)	\$ (0.34)
Diluted	\$ (4.47)	\$ (3.44)	\$ (3.04)	\$ (3.81)	\$ (3.38)	\$ 0.20	\$ 0.18	\$ (2.81)	\$ (4.27)	\$ (0.25)	\$ (0.34)
Weighted average shares outstanding:											
Basic	1,262	1,315	1,555	1,600	1,623	1,636	1,651	1,670	1,791	9,146	28,406
Diluted	1,262	1,315	1,555	1,600	1,623	2,913	3,017	1,670	1,791	9,146	28,406

Liquidity and Capital Resources

On June 5, 2013, we completed an initial public offering of our common stock, which resulted in the sale of 5,913,300 shares, including all additional shares available to cover over-allotments, at a price of \$15.00 per share. We received net proceeds before expenses from the IPO of \$82.5 million after deducting underwriting discounts and commissions paid by us. In connection with the closing of the IPO, all of our outstanding preferred stock automatically converted to common stock at a one-for-three ratio as of June 5, 2013.

Since our inception and through September 30, 2013, we have raised an aggregate of \$291.8 million to fund our operations, of which \$133.3 million was through our collaboration agreements, \$82.5 million was from the sale of our common stock in our initial public offering and \$76.0 million was from the sale of our preferred stock. In addition, as of September 30, 2013, we were entitled to receive \$2.2 million for research and development services provided in the third quarter of 2013. As of September 30, 2013, we had \$139.6 million in cash and cash equivalents.

In addition to our existing cash and cash equivalents, we receive research and development funding and are eligible to earn a significant amount of option exercise and milestone payments under our collaboration agreements. Our ability to earn these payments and the timing of earning these payments is dependent upon the outcome of our research and development activities and is uncertain at this time. Our rights to payments under our collaboration agreements are our only committed external source of funds.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, compensation and related expenses, third party clinical research and development services, laboratory and related supplies, clinical costs, legal and other regulatory expenses and general overhead costs. We believe our multinational network of CROs provides us with flexibility in managing our spending and limits our cost commitments at any point in time.

Table of Contents

Because our product candidates are in various stages of clinical and preclinical development and the outcome of these efforts is uncertain, we cannot estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates or whether, or when, we may achieve profitability. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity or debt financings and collaboration arrangements. Except for any obligations of our collaborators to reimburse us for research and development expenses, including global development co-funding provisions of our collaboration agreements, or to make option exercise, milestone or royalty payments under our agreements with them, upon completion of this offering, we will not have any committed external sources of liquidity. To the extent that we raise additional capital through the future sale of equity or debt, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. Our ability to enter into collaboration agreements for additional HMT targets is significantly limited until the end of the option period under the Celgene agreement and may continue to be limited after the end of the option period depending on how many other HMT targets Celgene elects to license, if any. If we raise additional funds through collaboration arrangements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise any additional funds that may be needed through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Outlook

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that the net proceeds to us from this offering, together with our existing cash and cash equivalents as of September 30, 2013, accounts receivable for milestones earned in December 2013 and research funding that we expect to receive under our existing collaborations, will enable us to fund our operating expenses and capital expenditure requirements until at least mid-2016, without giving effect to any potential option exercise fees or milestone payments we may receive under our collaboration agreements. Prior to such time, we expect to complete four ongoing and planned proof-of-concept trials in five genetically defined cancer patient groups: MLL-r adult patients, MLL-PTD adult patients, MLL-r pediatric patients, non-Hodgkin lymphoma patients with EZH2 point mutations and synovial sarcoma patients. We have based these expectations on assumptions that may prove to be wrong, particularly as the process of testing drug candidates in clinical trials is costly and the timing of progress in these trials is uncertain. As a result, we could use our capital resources sooner than we expect.

Cash Flows

The following is a summary of cash flows for the years ended December 31, 2011 and 2012 and the nine months ended September 30, 2012 and 2013:

	Year Ended December 31,		Nine Months Ended September 31,	
	2011	2012	2012	2013
	(in millions)			
Net cash provided by (used in) operating activities	\$ 10.0	\$ 44.2	\$ 48.4	\$ (38.0)
Net cash used in investing activities	(0.9)	(1.4)	(0.2)	(0.2)
Net cash provided by financing activities	19.1	21.9	21.9	79.9

Net Cash Provided by (Used in) Operating Activities

Edgar Filing: Epizyme, Inc. - Form 424B4

Net cash provided by operating activities of \$48.4 million during the nine months ended September 30, 2012 compared to net cash used in operating activities of \$38.0 million during the nine months ended

Table of Contents

September 30, 2013. The change from net cash provided by operating activities to net cash used in operating activities reflects the \$68.0 million received from Celgene and allocated to our collaboration agreement in April 2012, as well as increased spending in 2013.

Net cash provided by operating activities was \$10.0 million for the year ended December 31, 2011 compared to \$44.2 million for the year ended December 31, 2012. The increase in cash from operating activities was driven by an increase in cash from collaborations, primarily due to the execution of the Celgene agreement in 2012, for which we received an upfront payment of \$68.0 million, partially offset by an increase in operating expenses.

Net Cash Used in Investing Activities

Net cash used in investing activities relates to the purchase of property and equipment. The increase in property and equipment purchases in 2012 compared to 2011 consisted primarily of purchases of laboratory equipment, due to the growth of our research and development activities, and office furniture and equipment, related to our move to a larger office and laboratory facility in November 2012.

Net Cash Provided by Financing Activities

Net cash provided by financing activities of \$21.9 million during the nine months ended September 30, 2012 primarily reflects net cash received from the our sale of series C preferred stock to an affiliate of Celgene in April 2012, whereas net cash provided by financing activities of \$79.9 million during the nine months ended September 30, 2013 primarily reflects cash received from our initial public offering.

Net cash provided by financing activities during the years ended December 31, 2011 and 2012 primarily related to the sale of preferred stock in both years. In September 2011, we sold 18.1 million shares of series B preferred stock to our existing investors for net proceeds of \$19.0 million. In April 2012, we sold 9.8 million shares of series C preferred stock to an affiliate of Celgene for proceeds of \$25.0 million, of which \$3.0 million was considered to be a premium and was allocated to the deliverables under the collaboration agreement, resulting in \$22.0 million being allocated to the series C preferred stock.

Contractual Obligations and Contingent Liabilities

The following summarizes our significant contractual obligations as of September 30, 2013:

Contractual Obligations	Total	Less than 1 Year	1 to 3 Years (in thousands)	3 to 5 Years	More than 5 Years
Operating leases	\$ 11,891	\$ 3,215	\$ 5,476	\$ 3,200	\$
Research and development contract obligations	5,508	1,558	3,639	311	
Total obligations	\$ 17,399	\$ 4,773	\$ 9,115	\$ 3,511	\$

Operating Leases. Represents future minimum lease payments under non-cancelable operating leases in effect as of September 30, 2013, including the remaining payments under our operating lease for our current office and laboratory facility in Cambridge, Massachusetts, which was amended in September 2013 to include additional office space, and the remaining lease payments for our former facility in Cambridge, Massachusetts. In November 2013, we entered into a sub-lease for our former facility. The future minimum lease payments included in this table do not reflect the \$0.5 million of sublease rental income that we expect to receive through 2014 under this non-cancelable sublease. The minimum lease payments above do not include common area maintenance charges or real estate taxes.

Research and Development Contract Obligations. Represents obligations by us to make payments under long-term research and development contracts.

Table of Contents

The contractual obligations table does not include any potential future milestone or royalty payments we may be required to make under our license agreement with the University of North Carolina, under which we were granted an exclusive worldwide license to specified patent rights and a non-exclusive worldwide license to specified know-how and biological materials, or any potential future milestone or royalty payments we may be required to make under a non-exclusive license to a patent related to an excipient in the formulation of a therapeutic product candidate due to the uncertainty of the occurrence of the events requiring payment under that agreement. The table also excludes potential future payments we may be required to make if we elect to opt in to the co-development, co-commercialization and profit share arrangement provided for under our collaboration with Eisai, including our share of potential future milestone payments due under the Roche companion diagnostics development agreement.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under Securities and Exchange Commission rules.

JOBS Act

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period, and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

Quantitative and Qualitative Disclosures about Market Risk

The market risk inherent in our financial instruments and in our financial position represents the potential loss arising from adverse changes in interest rates. As of September 30, 2013, we had cash equivalents of \$121.4 million consisting of interest-bearing money market accounts and prime money market funds. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term maturities of our cash equivalents and the low risk profile of our investments, an immediate 100 basis point change in interest rates as of September 30, 2013 would not have a material effect on the fair market value of our cash equivalents.

We contract with CROs and contract manufacturers internationally. Transactions with these providers are predominantly settled in U.S. dollars and, therefore, we believe that we have only minimal exposure to foreign currency exchange risks. We do not hedge against foreign currency risks.

Table of Contents

BUSINESS

Overview

We are a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize innovative personalized therapeutics for patients with genetically defined cancers. 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 personalized therapeutics.

Our therapeutic strategy is to treat the underlying causes of genetically defined cancers by blocking the incorrect 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 20 of these HMTs for our drug discovery activities based on the potential oncogenic role of these HMTs, the clinical need of patients with the associated genetically defined 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 patients with a particular genetically defined cancer. For many of our therapeutic product candidates, we plan to develop a companion diagnostic for the identification of patients with the genetically defined cancers that we seek to treat with our therapeutic product candidates. Because we are tailoring our personalized therapeutics for specific, identifiable patient populations with genetically defined cancers, we believe that many of our products may qualify for orphan drug designation in the United States, the European Union and other regions. 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 United States Food and Drug Administration, or FDA, and, in January 2014, the European Commission granted orphan drug designation for EPZ-5676 for the treatment of AML and ALL.

We currently have two HMT inhibitors in clinical development for the treatment of patients with genetically defined cancers and believe we are the first company to conduct a clinical trial of an HMT inhibitor. We are conducting a Phase 1 clinical trial of our most advanced product candidate, EPZ-5676, an inhibitor targeting the DOT1L HMT, being developed for the treatment of acute leukemias with genetic alterations of the *MLL* gene, referred to as MLL-r and MLL-PTD. On January 6, 2014, we announced that we had earned a \$25.0 million proof-of-concept milestone in our collaboration with Celgene Corporation and Celgene International Sàrl, collectively referred to as Celgene, in December 2013 by achieving objective responses in two MLL-r patients enrolled in the dose escalation stage of our Phase 1 trial. We are also conducting a Phase 1/2 clinical trial of our second most advanced product candidate, EPZ-6438, an inhibitor targeting the EZH2 HMT, being developed for the treatment of a genetically defined subtype of non-Hodgkin lymphoma and solid tumors including INI1-deficient tumors, such as synovial sarcoma and malignant rhabdoid tumors, or MRT.

Edgar Filing: Epizyme, Inc. - Form 424B4

In 2014, we plan to have four clinical trials ongoing that are intended to assess the proof of concept of our product candidates in five genetically defined cancer patient groups:

The expansion stage of our ongoing Phase 1 clinical trial of EPZ-5676 in MLL-r adult patients and MLL-PTD adult patients;

Table of Contents

Our planned Phase 1b clinical trial of EPZ-5676 in MLL-r pediatric patients;

Our planned Phase 2 clinical trial of EPZ-6438 in non-Hodgkin lymphoma patients with EZH2 point mutations as part of our ongoing Phase 1/2 clinical trial of EPZ-6438; and

Our planned Phase 2 clinical trial of EPZ-6438 in synovial sarcoma patients.

The initiation of our proof-of-concept trials of EPZ-6438 is subject to our review of the data from the Phase 1 clinical trial of EPZ-6438 that we are conducting as part of our ongoing Phase 1/2 clinical trial of EPZ-6438.

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 genetically defined cancers, both hematological and solid tumors. Three of these HMT programs are currently partnered with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK. In December 2013, we earned a \$4.0 million milestone from GSK for achieving a development candidate milestone with respect to one of these programs.

The inclusion of patients who have the relevant genetic alteration as early as possible in our trials is a key element of our strategy. Accordingly, we are including patients who have the relevant genetic alterations in the Phase 1 clinical trial of EPZ-5676 and the Phase 1/2 clinical trial of EPZ-6438. If we see evidence of a therapeutic effect in these genetically defined patients, 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 FDA expedited review and approval programs, including breakthrough therapy and fast track designations.

We have entered into a number of strategic collaborations for our therapeutic programs and corresponding companion diagnostics. Our therapeutic collaborations have provided us with \$133.3 million in non-equity funding through September 30, 2013. Further, in December 2013, we earned an additional \$29.0 million in milestones from Celgene and GSK. Our therapeutic collaborations also provide us with research funding and the potential for more than \$1.0 billion of research, development, regulatory and sales-based milestone payments, as well as royalties or profit sharing on any net product sales. We have entered into three therapeutic collaborations 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 to license other HMT programs outside of the United States. 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 Eisai Co., Ltd., or Eisai, under which we have granted Eisai a worldwide license to our EZH2 program, including EPZ-6438. Eisai will pay 100% of global research and development costs for each licensed product candidate unless we exercise our right to opt in to a 50/50 co-development, co-commercialization and profit-share arrangement in the United States for a given licensed product candidate. We can exercise this right at any time prior to the initiation of a registration trial for such product candidate.

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

We have also entered into an agreement with Abbott Molecular Inc., or Abbott, for the development of a companion diagnostic for use with EPZ-5676 for MLL-r and an agreement with Roche Molecular Systems, Inc., or Roche, and Eisai for the development of a companion

diagnostic for use with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations.

Table of Contents

Strategy

Our goal is to be a leader in the discovery, development and commercialization of personalized therapeutics for the treatment of patients with genetically defined cancers. 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 oncogene. 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 a companion diagnostic to select the right patients for treatment. Because we are tailoring our personalized therapeutics for discrete patient populations with genetically defined cancers, we believe that many of our products may qualify for orphan drug designation in the United States, the European Union and other regions.

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 clinical trial of our most advanced product candidate, EPZ-5676, an inhibitor targeting the DOT1L HMT, being developed for the treatment of acute leukemias with genetic alterations of the *MLL* gene, referred to as MLL-r and MLL-PTD. We are also conducting a Phase 1/2 clinical trial of our second most advanced product candidate, EPZ-6438, an inhibitor targeting the EZH2 HMT, being developed for the treatment of a genetically defined subtype of non-Hodgkin lymphoma and solid tumors including INI1-deficient tumors such as synovial sarcoma and MRT. We have designed the Phase 1 clinical trial of EPZ-5676 and the Phase 1/2 clinical trial of EPZ-6438 to include some patients with the genetically defined cancer that we are seeking to treat. If we see evidence of a therapeutic effect in either 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 genetically defined population, 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 genetically 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 genetically defined cancers that may be treated with each of our product candidates beyond the initial indication of interest. MLL-PTD is an expansion indication for the EPZ-5676 product candidate that we identified internally. Similarly, we identified INI1-deficient tumors as potential expansion indications for EPZ-6438.

Leverage Collaborations. We have established therapeutic collaborations with Celgene, Eisai and GSK for our most advanced HMT programs. These collaborations provide us with significant funding for both our specific development programs and our product platform. They also provide us with access to the considerable scientific, development, regulatory and commercial capabilities of our collaborators. We believe that these collaborations 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. In the case of the Celgene and Eisai arrangements, we have retained commercialization or co-commercialization rights in the United States.

Establish Commercialization and Marketing Capabilities in the United States. We have retained commercialization or co-commercialization rights in the United States for all of our programs other than the three programs in our GSK collaboration. We plan to retain similar rights in connection with any future

Table of Contents

oncology collaborations. We intend to build a focused specialty sales force and marketing capabilities in the United States to commercialize any of our oncology drugs that receive regulatory approval.

Use Our Product Platform to Build a Pipeline of Proprietary HMT Inhibitors. There are 96 HMT enzymes in the HMTome. We have prioritized 20 of 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 20 HMT targets that we have prioritized. We have invented novel, potent small molecule inhibitors for 15 of these 20 prioritized HMTs. We intend to advance multiple other product candidates into clinical trials.

Develop Companion Diagnostics for Use with Our Therapeutic Product Candidates. For many of our therapeutic product candidates, we plan to develop a companion diagnostic for the identification of patients with the genetically defined 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 Abbott to develop a companion diagnostic for use with EPZ-5676 for MLL-r and with Roche and Eisai to develop a companion diagnostic for use with EPZ-6438 for non-Hodgkin lymphoma patients with EZH2 point mutations. Both of these companion diagnostics are based on currently available technologies.

Background

Cancer is a heterogeneous group of diseases characterized by uncontrolled cell division and growth. Cancerous cells that arise in the lymphatic system and bone marrow are referred to as hematological tumors. Cancer cells that arise in other tissues or organs are referred to as solid tumors. Researchers believe that exposure to some chemicals, viruses and various forms of radiation can cause genetic alterations that cause cancer. Genetic predispositions also can increase the risk of cancer in some people.

Cancer is the second leading cause of death in the United States, exceeded only by heart disease. The American Cancer Society estimated that in 2013 there would be approximately 1.6 million new cases of cancer and approximately 580,000 deaths from cancer in the United States.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. A cancer patient often receives treatment with a combination of these methods. Surgery and radiation therapy are particularly effective in patients in whom the disease is localized. Physicians generally use systemic drug therapies in situations in which the cancer has spread beyond the primary site or cannot otherwise be treated through surgery. The goal of drug therapy is to damage and kill cancer cells or to interfere with the molecular and cellular processes that control the development, growth and survival of cancer cells. In many cases, drug therapy entails the administration of several different drugs in combination. Over the past several decades, drug therapy has evolved from non-specific drugs that kill both healthy and cancerous cells, to drugs that target specific molecular pathways involved in cancer and more recently to therapeutics that target the specific oncogenic drivers of cancer.

Cytotoxic Chemotherapies. The earliest approach to pharmacological cancer treatment was to develop drugs, referred to as cytotoxic drugs, that kill rapidly proliferating cancer cells through non-specific mechanisms, such as disrupting cell metabolism or causing damage to cellular components required for survival and rapid growth. These drugs include Cytosar-U® and Efadex®. While these drugs have been effective in the treatment of some cancers, many unmet medical needs for the treatment of cancer remain. Also, cytotoxic drug therapies act in an indiscriminate manner, killing healthy as well as cancerous cells. Due to their mechanism of action, many cytotoxic drugs have a narrow dose range above which the toxicity causes unacceptable or even fatal levels of damage and below which the drugs are not effective in eradicating cancer cells.

Table of Contents

Targeted Therapies. The next approach to pharmacological cancer treatment was to develop drugs, referred to as targeted therapeutics, that target specific biological molecules in the human body that play a role in rapid cell growth and the spread of cancer. Targeted therapeutics include vascular disruptors, also referred to as angiogenesis inhibitors, that prevent the formation of new blood vessels and restrict a tumor's blood supply. Marketed vascular disruptors include Avastin® and Zaltrap®. Other targeted therapies, such as Sutent® and Nexavar®, affect cellular signaling pathways that are critical for the growth of cancer. While these drugs have been effective in the treatment of some cancers, most of them do not address the underlying cause of the disease. These drugs focus on processes that help the cancer cell survive, but not the oncogenes that are the drivers or cause of the cancer itself.

Oncogenic Therapies. A more recent approach to pharmacological cancer treatment is to develop drugs that affect the drivers that cause uncontrolled growth of cancer cells because of a specific genetic alteration. In some cases, these agents were identified as therapeutics without knowledge of the underlying genetic change causing the disease. To date, the shortcoming of this approach has been that it is not systematic, but instead often follows a conventional trial and error approach to drug discovery. In this approach, clinical development involves the treatment of large populations from which a defined subpopulation that responds to treatment is identified. As a result, this approach can be time-consuming and costly, with success often uncertain.

The Epizyme Approach

We are discovering and developing HMT inhibitors as personalized therapeutics for patients with genetically defined cancers. We are applying our approach to the HMTome, with a focus on the 20 HMTs that we believe have strong evidence of being oncogenic.

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 affecting HMTs;

defining an oncogenic hypothesis for the affected HMT;

Table of Contents

developing assays to test the oncogenic hypothesis; and

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

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 personalized 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 for use with our therapeutic product candidates.

We invented EPZ-5676 and EPZ-6438, 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 20 of the 96 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.

Edgar Filing: Epizyme, Inc. - Form 424B4

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.

Table of Contents

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 20 high priority HMTs. We have also included a number of other HMTs to determine whether the compounds that we screen bind selectively with the HMT of interest and not with any other HMT.

We have created more than 300 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 22,000 compounds in 22 distinct chemical series. Within these 22 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. An important element of our personalized approach to cancer treatment is to develop a companion diagnostic for use with each therapeutic product candidate. We are working with collaborators to develop these companion diagnostics, 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 patients for our clinical trials who have the genetically defined disease that we are seeking to treat with our therapeutic product candidates. 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 personalized therapeutics to treat the genetically defined cancers caused by these HMTs.

Table of Contents**Product Pipeline**

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

Genetically Defined Populations			Commercial Rights	Diagnostic Collaborator
Product Candidate	(Genetic Alteration)	Stage of Development		
EPZ-5676 (DOT1L inhibitor)	Acute leukemias with alterations in the <i>MLL</i> gene	Phase 1 clinical trial ongoing	Epizyme: United States; Celgene: Rest of world	Abbott (MLL-r)
	MLL-r subtype of acute myeloid leukemia, or AML, and acute lymphoblastic leukemia, or ALL, in adult patients (Chromosomal translocation involving the <i>MLL</i> gene)	Dose escalation stage fully enrolled in MLL-r adult patient trial		
	MLL partial tandem duplication, or MLL-PTD, subtype of AML in adult patients (Partial tandem duplication of the <i>MLL</i> gene)	MLL-r / MLL-PTD only adult patient expansion stage enrolling		
	MLL-r in pediatric patients (Chromosomal translocation involving the <i>MLL</i> gene)	Phase 1b MLL-r pediatric patient trial expected to initiate in 2014		
EPZ-6438 (EZH2 inhibitor)	Non-Hodgkin lymphoma (Point mutations in EZH2)	Phase 1/2 clinical trial ongoing	Eisai: Worldwide rights, subject to Epizyme's opt-in on 50.0% of United States rights	Roche (Non-Hodgkin lymphoma with EZH2 point mutations)
	Other solid tumors including INI1-deficient tumors, such as synovial sarcoma and MRT	Phase 2 trial for non-Hodgkin lymphoma patients with point mutations in EZH2 expected to initiate in 2014 pending our review of data from the Phase 1 dose escalation trial		
		Phase 2 trial for synovial sarcoma patients expected to initiate in 2014 pending our review of data from the Phase 1 dose escalation trial		

In addition to the therapeutic programs listed above, we are actively working with GSK on three specified HMT inhibitors 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-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, and partial tandem duplications of the *MLL* gene, referred to as MLL-PTD. We invented EPZ-5676 using our proprietary product platform. We initiated a Phase 1 clinical trial of this product candidate in September 2012. The dose escalation stage of this trial includes patients with advanced hematologic malignancies, including some patients with alterations involving the *MLL* gene. The dose escalation stage was fully enrolled as of December 31, 2013, and, in December 2013, we began enrolling patients in the expansion stage of this ongoing Phase 1 trial. This stage will only include patients with MLL-r or MLL-PTD, while continuing to allow for dose escalation. We also plan to initiate a Phase 1b trial of EPZ-5676 in pediatric patients with MLL-r in 2014.

Table of Contents

We retain all U.S. rights to EPZ-5676. We have granted Celgene an exclusive license to EPZ-5676 outside of the United States. We are working with Abbott to develop a companion diagnostic to identify patients with the MLL-r genetic alteration for this program and plan to seek to enter into a similar collaboration for the development of a companion diagnostic to identify patients with the MLL-PTD genetic alteration.

In August 2013, we were granted orphan drug designation for EPZ-5676 for the treatment of AML and 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.

Background on DOT1L Cancers. DOT1L is an HMT that can become oncogenic and cause certain genetically defined subtypes of acute leukemia, such as MLL-r and MLL-PTD.

MLL-r. MLL-r is an aggressive, genetically defined subtype of two of the most common forms of acute leukemia, ALL and AML. In an article in the journal *Blood* in December 2002, the authors estimated that the five-year overall survival rate for adult patients with the MLL-r subtype of AML ranges from approximately 5 to 24%. In an article from 2004 in the *New England Journal of Medicine*, the authors estimated that the five-year event free survival rate in pediatric patients with the most common MLL-r subtype of ALL is approximately 27%. In a report that we commissioned, Clarion Healthcare, LLC, or Clarion Healthcare, estimated that the total annual incidence of MLL-r in all patients in the major pharmaceutical markets is approximately 4,900 patients. Patients with MLL-r are routinely diagnosed using existing technologies that are commonly used in clinical settings. As a result, there is high awareness of MLL-r among oncologists. The disease predominantly occurs in two different age ranges, an adult population and an infant/pediatric population. While they share a common genetic alteration, the adult disease is frequently a secondary leukemia resulting from prior chemotherapy for a different, unrelated cancer and the childhood disease is of unknown origin. MLL-r is caused by a chromosomal translocation involving the *MLL* gene. The translocation results in DOT1L being recruited to a specific place in the chromosome where it would not normally be present. As a result, DOT1L causes inappropriate methylation at this location, which results in the increased expression of genes involved in causing leukemia.

There are no approved therapies specifically indicated for MLL-r. Physicians treat this hematological cancer with therapies approved for other acute leukemias. Patients with AML and ALL typically are treated with intensive multi-agent chemotherapy and high risk patients with ALL and AML who enter remission and have a matched donor often receive an allogeneic stem cell transplant. However, some patients, especially those who are older, are too fragile for any of these treatments and, as a result, remain untreated.

MLL-PTD. MLL-PTD is an aggressive, genetically defined subtype of the most common form of adult leukemia, AML, caused by a partial tandem duplication in the *MLL* gene. MLL-PTD patients are considered to have adverse cytogenetics, a characterization of their prognostic outcome, and as a group have a worse-than-average remission duration compared with adults with AML lacking the MLL-PTD alteration. In a report that we commissioned, Clarion Healthcare estimated that the total annual incidence of MLL-PTD in all patients in the major pharmaceutical markets is approximately 2,300 patients.

There are no approved therapies specifically indicated for MLL-PTD. Physicians treat this hematological cancer with therapies approved for other acute leukemias. Patients with AML typically are treated with intensive multi-agent chemotherapy and high risk patients with AML who enter remission and have a matched donor often receive an allogeneic stem cell transplant. However, some patients, especially those who are older, are too fragile for any of these treatments and, as a result, remain untreated.

Phase 1 Clinical Trial. Our Phase 1 clinical trial of EPZ-5676 is an open label, multicenter trial that has two stages. The first stage is a dose escalation stage in patients with advanced hematologic malignancies, including some MLL-r patients. The dose escalation stage was completely enrolled as of December 31, 2013. The second stage is an expansion stage that is only enrolling MLL-r and MLL-PTD patients. The expansion

stage began enrolling in December 2013 with a dose and administration schedule based on the initial findings from the

Table of Contents

dose escalation stage. This trial has a starting dose at 90 mg/m²/day and also allows for dose escalation. We are currently conducting this trial at six sites in the United States. We plan to add more sites and expect to have as many as 12 sites participating in the expansion stage of this trial, including sites in the United States and 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 process by which EPZ-5676 is distributed and metabolized in the body, which is referred to as pharmacokinetics;

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 any early evidence of anti-tumor activity in patients with MLL-r.

Dose Escalation Stage. The dose escalation stage of the Phase 1 trial began enrolling patients in September 2012 and completed enrolling patients in the fifth and final dose cohort in December 2013. We have not reported results for the fifth dose cohort, which is ongoing, and plan to do so as part of a full Phase 1 data disclosure planned for 2014. Under the dose escalation protocol, patients in the trial received EPZ-5676 on a 21-day on drug, 7-day off drug schedule via continuous intravenous administration. A total of five dose cohorts were enrolled at dose levels of 12, 24, 36, 54, or 80 mg/m²/day with a total of 19 patients enrolled. This dose escalation stage allowed for, but did not require, the enrollment of patients with the targeted *MLL* genetic alterations, MLL-r and MLL-PTD. The majority of patients had a diagnosis of AML. Other diagnoses included ALL and chronic myelomonocytic leukemia, or CMML. This patient population was heavily pre-treated. Through the first four cohorts, the average number of prior treatments was four per patient, and six of the patients were in relapse after undergoing an allogeneic stem cell transplantation. In December 2013, two patients in the fourth dose cohort of the ongoing Phase 1 trial had objective responses. These patients had demonstrated treatment-related effects and were switched from the original intravenous administration schedule 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.

Based on the trial results to date, EPZ-5676 has demonstrated a favorable safety and tolerability profile. Specifically, no dose-limiting toxicities, drug-related trial discontinuations, or serious adverse events considered by the clinical site investigators to be related to EPZ-5676 have been reported. This may indicate that we have not yet dosed at either the minimum effective dose or the maximum tolerated dose, which is the basis for the continuation of dose escalation in the expansion stage. Leukocytosis, an elevated white blood cell count, has been observed in some patients and is considered treatment-related but is consistent with the therapeutic mechanism of action of EPZ-5676 and is not considered an adverse event.

The pharmacokinetic profile of EPZ-5676 shows that, through the fourth cohort of the trial, steady-state exposure levels of EPZ-5676 have been dose-proportional. Steady-state exposure variability has been modest at two to two-and-a-half fold, with the exception of a single high-exposure outlier in the third dose cohort.

The pharmacodynamic effects of EPZ-5676 on DOT1L target inhibition, measured by methyl mark inhibition of the DOT1L target, H3K79, in peripheral blood mononuclear cells, have been informative. First, at doses greater than or equal to 36 mg/m², methyl mark reduction has been consistently observed. Secondly, on average in the third and fourth dose cohorts, the kinetics of methyl mark inhibition demonstrated declining levels of methyl mark over time throughout the 21-day treatment course, with a recovery of methyl mark approaching approximately 80% of baseline levels after the 7-day off-drug period. Based on these findings, we believe that an uninterrupted administration schedule of EPZ-5676

Edgar Filing: Epizyme, Inc. - Form 424B4

may be required to maximize target inhibition. The safety profile seen to date also supports this uninterrupted schedule of administration. We are using the uninterrupted schedule of administration in the MLL-r/MLL-PTD only expansion stage of the trial that began enrolling patients in December 2013.

Table of Contents

During the dose escalation stage of the trial, in addition to the two objective responses, we observed treatment effects of EPZ-5676 in some other patients with MLL-r in the trial, 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. Consistent with the genetically defined therapeutic mechanism of action of EPZ-5676, no treatment effects were seen in the non-MLL-r patients.

Expansion Stage. Based on the findings to date from the dose escalation stage of the ongoing Phase 1 trial, we began enrolling the MLL-r/MLL-PTD expansion stage in December 2013. This stage of the trial will only enroll MLL-r and MLL-PTD patients and is designed to provide an initial assessment of efficacy, or proof of concept, in two distinct patient populations. We plan to enroll 15 to 20 MLL-r patients and 15 to 20 MLL-PTD patients. These patients will receive EPZ-5676 with uninterrupted intravenous administration. This trial has a starting dose at 90 mg/m²/day and also allows for dose escalation as warranted. We plan to provide data from the Phase 1 clinical trial, including from the dose escalation stage and the MLL-r/MLL-PTD expansion stage, in 2014.

It is important to note that the objective responses and treatment effects that were observed in the dose escalation stage were experienced by only some of the MLL-r patients enrolled in the trial, were observed in an open-label setting and might not be experienced by other patients treated with EPZ-5676. Additionally, the disease did progress in some of these MLL-r patients, as well as other MLL-r patients, enrolled in the dose escalation stage. This Phase 1 trial is not powered 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-5676. This trial design is typical of Phase 1 and some Phase 2 clinical trials, the principal purpose of which is to provide the basis for the design of larger, definitive trials that are powered by the addition of more patients to potentially show statistical significance. 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 based on the clinical data observed in earlier trials.

MLL-r Pediatric Trial. We believe that the data from the dose escalation trial in adults supports the initiation of a Phase 1b clinical trial of EPZ-5676 in pediatric patients in 2014. This clinical trial will be restricted to pediatric patients with MLL-r acute leukemia and will be similar in design to the adult trial, with a dose escalation stage and an expansion stage that we would expect to provide an initial assessment of clinical efficacy, or proof of concept. Patients in this trial will receive uninterrupted administration of EPZ-5676.

Preclinical Studies. Based on a comprehensive program of preclinical testing of EPZ-5676, including several *in vitro* analyses and *in vivo* xenograft studies, we concluded that EPZ-5676 had exhibited appropriate pharmaceutical potential to advance it into clinical development. Key findings from this preclinical program included the following:

In cell lines that include the MLL-r gene alteration, EPZ-5676 inhibited the methylation caused by DOT1L activity in a concentration dependent manner. In these *in vitro* experiments, EPZ-5676 acted in a highly selective manner, inhibiting only the targeted DOT1L-associated methylation and no other histone methyl marks. In addition, in these cell lines, EPZ-5676 inhibited proliferation and killed cells containing the MLL-r genetic alteration, but had minimal effect on cells without this alteration.

We treated nude rat xenograft models in which human MLL-r cells were implanted subcutaneously and allowed to establish tumors. We administered EPZ-5676 to these rats in three dose levels for 21 days by continuous intravenous infusion. Each dose group consisted of ten animals. Dose 1 was 35 mg/kg per day; dose 2 was 70 mg/kg per day; and dose 3 was the delivery vehicle alone, with no EPZ-5676, designed to create a baseline against which the other doses could be compared. In comparison with animals receiving only the vehicle, the 35 mg/kg per day treated group displayed significant tumor growth inhibition,

Table of Contents

resulting in tumor stasis in seven of the ten animals that continued for up to seven days past the discontinuation of drug treatment. At the higher dose of 70 mg/kg per day, tumors in nine of the ten animals were reduced to undetectable volumes by the end of the 21 day treatment period. In addition, no tumor regrowth was observed in eight of these nine animals through the end of the study, which was 32 days after the end of the treatment period. These results are illustrated in the graph below.

Median Tumor Volume

Data that we presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston in October 2013 showed that in the preclinical studies presented, MLL-PTD cell lines, like MLL-r cell lines, were sensitive to DOT1L inhibition. MLL-PTD leukemia cells showed aberrant gene expression patterns involving leukemogenic genes similar to those observed in MLL-r leukemia cells. When treated with a DOT1L inhibitor, MLL-PTD cells lines also similarly underwent programmed cell death, or apoptosis.

Companion Diagnostic. While commercially available diagnostics are commonly used by clinicians to identify and diagnose MLL-r patients, it is possible that regulatory authorities will require that we develop and have approved a companion *in vitro* diagnostic for use with EPZ-5676. To address this potential requirement, we have entered into an agreement with Abbott for the development of a diagnostic for use with EPZ-5676 which is similar to the type of diagnostic that is used to test for the HER2 gene in connection with the use of the breast cancer drug Herceptin. Under this agreement, Abbott will have the right to commercialize the diagnostic. We anticipate that Abbott and we will coordinate our marketing and sales activities for EPZ-5676 for MLL-r patients and the companion diagnostic.

The MLL-PTD genetic alteration is not currently identified as part of standard diagnostic care, and we may seek to collaborate with an established diagnostics company to create a companion diagnostic for this potential indication. Some leading oncology hospitals do currently identify MLL-PTD patients. We believe that we will be able to identify and enroll MLL-PTD patients for our ongoing Phase 1 trial prior to developing a companion diagnostic.

Table of Contents**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 who have an oncogenic point mutation in EZH2 and for the treatment of certain INI1-deficient solid tumors, such as synovial sarcoma, a soft tissue sarcoma, and malignant rhabdoid tumor, a pediatric cancer. In June 2013, Eisai and we initiated a Phase 1/2 clinical trial of EPZ-6438. This trial is currently enrolling patients with advanced solid tumors or with relapsed or refractory B cell lymphoma to the Phase 1 dose escalation trial at clinical sites in France. The current design for the Phase 2 clinical trial is focused on the evaluation of EPZ-6438 for the treatment of non-Hodgkin lymphoma patients with a point mutation in EZH2. Subject to enrolling patients on our planned schedule, we expect to announce top-line results from the Phase 1 trial in 2014. Pending our review of the data from the Phase 1 trial, we expect to initiate the Phase 2 trial in 2014. The Phase 2 trial is currently planned to only enroll patients with a point mutation in EZH2. In addition, pending our review of the data from the Phase 1 trial, we plan to initiate a Phase 2 trial of EPZ-6438 for the treatment of synovial sarcoma in 2014. These two Phase 2 trials are intended to provide an initial assessment of efficacy, or proof of concept, in the two genetically defined cancers that we currently seek to treat with EPZ-6438.

We have granted Eisai a worldwide license to EPZ-6438, which Eisai refers to E7438, subject to our right to opt in to a 50/50 co-development, co-commercialization and profit-share arrangement with Eisai in the United States prior to the initiation of a registration trial. We are working with Roche and Eisai to develop a companion diagnostic to identify patients with a point mutation of EZH2.

Background on EZH2 Cancers. EZH2 is an HMT that can become oncogenic and cause non-Hodgkin lymphoma and a variety of other solid tumors, such as synovial sarcoma and malignant rhabdoid tumors. As a result, EZH2 has become an important target of oncological drug research.

Non-Hodgkin Lymphoma. In an article in *The New England Journal of Medicine* in December 1995, the authors estimated that patients with relapsed or refractory non-Hodgkin lymphoma who are not eligible for a stem cell transplant have a five-year overall survival rate ranging from approximately 10 to 15%. Two types of non-Hodgkin lymphoma, diffuse large B-cell lymphoma of germinal-center origin, or DLBCL, and follicular lymphoma, or FL, are particularly associated with oncogenic EZH2 mutations. In a report that we commissioned, Clarion Healthcare estimated that the annual incidence rate in the major markets of DLBCL is approximately 24,000 patients and the annual incidence rate of FL in the major markets is approximately 30,000 patients. Clarion Healthcare further estimated that approximately 12,000 of these patients, approximately 5,400 with DLBCL and approximately 6,600 with FL, carry the EZH2 oncogenic point mutation. Many patients with DLBCL and FL survive beyond the year in which they are diagnosed. Accordingly, we believe that the prevalence of DLBCL and FL in the major pharmaceutical markets is significantly higher than the annual incidence of 54,000 patients. Because some of these patients carry an EZH2 oncogenic point mutation, they comprise part of the potential market for EPZ-6438.

There are no therapies approved specifically for the treatment of cancer associated with an EZH2 point mutation. The most common treatments for both DLBCL and FL are multi-agent chemotherapy, usually combined with Rituxan[®]. Some patients with DLBCL are treated with an allogeneic stem cell transplant. A number of other widely used anti-cancer agents have broad labels that include non-Hodgkin lymphoma. While these therapies have enjoyed meaningful success in treating non-Hodgkin lymphoma, there remains an unmet medical need in patients with relapsed or refractory disease.

INI1-Deficient Tumors. INI1 is a regulatory complex that opposes the enzymatic function of EZH2. Due to a variety of genetic alterations, INI1 can lose its regulatory function. As a result, EZH2 activity is misregulated, causing EZH2 to play a driving, oncogenic role in a set of genetically defined cancers that include synovial sarcomas and malignant rhabdoid tumors. In a report that we commissioned, Clarion Healthcare estimated that the total annual incidence of synovial sarcoma patients in the major pharmaceutical markets is approximately 1,700 patients and other INI1-deficient tumors have an estimated annual incidence of 700 patients.

Table of Contents

Synovial Sarcoma. Synovial sarcoma is one of the most common soft tissue tumors in adolescents and young patients, with approximately one in three cases occurring in the first two decades of life. Mean age of patients at diagnosis is approximately 30 years. Current treatment consists of wide surgical resection, radiotherapy, and chemotherapy. In an article in the journal *Annals of Oncology* in January 2011, the authors estimate that long-term prognosis is poor due to late local recurrence, seen in 47% of patients, and distant metastases, seen in 50-70% of cases. Overall survival is 38.7% and 15-year survival is 46%.

Malignant Rhabdoid Tumors. Malignant rhabdoid tumors, or MRT, are a rare and deadly form of childhood cancer that is caused by a specific genetic alteration that is associated with the absence of the tumor suppression gene INI1. MRT typically presents either in the kidney or brain and in children less than two years of age. Current treatment consists of intensive chemotherapy and radiation therapy. In an article in the journal *Pediatric Blood & Cancer* in December 2011, the authors estimated that patients with MRT have event-free survival rates of less than 20% in both kidney and brain presentations. Moreover, there is considerable treatment-related morbidity in those few patients who achieve a durable remission, particularly in those who receive cranial irradiation as part of therapy.

Phase 1/2 Clinical Trial. We and Eisai are conducting the Phase 1/2 clinical trial of EPZ-6438 in two parts. The Phase 1 clinical trial is an open label dose escalation trial. The Phase 2 clinical trial will be conducted in two stages. In the first stage, all patients will be dosed at the maximum tolerated dose as determined in the Phase 1 clinical trial. Depending upon the number of responses observed in the first stage of the Phase 2 part of this clinical trial, we may initiate a second stage in which patients will be randomized in a 2:1 manner to receive either EPZ-6438 or the existing standard of care treatment. 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 objectives.

The primary objective of the Phase 1 clinical trial is to evaluate the safety and tolerability of EPZ-6438 and to determine its maximum tolerated dose when administered as a single agent twice daily in 28-day cycles in patients with advanced solid tumors or with relapsed or refractory B cell lymphoma. Subject to enrolling patients on our planned schedule, we expect to announce top-line results from the Phase 1 clinical trial in 2014.

Secondary objectives of the Phase 1 clinical trial are to:

determine the oral bioavailability, meaning the fraction of an orally administered drug that reaches systemic circulation, of EPZ-6438;

determine the potential for drug/drug interactions with EPZ-6438;

preliminarily assess activity of EPZ-6438; and

evaluate early evidence of anti-tumor activity in patients with an EZH2 point mutation.

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 and an EZH2 point mutation. The secondary objective of the Phase 2 clinical trial will be to assess progression-free survival, disease control rate and the clinical benefit rate of EPZ-6438 as a single agent.

Pending our review of the data from the Phase 1 trial, we plan to initiate a Phase 2 trial of EPZ-6438 for the treatment of synovial sarcoma in 2014. This trial will only enroll synovial sarcoma patients and is currently designed to provide an initial assessment of efficacy, or proof of concept, in this patient population.

The planned Phase 1/2 clinical trial is not powered to show results with statistical significance. 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 based on the clinical data observed in earlier trials.

Table of Contents

Preclinical Studies Non-Hodgkin Lymphoma. Based on a comprehensive program of preclinical testing of EPZ-6438, including several in vitro analyses and in vivo xenograft studies, we concluded that EPZ-6438 had exhibited appropriate pharmaceutical potential to advance it into clinical development for the treatment of non-Hodgkin lymphoma. Key findings from this preclinical program included the following:

In non-Hodgkin lymphoma cell lines that bear a point mutation in EZH2, EPZ-6438 inhibited the methylation associated with EZH2 activity in a concentration dependent manner. In these in vitro experiments, EPZ-6438 acted in a highly selective manner, inhibiting only the targeted EZH2-associated methylation and no other histone methyl marks. In addition, in these cell lines EPZ-6438 inhibited proliferation and killed cells containing the oncogenic EZH2 mutations but did not affect cells that did not contain these mutations.

We treated mouse xenograft models in which human EZH2 mutant-bearing non-Hodgkin lymphoma cells were implanted subcutaneously and allowed to establish tumors. Each dose group consisted of nine animals. We administered EPZ-6438 twice daily to these mice at four dose levels for 28 days by oral administration. Dose 1 was 80.5 mg/kg per dose; dose 2 was 161 mg/kg per dose; dose 3 was 322 mg/kg per dose; and dose 4 was the vehicle alone, with no EPZ-6438. In comparison with animals receiving only the vehicle, the 80.5 mg/kg treated group displayed significant tumor growth inhibition. In the 161 and 322 mg/kg treatment groups, tumors in all animals were reduced to undetectable volumes by the end of the 28 day treatment period, at which point the study ended. The results are illustrated in the graph below.

Median Tumor Volume

In a separate test, we studied the durability of drug efficacy. Mice were again treated twice daily either with the vehicle or with EPZ-6438 at the 322 mg/kg dose for 28 days. We measured tumor volume during this 28 day treatment period and for an additional 63 days beyond the treatment period, at which point the study ended. As in the first study, tumors in all animals in the 322 mg/kg treatment group were reduced to undetectable volumes by the end of the 28 day treatment period. No regrowth of tumor was observed in any of the treated animals through the end of the study, which was 91 days.

Table of Contents

Preclinical Studies INI1-Deficient Tumors. INI1 is a critical component of a protein complex known as SWI/SNF, that regulates EZH2 function. A variety of genetic alterations cause this protein complex to lose its regulatory function. In these cases, EZH2 becomes misregulated and a driving oncogene in specific, identifiable cancers. Collectively, these cancers are called INI1-deficient tumors.

Synovial sarcoma is an INI1-deficient tumor of particular interest for treatment with an EZH2 inhibitor. All synovial sarcomas have a specific genetic alteration in the SWI/SNF complex referred to as a chromosomal translocation. This chromosomal translocation results in the loss of SWI/SNF's regulatory function conferring sensitivity to EZH2 inhibitors. In a synovial sarcoma cell line that was confirmed to contain the specific chromosomal translocation product, treatment with the EZH2 inhibitor EPZ-6438 led to dose-dependent cell killing, similar to what we have observed in other cancer cell lines in which EZH2 plays an oncogenic role, such as MRT that is described below. In contrast, a control sarcoma cell line that lacked the specific chromosomal translocation and showed normal levels of INI1 was not sensitive to EPZ-6438 inhibition over the same range of doses. Pending our review of data from the ongoing Phase 1 trial of EPZ-6438, we plan to initiate a Phase 2 study in synovial sarcoma patients in 2014.

Similarly, EZH2 is oncogenic in 98% of MRT patients due to a specific genetic alteration referred to as an INI1 deletion that leads to a misregulated EZH2 activity. Key findings from our preclinical program included the following:

In *in vitro* studies of MRT cell lines with an INI1 deletion, EPZ-6438:

- i inhibited the methylation associated with EZH2 activity in a concentration dependent manner;
- i acted in a highly selective manner, inhibiting only the targeted EZH2-associated methylation and no other histone methyl marks; and
- i inhibited proliferation and killed cells containing the INI1 deletion but did not affect cells that did not contain the INI1 deletion.

In the *in vivo* preclinical animal model studies:

- i We treated mouse xenograft models in which human INI1-deleted MRT cells were implanted subcutaneously and allowed to establish tumors.
- i We administered EPZ-6438 twice daily to 16 mice at each of four dose levels for 21 days by oral administration. Dose 1 was 125 mg/kg per dose; dose 2 was 250 mg/kg per dose; dose 3 was 500 mg/kg per dose; and dose 4 was the vehicle alone, with no EPZ-6438.
- i Half of the mice in each group, or eight mice per group, were euthanized after 21 days of treatment so that tissue samples could be collected and analyzed for methyl mark changes. The other eight mice in each group continued to receive treatment for an additional seven days, for a total of 28 days of treatment.
- i In the 125 mg/kg treatment group, methyl mark levels were reduced by over 80% compared to the vehicle control group at day 21 with significant tumor growth inhibition in comparison to the animals receiving only the vehicle.

Edgar Filing: Epizyme, Inc. - Form 424B4

- i In the 250 and 500 mg/kg treatment groups, methyl mark levels were reduced by 90% or more compared to the vehicle control group at day 21, and tumors in all animals were reduced to volumes below the limits of detection by the end of the 28-day treatment period.

- i Mice in this study were kept alive until their tumors reached a volume of 2,000 cubic millimeters or until the end of the study, which was 32 days after the end of the dosing period. No regrowth of tumors was observed in any of the mice in the 250 and 500 mg/kg per dose treatment groups up to the end of the study.

Table of Contents

The tumor volume results are illustrated in the graph below.

Median Tumor Volume

We may also conduct clinical studies with EZH2 inhibitors for the treatment of MRT.

Companion Diagnostic. Eisai and 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. 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 Roche, Eisai and we 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.

HMT Collaborations

We have entered into three strategic collaborations for our therapeutic programs. These therapeutic collaborations have provided us with \$133.3 million in non-equity funding through September 30, 2013. With the additional \$29.0 million in milestones earned from Celgene and GSK in December 2013, our therapeutic collaborations will have provided us with \$162.3 million in non-equity funding. Our therapeutic collaborations also provide us with research funding and the potential for more than \$1.0 billion of 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 collaborations to develop companion diagnostics with Abbott and Roche. Key terms of these five collaborations are summarized below.

Therapeutic Collaborations

Celgene

Overview. 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 and any other HMT targets from our product platform for patients with genetically defined cancers, excluding targets covered by our two other existing therapeutic collaborations, which we refer to as the available targets.

Table of Contents

Under the terms of the agreement, through September 30, 2013, we received a \$65.0 million upfront payment and \$25.0 million from the sale of our series C preferred stock to an affiliate of Celgene, of which \$3.0 million was considered a premium and included as collaboration arrangement consideration for a total upfront payment of \$68.0 million, and in December 2013, we earned a \$25.0 million clinical development milestone. In addition, we are eligible to earn up to \$35.0 million in clinical development milestone payments and up to \$100.0 million in regulatory milestone payments related to DOT1L. We are also eligible to earn up to \$65.0 million in payments, including a combination of clinical development milestone payments and an option exercise fee, and up to \$100.0 million in regulatory milestone payments for each available target as to which Celgene exercises its option during an initial option period ending in July 2015. Celgene has the right to extend the option period until July 2016 by making a significant option extension payment. As to DOT1L and each available target as to which Celgene may exercise its option, we retain all product rights in the United States and are eligible to receive royalties for each target at defined percentages ranging from the mid-single digits to the mid-teens on net product sales outside of the United States, subject to reductions in specified circumstances.

Under the agreement, we granted Celgene an exclusive license, for all countries other than the United States, to HMT inhibitors directed to DOT1L and an option, on a target-by-target basis, to exclusively license, for all countries of the world other than the United States, rights to HMT inhibitors directed to any other HMT targets during the option period, excluding targets covered by our other collaborations. During the option period specified in the agreement, which could extend until July 2016, Celgene has the right to exercise its option to non-U.S. rights to additional HMT targets other than DOT1L until the effectiveness of an IND for an HMT inhibitor directed to such additional HMT target. If Celgene does not exercise its option with respect to an additional HMT target during the applicable exercise period, we retain worldwide rights to HMT inhibitors directed to such target, other than HMT inhibitors that may be provided by Celgene if we were to agree to their introduction.

Research Obligations. We are primarily responsible for the research strategy under the collaboration. During the option period and, as to targets licensed by Celgene during the option period, until effectiveness of an IND for an HMT inhibitor directed to the applicable target if such an IND is not effective upon expiration of the option period, we are required to use commercially reasonable efforts to conduct platform discovery activities necessary to characterize and identify additional targets and HMT inhibitors directed to additional targets and targets licensed to Celgene. For the DOT1L target, we are obligated to conduct and solely fund development costs of the Phase 1 clinical trials for EPZ-5676, after which point Celgene and we will equally co-fund global development and each party will solely fund territory-specific development costs for its territory. For each other HMT target licensed to Celgene, we are obligated to conduct and solely fund research and development activities generally through the effectiveness of the first IND for an HMT inhibitor directed to such target, after which point Celgene and we will equally co-fund global development and each party will solely fund territory-specific development costs for its territory for such target. In the third quarter of 2013, we recorded accounts receivable of \$0.7 million related to non-Phase 1 global development costs subject to the co-funding provisions of this agreement. Co-funded amounts from Celgene are recorded as a reduction to research and development expense.

Governance. Our collaboration with Celgene is guided by joint research, development and commercialization committees. Subject to limitations specified in the agreement, if the applicable governance committee is not able to make a decision by consensus and the parties are not able to resolve the issue through escalation to specified senior executive officers of the parties, then as to licensed programs we generally have final decision-making authority over research and development matters prior to clinical proof-of-concept, Celgene generally has final decision-making authority over global development matters, including over global activities and related expenses that we are obligated to co-fund unless we exercise our opt-out right as to such licensed program, following clinical proof-of-concept. Each party has final decision-making authority over commercialization matters in its respective territory.

Opt-Out Right. On a licensed target-by-licensed target basis, we have the right, in our sole discretion, to opt-out of further participation in and co-funding of development, other than specified costs necessary to complete development activities in process at the time we exercise our opt-out right. We can exercise our opt-out

Table of Contents

right at specified times before the scheduled initiation of the first pivotal clinical trial or before the estimated date of filing of the first new drug application for an HMT inhibitor directed to the licensed target or any time after regulatory approval of an HMT inhibitor directed to the licensed target. Following an opt-out, we are no longer required to co-fund global development for the applicable program other than specified costs necessary to complete development activities in process at the time we exercise our opt-out right, and we are obligated to grant Celgene an exclusive license to HMT inhibitors directed to the applicable target in the United States. Following our opt-out, if any, we would be eligible to receive specified milestone payments and royalties based on net product sales in the United States of HMT inhibitors directed to the licensed target in the event that Celgene develops and commercializes a product in the United States, which Celgene is not obligated to do.

Exclusivity Restrictions. Subject to exceptions specified in the agreement, during the option period, we may not research, develop or commercialize HMT inhibitors directed to any additional target, other than pursuant to the agreement, and, following the option period, we may not research, develop or commercialize HMT inhibitors directed to any target licensed by Celgene, other than pursuant to the agreement.

Right of First Negotiation. In addition, we granted to Celgene a right of first negotiation with respect to business combination transactions that we may desire to pursue with third parties during the option period under our agreement with Celgene, which includes any extension of this period. During the option period, we are required to notify Celgene if we desire to pursue a specified business combination transaction with a third party prior to negotiating terms with the third party, and after so notifying Celgene we have agreed not to, directly or indirectly, solicit, initiate or encourage proposals from, discuss or negotiate with, or provide any information to, any third party related to the proposed transaction for a specified period from the date we first notify Celgene of such proposed transaction, or the Celgene negotiation period. If Celgene notifies us that it is interested in entering into the proposed transaction, we have agreed to negotiate in good faith with Celgene during the Celgene negotiation period. Following the Celgene negotiation period, if we have not entered into the proposed transaction with Celgene, or if Celgene does not notify us that it is interested in entering into the proposed transaction, we are free to enter into the proposed transaction with a third party for a period of 225 days following the expiration of the Celgene negotiation period, but we are obligated to re-offer the proposed transaction to Celgene if during the option term we propose to enter into the proposed transaction with a third party on terms that, in specified respects, are less favorable to us than the terms last offered by Celgene.

Term and Termination. Our agreement with Celgene will expire on a product-by-product and country-by-country basis on the date of the expiration of the applicable royalty term with respect to each licensed product in each country and in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries. The royalty term for each licensed product in each country is the period commencing with first commercial sale of the applicable licensed product in the applicable country and ending on the latest of expiration of specified patent coverage, specified regulatory exclusivity or 15 years following the first commercial sale in the applicable country. Celgene has the right to terminate the agreement in its entirety, upon 60 or 120 days notice depending on the timing of such termination. The agreement may also be terminated in its entirety during the option period, and on a licensed target-by-licensed target basis after the option period, by either Celgene or us in the event of a material breach by the other party. The agreement may be terminated on a licensed target-by-licensed target basis by either Celgene or us in the event the other party, or an affiliate or sublicensee of the other party, participates or actively assists in a legal challenge to specified patents of the terminating party or in its entirety in the event the other party becomes subject to specified bankruptcy, insolvency or similar circumstances.

Eisai

Overview. In April 2011, we entered into a collaboration and license agreement with Eisai under which we granted Eisai an exclusive worldwide license to our small molecule HMT inhibitors directed to EZH2, 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. Additionally, as part of the research collaboration we agreed to provide research and development services related to the licensed compounds through December 31, 2014.

Table of Contents

Under the terms of the agreement, we have received a \$3.0 million upfront payment, \$7.0 million in preclinical research and development milestone payments, and a \$6.0 million clinical development milestone payment and cash payments and accounts receivable totaling \$16.5 million for research and development services through September 30, 2013. We are eligible to earn up to \$25.0 million in additional preclinical research and development milestone payments, up to \$55.0 million in regulatory milestone payments and up to \$115.0 million in sales-based milestone payments. We are also eligible to receive royalties at a percentage in the mid-single digits on any net product sales outside of the United States and from the mid-single digits to low double-digits on any product sales in the United States, subject to reductions in specified circumstances.

Eisai solely funds all research, development and commercialization costs for licensed compounds, except for the cost obligations that we will undertake if we exercise our opt-in right to co-develop, co-commercialize and share profits with Eisai as to licensed products in the United States.

Opt-in Right. Our opt-in right to co-develop, co-commercialize and share profits may be exercised on a licensed compound-by-licensed compound basis any time prior to the end of a specified period following Eisai's provision to us of specified information following the licensed compound's achievement of clinical proof-of-concept. If we exercise our opt-in right as to a licensed compound, the licensed compound becomes a shared product as to which:

Eisai's obligation to pay royalties to us as to such shared product in the United States will terminate;

Eisai and we will share equally in net profits or losses with respect to such shared product in the United States;

25.0% of specified past development costs will become creditable by Eisai against future milestone payments or royalties due to us, subject to certain limitations specified in the agreement;

Eisai and we will share equally in subsequent development costs allocated to the United States; and

all subsequent milestones that become payable by Eisai to us based on the shared product will be decreased by 50.0%.

If we undergo a specified change of control event in which we are acquired by or combine with an entity with a specified competing business, or if following a change of control event we materially breach the agreement and do not cure such breach within the specified cure period, Eisai will have the right to terminate our co-development, co-commercialization and profit sharing option and, if we have previously exercised our option, our co-development, co-commercialization and profit sharing rights. Subject to the foregoing, our agreement with Eisai may be assigned by us without Eisai's consent to a successor in interest by way of merger or consolidation or in connection with the sale of all or substantially all of our business or assets to which the agreement relates, subject to notice provisions and the assignee's written assumption of the obligations.

Governance. Research and development through clinical proof-of-concept under our collaboration with Eisai are guided by a joint steering committee. If the joint steering committee is not able to make a decision by consensus and the parties are not able to resolve the issue through escalation to specified senior executive officers of the parties, then as to specified issues of a scientific or technical nature, the issue will be submitted to a third party technical expert for resolution, and as to other issues, the issue will remain deadlocked until the parties are able to reach consensus. If we exercise our opt-in right to co-develop, co-commercialize and share profits in the United States, we and Eisai will enter into an additional agreement that will allocate responsibilities for later stage development and commercialization activities for the shared product between the parties and will extend the foregoing governance structure to those activities.

Exclusivity Restrictions. Subject to exceptions specified in the agreement, during the term of the agreement, we may not research, develop or commercialize HMT inhibitors directed to EZH2, other than pursuant to the agreement.

Table of Contents

Term and Termination. Our agreement with Eisai will remain in effect until the later of expiration of all royalty obligations under the agreement with respect to all licensed products or, if we exercise our option, until the shared product is no longer being developed or commercialized by the parties in or for the United States or the parties' agreement with respect to co-commercialization and profit sharing otherwise terminates. The royalty term for each licensed product in each country, other than shared products in the United States, is the period commencing with first commercial sale of the applicable licensed product in the applicable country and ending on the latest expiration of specified patent coverage, specified regulatory exclusivity or ten years following the first commercial sale. Eisai may terminate the agreement for its convenience in its entirety or as to one or more major market countries, as defined in the agreement, upon 90 days' prior written notice to us. Eisai also has the right to terminate the agreement in its entirety immediately if, in good faith, it believes that it is not advisable for it to continue to develop or commercialize the licensed products from a scientific, regulatory or ethical perspective as a result of a bona fide serious safety issue regarding the use of any licensed product. The agreement may also be terminated by either party in the event of an uncured material breach by the other party or by us in the event Eisai, or an affiliate or sublicensee, participates or actively assists in an action or proceeding challenging or denying the validity of one of our patents.

GlaxoSmithKline

Overview. In January 2011, we entered into a collaboration and license agreement with GSK to discover, develop and commercialize novel small molecule HMT inhibitors directed to available targets from our product platform. Under the terms of the agreement, we granted GSK the option to obtain exclusive worldwide license rights to HMT inhibitors directed to three targets. Additionally, as part of the research collaboration provided for in the agreement, we agreed to provide research and development services related to the licensed targets pursuant to agreed upon research plans during a research term that ends January 8, 2015.

Under the agreement, we have received a \$20.0 million upfront payment, \$8.0 million in preclinical research and development milestone payments, and \$6.0 million of fixed research funding through September 30, 2013, and in December 2013, we earned a \$4.0 million preclinical research and development milestone. We are eligible to receive up to \$17.0 million in additional preclinical research and development milestone payments, up to \$99.0 million in clinical development milestone payments, up to \$240.0 million in regulatory milestone payments and up to \$270.0 million in sales-based milestone payments. In addition, GSK is required to pay us royalties at percentages between the mid-single digits to the low double-digits, on a licensed product-by-licensed product basis, on worldwide net product sales, subject to reductions in specified circumstances. If GSK decides during the research term that it no longer wishes to continue the research and development of licensed products directed to a selected target, such target would no longer be included in the collaboration and GSK would grant us a license to research, develop and commercialize licensed products directed to such target. In such event, we will be obligated to pay GSK a low-single digit royalty on our net product sales of such licensed products.

For each selected target in the collaboration, we are primarily responsible for research until the selection of the development candidate, and GSK is solely responsible for subsequent development and commercialization. GSK provided a fixed amount of research funding during the second and third years of the research term and is obligated to provide research funding equal to 100.0% of mutually agreed research and development costs, subject to specified limitations, for any research activities we conduct in the fourth year of the research term. In December 2013, we and GSK agreed to the selection of a development candidate for one of the three targets under the agreement. As to this target, GSK is solely responsible for subsequent development and commercialization.

Exclusivity Provisions. Subject to exceptions specified in the agreement, during the term of the agreement, we may not research, develop or commercialize HMT inhibitors directed to the three targets selected by GSK, other than pursuant to the agreement.

Table of Contents

Equity Participation Right. Under the agreement, we also granted GSK the option to acquire up to 10.0% of the securities issued in our next qualified venture capital financing, if any, which meets conditions set forth in the agreement. We are not obligated to undertake any such financing and one has not occurred since we granted GSK this right.

Term and Termination. The agreement will expire in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries. The royalty term for each licensed product in each country is the period commencing with first commercial sale of the applicable licensed product in the applicable country and ending on the later of expiration of specified patent coverage or ten years following the first commercial sale. GSK has the right to terminate the agreement at any time with respect to one or more selected targets or in its entirety, upon 90 days' prior written notice to us. The agreement may also be terminated with respect to one or more selected targets or in its entirety by either GSK or us in the event of a material breach by the other party. The agreement may be terminated with respect to selected targets by us in the event GSK participates or actively assists in a legal challenge to one of the patents exclusively licensed to GSK under the agreement with respect to the applicable selected target.

Companion Diagnostics

Abbott. In February 2013, we entered into an agreement with Abbott under which we agreed to fund Abbott's development of a companion diagnostic to identify patients with the MLL-r genetic alteration targeted by EPZ-5676. Under the terms of the agreement, we paid Abbott an upfront payment of \$0.9 million upon the execution of the agreement, are obligated to make aggregate milestone-based development payments of up to \$6.0 million and are obligated to reimburse Abbott for specified costs expected to be incurred in connection with Abbott conducting clinical trials to obtain the necessary regulatory approvals for the companion diagnostic which are not to exceed \$0.9 million unless agreed to in advance by both Abbott and us.

Under our agreement with Abbott, Abbott is obligated to use commercially reasonable efforts to develop and make commercially available the companion diagnostic. Abbott has exclusive rights to commercialize and retain all proceeds from its commercialization of the companion diagnostic.

Our agreement with Abbott will expire when we are no longer commercializing EPZ-5676. We may terminate the agreement for convenience by giving Abbott 60 days' written notice, and we will be obligated to pay Abbott a termination fee if we exercise such right after the date 18 months following the execution of the agreement but prior to the completion of the development program for the companion diagnostic. Either Abbott or we may also terminate the agreement in the event of a material breach by the other party, in the event of specified injunctions that may issue in the future based on infringement of third party patents or in the event of specified bankruptcy or similar circumstances.

Roche. In December 2012, Eisai and we entered into an agreement with Roche under which Eisai and we are funding Roche's development of a companion diagnostic to identify patients who possess certain point mutations of EZH2. The development costs under the agreement with Roche will be the responsibility of Eisai until such time, if any, as we exercise our opt-in right under our collaboration agreement with Eisai. Under the terms of the agreement, Eisai agreed to pay Roche defined milestone payments of up to \$21.0 million to develop and to make commercially available the companion diagnostic. In October 2013, we amended this agreement to include additional point mutations in EZH2 for additional milestone payments of \$0.5 million, resulting in total potential defined milestone payments under this amended agreement of up to \$21.5 million. If we exercise our opt-in right to co-develop, co-commercialize and share profits in the United States as to EPZ-6438, Eisai will be entitled to offset up to 25% of the funding amount it has previously paid to Roche against future milestone payments and royalties that Eisai may be obligated to pay to us under our collaboration and license agreement with Eisai, and we will become obligated to fund up to half of the defined milestones that remain payable to Roche as of the time we opt-in.

Table of Contents

Under our agreement with Roche, Roche is obligated to use commercially reasonable efforts to develop and to make commercially available the companion diagnostic. Roche has exclusive rights to commercialize the companion diagnostic.

Our agreement with Roche will expire when Eisai and we are no longer developing or commercializing EPZ-6438. Eisai and we may terminate the agreement by giving Roche 90 days written notice if we and Eisai discontinue development and commercialization of EPZ-6438 or determine, in conjunction with Roche, that the companion diagnostic is not needed for use with EPZ-6438. Either Eisai and we or Roche may also terminate the agreement in the event of a material breach by the other party, in the event of material changes in circumstances that are contrary to key assumptions specified in the agreement or in the event of specified bankruptcy or similar circumstances. Under specified termination circumstances, Roche may become entitled to specified termination fees, which Eisai and we would be obligated to bear in the same manner that we bear the funding amounts payable to Roche.

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technology and other inventions that are important to our business. As more fully described below, in 2013, two U.S. patents covering the composition of matter of our DOT1L and EZH2 product candidates were issued. These patents will expire in 2032. In addition to patent protection, we also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen, and maintain our proprietary position in the field of HMTs.

A third party may hold intellectual property, including patent rights, that is important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

We plan to continue to expand our intellectual property estate by filing patent applications directed to dosage forms, methods of treatment and additional HMT inhibitor compounds and their derivatives. Specifically, we seek patent protection in the United States and internationally for novel compositions of matter covering the compounds, the chemistries and processes for manufacturing these compounds and the use of these compounds in a variety of therapies.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover,

Table of Contents

we may have to participate in interference proceedings declared by the United States Patent and Trademark Office, or USPTO, or a foreign patent office to determine priority of invention or in post-grant challenge proceedings, such as oppositions, that challenge priority of invention or other features of patentability. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us.

The patent portfolios for our most advanced programs are summarized below.

DOT1L. Our DOT1L patent portfolio is wholly owned by us and includes U.S. Patent No. 8,580,762 covering the composition of matter of EPZ-5676. The patent issued on November 12, 2013 and will expire in 2032. Patent applications in the same family as U.S. Patent No. 8,580,762 are pending in a variety of worldwide jurisdictions, including the United States. The DOT1L portfolio encompasses additional pending patent applications relating to compositions of matter and methods of making and use including three patent families with applications filed in a variety of worldwide jurisdictions, including in the United States, three Patent Cooperation Treaty, or PCT, applications that are eligible for filing in most worldwide jurisdictions, including the United States, and eight U.S. provisional applications that may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. If issued, these patents are predicted to expire between 2031 and 2034.

EZH2. Our EZH2 patent portfolio is wholly owned by us and includes U.S. Patent No. 8,410,088 covering the composition of matter of EPZ-6438. This patent issued on April 2, 2013 and will expire in 2032. Our EZH2 portfolio also includes U.S. Patent No. 8,598,167 which issued on December 3, 2013 and will expire in 2032. The claims of this patent cover the composition of matter of another EZH2 inhibitor compound. Patent applications in the same families as U.S. Patents Nos. 8,410,088 and 8,598,167 are pending in a variety of worldwide jurisdictions, including in the United States, and are wholly owned by us. The EZH2 portfolio encompasses additional pending patent applications relating to compositions of matter and methods of making and use including four patent families with applications filed in a variety of worldwide jurisdictions, including in the United States, eight PCT applications that are eligible for filing in most worldwide jurisdictions, including in the United States, and 12 U.S. provisional applications that may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. These patent applications are wholly owned by us or jointly owned by us and Eisai. If issued, these patents are predicted to expire between 2031 and 2034.

Other. In addition, we have patent portfolios that are directed to a number of targets other than DOT1L and EZH2. These patent portfolios are wholly owned by us and include five pending U.S. patent applications and six PCT applications that are eligible for filing in most worldwide jurisdictions, including in the United States, and 12 pending U.S. provisional patent applications that may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. These portfolios include compositions and methods of making and using of compounds that target HMTs other than DOT1L and EZH2. If issued, these patents are predicted to expire in 2033 or 2034.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other non-United States jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We intend to seek patent term

Table of Contents

extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

UNC In-Licensed Portfolio. In January 2008, we entered into a license agreement with the University of North Carolina at Chapel Hill, or UNC, to discover, develop and commercialize products utilizing specified inventions of UNC. Under the terms of the agreement, we were granted an exclusive, worldwide license under specified patent rights and a non-exclusive worldwide license under specified know-how and biological materials, in each case to discover, develop, manufacture and commercialize pharmaceutical and diagnostic products. The intellectual property we license from UNC includes four issued U.S. patents, five pending U.S. patent applications, 20 patents issued in other jurisdictions and five patent applications pending in other jurisdictions. The issued patents are predicted to expire between 2024 and 2030, and the pending applications, if issued, are predicted to expire between 2024 and 2026. The intellectual property we have licensed from UNC is not directly related to our current product candidates, EPZ-5676 and EPZ-6438, and relates solely to screening methods and related materials.

Under the agreement, UNC retained rights, on behalf of itself and other non-profit academic institutions, to practice under the licensed rights for non-profit purposes. The license rights granted to us are further subject to a non-exclusive license granted by UNC to the Howard Hughes Medical Institute for research purposes and any rights the United States Government may have in such licensed rights due to its sponsorship of research that led to the creation of the licensed rights. We agreed to pay UNC specified research, development and sales milestone payments aggregating up to \$1.9 million and additional payments upon the grant, if any, of sublicenses to non-affiliated third parties. In addition, we are required to pay UNC royalties in the low single-digits on worldwide net product sales of screening method technologies and related materials, but not on any drugs, during the term of the agreement. These royalties do not cover the manufacture, sale or use of any drug products that have been identified and developed by us, such as our DOT1L and EZH2 therapeutics, including EPZ-5676 and EPZ-6438. In connection with the execution of this license agreement in 2008, we issued 98,666 shares of common stock and paid a license fee of \$0.1 million to UNC. Through September 30, 2013, we have paid an aggregate of \$0.1 million in milestone payments to UNC. We have not paid any royalties to UNC.

The agreement terminates upon the expiration of the last valid claim of the licensed patent rights. We may terminate the agreement at any time by giving UNC 60 days' written notice. The agreement may also be terminated by UNC in the event of a material breach by us or in the event we become subject to specified bankruptcy or similar circumstances.

Table of Contents

Manufacturing

We do not have any manufacturing facilities or personnel. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. To date, we have obtained materials for EPZ-5676 from multiple third party manufacturers. Eisai currently manufactures the active pharmaceutical ingredient for EPZ-6438 for clinical testing. For both EPZ-5676 and EPZ-6438, we intend to identify and qualify multiple manufacturers to provide the active pharmaceutical ingredient and fill-and-finish services prior to submission of a new drug application to the FDA.

All of our drug candidates are small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale up and does not require unusual equipment in the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

We generally expect to rely on third parties for the manufacture of our companion diagnostics. We are currently collaborating with Abbott for the development of a companion diagnostic for use with EPZ-5676 and with Roche for a diagnostic for use with EPZ-6438, and we expect to rely on them for the manufacture of the diagnostics they are developing. We expect to enter into similar agreements for the manufacture of other companion diagnostics.

Commercialization

We have not yet established a sales, marketing or product distribution infrastructure because our lead candidates are still in early clinical development. We generally expect to retain commercial rights in the United States for our product candidates for which we receive marketing approvals and have done so to date in our collaborations other than our GSK collaboration. We believe that it will be possible for us to access the United States oncology market through a focused, specialized sales force.

Subject to receiving marketing approvals, we expect to commence commercialization activities by building a focused sales and marketing organization in the United States to sell our products. We believe that such an organization will be able to address the community of oncologists who are the key specialists in treating the patient populations for which our product candidates are being developed. Outside the United States, we expect to enter into distribution and other marketing arrangements with third parties for any of our product candidates that obtain marketing approval.

We also plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with thought leaders in relevant fields of medicine.

We expect that our collaborators for any companion diagnostics we may develop in the future for use with our therapeutic products will hold the commercial rights to these diagnostic products, as is the case for our collaborations with Abbott and Roche. We expect to coordinate closely with our diagnostic collaborators in connection with the marketing and sale of our related therapeutic products.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential

Table of Contents

competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. In addition, many companies are developing cancer therapeutics that work by targeting epigenetic mechanisms other than HMTs, and some including Celgene and Eisai, are now marketing cancer treatments that work by targeting epigenetic mechanisms other than HMTs. There are also companies developing new epigenetic treatments for cancer that target HMTs, including GSK, Novartis AG, Pfizer, Inc. and Genentech, Inc.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of all of our therapeutic product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of companion diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third party payors seeking to encourage the use of generic products. Generic products that broadly address these indications are currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates may compete with many existing drug and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates will not be competitive with them. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third party payors.

In addition to currently marketed therapies, there are also a number of products in late stage clinical development to treat cancer. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

Table of Contents

If our lead product candidates are approved for the indications for which we are currently undertaking clinical trials, they will compete with the therapies and currently marketed drugs discussed below.

EPZ-5676. There are no approved therapies specifically indicated for MLL-r or MLL-PTD. There are, however, currently approved therapies for acute leukemias in general and a variety of other malignancies. The current standard of care depends on the specific lineage of the leukemia. Patients with AML and ALL typically are treated with intensive multi-agent chemotherapy and high risk patients who enter remission and have a matched donor often receive an allogeneic stem cell transplant.

EPZ-6438. No therapies are approved specifically for the treatment of tumors associated with the oncogenic mutation of EZH2. The most common treatments for DLBCL and FL are chemotherapies, usually combined with the monoclonal antibody Rituxan[®]. While Rituxan[®] is currently the only therapy with specific indications for DLBCL and FL, a number of other widely used anti-cancer agents have broad labels that include non-Hodgkin lymphoma. The clinical course of synovial sarcoma is characterized by frequent and late local or metastatic recurrence and there are no specific or effective treatments available for synovial sarcoma after failure of ifosfamide-based treatment. Current treatment for MRTs consists of intensive chemotherapy and radiation therapy.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending new drug applications, or NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;

Edgar Filing: Epizyme, Inc. - Form 424B4

submission to the FDA of an IND which must become effective before human clinical trials may begin;

approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;

performance of human clinical trials, including adequate and well-controlled clinical trials, in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;

submission to the FDA of an NDA;

satisfactory completion of an FDA advisory committee review, if applicable;

Table of Contents

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites to determine GCP compliance; and

FDA review and approval of the NDA.

Preclinical Studies. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials. Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Marketing Approval. Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA

Table of Contents

is subject to a substantial application user fee. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has agreed to certain performance goals regarding the timing of its review of an application.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to mitigate any identified or suspected serious risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA typically refers a question regarding a novel drug to an external advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Table of Contents

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Special FDA Expedited Review and Approval Programs. The FDA has various programs, including fast track designation, accelerated approval, priority review and breakthrough designation, that are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures. To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors.

The FDA may give a priority review designation to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. These six and ten month review periods are measured from the filing date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures.

Moreover, under the provisions of the new Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a breakthrough therapy. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Table of Contents

FDA Regulation of Companion Diagnostics. Our drug products may rely upon *in vitro* companion diagnostics for use in selecting the patients that we believe will respond to our cancer therapeutics. FDA officials have issued draft guidance that, if finalized, would address issues critical to developing *in vitro* companion diagnostics, such as biomarker qualification, establishing clinical validity, the use of retrospective data, the appropriate patient population and when the FDA will require that the device and the drug be approved simultaneously. The draft guidance issued in July 2011 states that if safe and effective use of a therapeutic product depends on an *in vitro* diagnostic, then the FDA generally will require approval or clearance of the diagnostic at the same time that the FDA approves the therapeutic product. The FDA has yet to issue further guidance, and it is unclear whether it will do so, or what the scope would be.

The FDA previously has required *in vitro* companion diagnostics intended to select the patients who will respond to the cancer treatment to obtain Pre-Market Approval, or PMA, simultaneously with approval of the drug. Based on the draft guidance, and the FDA's past treatment of companion diagnostics, we believe that the FDA will require PMA approval of one or more *in vitro* companion diagnostics to identify patient populations suitable for our cancer therapies. The review of these *in vitro* companion diagnostics in conjunction with the review of our cancer treatments involves coordination of review by the FDA's Center for Drug Evaluation and Research and by the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

Post-Approval Requirements. Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;

finer, warning letters or holds on post-approval clinical trials;

Table of Contents

refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;

product seizure or detention, or refusal to permit the import or export of products; or

injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies generally are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Federal and State Fraud and Abuse and Data Privacy and Security Laws and Regulations. In addition to FDA restrictions on marketing of pharmaceutical products, federal and state fraud and abuse laws restrict business practices in the biopharmaceutical industry. These laws include anti-kickback and false claims laws and regulations as well as data privacy and security laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term remuneration has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some common activities from prosecution, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

The reach of the Anti-Kickback Statute was also broadened by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively PPACA, which, among other things, amended the intent requirement of the federal Anti-Kickback Statute such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, PPACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. PPACA also created new federal requirements for reporting, by applicable manufacturers of covered drugs, payments and other transfers of value to physicians and teaching hospitals.

Edgar Filing: Epizyme, Inc. - Form 424B4

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes any

Table of Contents

request or demand for money or property presented to the U.S. government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to business associates, defined as independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Coverage and Reimbursement. The commercial success of our product candidates and our ability to commercialize any approved product candidates successfully will depend in part on the extent to which governmental authorities, private health insurers and other third party payors provide coverage for and establish adequate reimbursement levels for our therapeutic product candidates and related companion diagnostics. Government health administration authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. In particular, in the United States, private health insurers and other third party payors often provide reimbursement for products and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the European Union and other potentially significant markets for our product candidates, government authorities and third party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

Third party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for medical products. For example, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Legislative proposals to reform healthcare

Table of Contents

or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidates or exclusion of our products and product candidates from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates. We cannot provide any assurances that we will be able to obtain and maintain third party coverage or adequate reimbursement for our product candidates in whole or in part.

Impact of Healthcare Reform on Coverage, Reimbursement, and Pricing. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Part D plans include both standalone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, any negotiated prices for our future products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. If third party payors do not consider our product candidates to be cost-effective compared to other available therapies, they may not cover our product candidates, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives, including, most recently, PPACA, which became law in March 2010 and substantially changes the way healthcare is financed by both governmental and private insurers. Among other cost containment measures, the PPACA establishes an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit the prices we are able to charge for our product candidates, once approved, or the amounts of reimbursement available for our product candidates once they are approved.

Table of Contents

Exclusivity and Approval of Competing Products

Hatch-Waxman Patent Exclusivity. In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA, or 505(b)(2) NDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths, dosage form and route of administration as the listed drug and has been shown to be bioequivalent through *in vitro* or *in vivo* testing or otherwise to the listed drug. ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug. 505(b)(2) NDAs generally are submitted for changes to a previously approved drug product, such as a new dosage form or indication.

The ANDA or 505(b)(2) NDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. Specifically, the applicant must certify with respect to each patent that:

the required patent information has not been filed;

the listed patent has expired;

the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or

the listed patent is invalid, unenforceable, or will not be infringed by the new product.

Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except when the ANDA or 505(b)(2) NDA applicant challenges a listed drug. A certification that the proposed product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA or 505(b)(2) NDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of notice of the Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

Hatch-Waxman Non-Patent Exclusivity. Market and data exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United

Edgar Filing: Epizyme, Inc. - Form 424B4

States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the activity of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company that contains the previously approved active moiety. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

Table of Contents

The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application or supplement. Three-year exclusivity may be awarded for changes to a previously approved drug product, such as new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Orphan Drug Exclusivity. The Orphan Drug Act provides incentives for the development of drugs intended to treat rare diseases or conditions, which generally are diseases or conditions affecting less than 200,000 individuals annually in the United States. If a sponsor demonstrates that a drug is intended to treat a rare disease or condition, the FDA grants orphan drug designation to the product for that use. The benefits of orphan drug designation include research and development tax credits and exemption from user fees. A drug that is approved for the orphan drug designated indication is granted seven years of orphan drug exclusivity. During that period, the FDA generally may not approve any other application for the same product for the same indication, although there are exceptions, most notably when the later product is shown to be clinically superior to the product with exclusivity. We intend to seek orphan drug designation and exclusivity for our products whenever it is available.

Pediatric Exclusivity. Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan drug exclusivity periods described above. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or Orange Book listed patent protection cover the drug are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve an ANDA or 505(b)(2) application owing to regulatory exclusivity or listed patents. When any of our products is approved, we anticipate seeking pediatric exclusivity when it is appropriate.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. For example, in the European Union, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

European Union Drug Approval Process. To obtain marketing approval of a drug under European Union regulatory systems, we may submit marketing authorization applications, or MAAs, either under a centralized or

Table of Contents

decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization that is valid for all European Union member states. The centralized procedure is compulsory for medicines produced by specified biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of specified diseases, and optional for those products that are highly innovative or for which a centralized process is in the interest of patients. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Scientific Advice Working Party of the Committee of Medicinal Products for Human Use, or the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, defined by three cumulative criteria: the seriousness of the disease, such as heavy disabling or life-threatening diseases, to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In this circumstance, the European Medicines Agency, or EMA, ensures that the opinion of the CHMP is given within 150 days.

The EMA grants orphan drug designation to promote the development of products that may offer therapeutic benefits for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the European Union. In addition, orphan drug designation can be granted if the drug is intended for a life threatening, seriously debilitating or serious and chronic condition in the European Union and without incentives it is unlikely that sales of the drug in the European Union would be sufficient to justify developing the drug. Orphan drug designation is only available if there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients. Orphan drug designation provides opportunities for free protocol assistance, fee reductions for access to the centralized regulatory procedures before and during the first year after marketing authorization and 10 years of market exclusivity following drug approval. Fee reductions are not limited to the first year after authorization for small and medium enterprises. The exclusivity period may be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state, known as the reference member state. Under this procedure, an applicant submits an application, or dossier, and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points may eventually be referred to the European Commission, whose decision is binding on all member states. For the EMA, a Pediatric Investigation Plan, or a request for waiver or deferral, is required for submission prior to submitting an MAA for use for drugs in pediatric populations.

In the European Union, new chemical entities qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from assessing a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted but not approved for two years. Even if a compound is considered to be a new chemical entity and the sponsor is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the drug if such company can complete a full MAA with a complete human clinical trial database and obtain marketing approval of its product.

Legal Proceedings

We are not currently a party to any material legal proceedings.

Table of Contents

Facilities

Our headquarters are located in Cambridge, Massachusetts, where we occupy approximately 32,000 square feet of office and laboratory space. The term of the lease expires November 30, 2017. On September 30, 2013, we entered into an amendment to the lease for our headquarters under which we leased an additional 10,500 square feet of office space. We expect to occupy this additional space beginning in the first quarter of 2014 through November 30, 2017. We also lease approximately 18,000 square feet of office and laboratory space at a second facility in Cambridge, where our headquarters were located until November 2012, under a lease that expires on December 31, 2014. In November 2013, we entered into a sublease for this space for the remainder of the lease term.

Employees

As of December 31, 2013, we had 74 full-time employees, 56 of whom were primarily engaged in research and development activities and 40 of whom had an M.D. or Ph.D. degree.

Table of Contents**MANAGEMENT**

The following table sets forth the name, age and position of each of our executive officers and directors.

Name	Age	Position
Robert J. Gould, Ph.D.	59	Chief Executive Officer and Director
Jason P. Rhodes	44	President, Chief Financial Officer and Treasurer
Robert A. Copeland, Ph.D.	57	Executive Vice President and Chief Scientific Officer
Eric E. Hedrick, M.D.	49	Chief Medical Officer
Carl Goldfischer, M.D.(1)(3)	55	Director
Thomas Daniel, M.D.(2)	60	Director
David M. Mott(2)	48	Director
Richard F. Pops(1)	51	Director
Beth Seidenberg, M.D.(2)(3)	56	Director
Kazumi Shiosaki, Ph.D.(1)(3)	59	Director

- (1) Member of the Audit Committee.
- (2) Member of the Compensation Committee.
- (3) Member of the Nominating and Corporate Governance Committee.

Robert J. Gould, Ph.D. has served as a director since March 2008 and our Chief Executive Officer since March 2010. Prior to joining Epizyme, from November 2006 to March 2010, Dr. Gould served as Director of Novel Therapeutics at The Broad Institute of MIT and Harvard, or Broad, a research institute. Prior to that, Dr. Gould was Vice President, Licensing and External Research, Merck Research Laboratories, at Merck & Co., Inc., or Merck, a healthcare company, where he held a variety of leadership positions during his tenure of over 20 years. Dr. Gould received a B.A. from Spring Arbor College and a Ph.D. from The University of Iowa and undertook post-doctoral studies at The Johns Hopkins University. We believe that Dr. Gould's detailed knowledge of our company and his over 30 years in the pharmaceutical and biotechnology industries, including his roles at Broad and at Merck, provide a valuable contribution to our board of directors.

Jason P. Rhodes has served as our President, Chief Financial Officer and Treasurer since July 2013 and previously served as our Executive Vice President, Chief Financial Officer and Treasurer from March 2013 to July 2013 and Executive Vice President, Chief Business Officer and Treasurer from March 2010 to March 2013. Prior to joining Epizyme, from July 2007 to March 2010, Mr. Rhodes served as Vice President, Business Development at Alnylam Pharmaceuticals, Inc., or Alnylam, a biopharmaceutical company. Prior to Alnylam, he was a founder and partner with Fidelity Biosciences, Fidelity Investments' biopharma venture capital group. Mr. Rhodes received a B.A. from Yale University and an M.B.A. from the Wharton School of the University of Pennsylvania.

Robert A. Copeland, Ph.D. has served as our Executive Vice President and Chief Scientific Officer since September 2008. Prior to joining Epizyme, from January 2003 to September 2008, Dr. Copeland was Vice President, Cancer Biology, Oncology Center of Excellence in Drug Discovery, at GSK, a pharmaceutical company. Before joining GSK, Dr. Copeland held scientific staff positions at Merck Research Laboratories of Merck and Bristol-Myers Squibb Company, a biopharmaceutical company, and a faculty position at the University of Chicago Pritzker School of Medicine. Dr. Copeland received a B.S. in chemistry from Seton Hall University, a Ph.D. in chemistry from Princeton University and did postdoctoral studies as the Chaim Weizmann Fellow at the California Institute of Technology.

Eric E. Hedrick, M.D. has served as our Chief Medical Officer since May 2012. Prior to joining Epizyme, Dr. Hedrick served as Vice President, Oncology Development, at Pharmacyclics, Inc., or Pharmacyclics, a biopharmaceutical company, from August 2010 to April 2012, and Interim

Edgar Filing: Epizyme, Inc. - Form 424B4

Chief Medical Officer from May 2011 to April 2012. From October 2009 to August 2010, Dr. Hedrick was an independent drug development consultant, including consulting with Pharmacyclics. From November 2000 to September 2009, Dr. Hedrick held a variety of positions at Genentech, Inc., or Genentech, a biotechnology company, including Medical Director,

Table of Contents

Group Medical Director and clinical scientist. Prior to his time at Genentech, Dr. Hedrick was an Associate Attending Physician at Memorial Sloan-Kettering Cancer Center where he focused on clinical research in non-Hodgkin lymphoma, myelodysplastic syndromes, multiple myeloma and hematopoietic growth factors. He is a board-certified medical oncologist who was formerly a fellow and staff physician on the Hematology Service at Memorial Sloan Kettering Cancer Center. Dr. Hedrick received a B.A. in biology from Boston University and an M.D. from the University of Maryland.

Carl Goldfischer, M.D. has served as a director since September 2009. Dr. Goldfischer has served as an Investment Partner and Managing Director of Bay City Capital LLC, or Bay City Capital, serving as a member of the board of directors and executive committee, and has been with the firm since January 2000. Prior to joining Bay City Capital, Dr. Goldfischer was Chief Financial Officer of ImClone Systems Incorporated, a biopharmaceutical company. Since 2004, Dr. Goldfischer has served on the board of directors of EnteroMedics Inc., a publicly traded medical device company. He has previously served on the board of directors of two other publicly traded companies, MAP Pharmaceuticals, Inc. from 2004 to 2011 and Poniard Pharmaceuticals, Inc. from 2000 to 2012. Dr. Goldfischer received a B.A. from Sarah Lawrence College and an M.D. with honors in Scientific Research from Albert Einstein College of Medicine. We believe that Dr. Goldfischer's extensive finance and investment experience, his experience as an executive and his service on the board of directors of numerous public and privately held companies allow him to be a key contributor to our board of directors.

Thomas O. Daniel, M.D. has served as a director since May 2012. Dr. Daniel has served as Executive Vice President and President, Research and Early Development of Celgene, since December 2006. Prior to joining Celgene, he served as the Chief Scientific Officer of, and a member of the board of directors at, Ambrx Inc., a biotechnology company focused on discovering and developing protein-based therapeutics. Dr. Daniel previously served as Vice President, Research at Amgen Inc., a biotechnology company, where he was Research Site Head of Amgen Washington and Therapeutic Area Head of Inflammation. Dr. Daniel received an M.D. from the University of Texas, Southwestern, and completed medical residency at Massachusetts General Hospital. We believe that Dr. Daniel's extensive experience in the pharmaceutical industry, his status as an officer of our collaboration partner, Celgene, and his scientific knowledge make him a valuable member of our board of directors.

David M. Mott has served as a director since December 2009. Mr. Mott has served as a general partner of New Enterprise Associates, Inc., an investment firm focused on venture capital and growth equity investments, since September 2008, where he leads the healthcare investing practice. From 1992 until 2008, Mr. Mott worked at MedImmune, Inc., or MedImmune, a biotechnology company and subsidiary of AstraZeneca Plc, or AstraZeneca, and served in numerous roles during his tenure, including Chief Financial Officer, President and Chief Operating Officer, and most recently as Chief Executive Officer from October 2000 to July 2008. During that time, Mr. Mott also served as Executive Vice President of AstraZeneca from June 2007 to July 2008 following AstraZeneca's acquisition of MedImmune in June 2007. Prior to joining MedImmune, Mr. Mott was a Vice President in the healthcare investment banking group at Smith Barney, Harris Upham & Co. Inc. Mr. Mott received a B.A. from Dartmouth College. Mr. Mott also serves as the Chairman of the Board of Directors of TESARO, Inc., or TESARO. We believe that Mr. Mott's extensive experience in the life sciences industry as a senior executive and venture capitalist, as well as his service on the boards of directors of other life sciences companies, provide him with the qualifications and skills to serve as a director of our company.

Richard F. Pops has served as a director since September 2008. Mr. Pops has served as Chief Executive Officer of Alkermes plc, or Alkermes, a publicly traded biopharmaceutical company since 1991. Mr. Pops has been a director of Alkermes since February 1991 and has been Chairman of the Board of Directors since April 2007. Since 1998, Mr. Pops has served on the board of directors of Neurocrine Biosciences, Inc., a publicly traded biopharmaceutical company. He has previously served on the board of directors of two other publicly traded biopharmaceutical companies, Sirtis Pharmaceuticals, from 2004 until 2008, and CombinatoRx, Incorporated, from 2001 until 2009. Mr. Pops received a B.A. in economics from Stanford University. We believe that Mr. Pops' leadership experience, including as chief executive officer of a public pharmaceutical company, his business judgment and his industry knowledge provide him with the qualifications to serve as a director of our company.

Table of Contents

Beth Seidenberg, M.D. has served as a director since February 2008. Dr. Seidenberg has been a partner at Kleiner Perkins Caufield & Byers, a venture capital firm, since May 2005, where she has primarily focused on life sciences investing. Dr. Seidenberg was previously the Senior Vice President, Head of Global Development and Chief Medical Officer at Amgen, Inc., a biotechnology company. In addition, Dr. Seidenberg was a senior executive in research and development at Bristol Myers Squibb Company, a biopharmaceutical company, and Merck. Dr. Seidenberg received a B.S. from Barnard College and an M.D. from the University of Miami School of Medicine and completed her post-graduate training at The Johns Hopkins University, George Washington University and the National Institutes of Health. Dr. Seidenberg serves on the board of directors of TESARO. We believe that Dr. Seidenberg's extensive experience in the life sciences industry as a senior executive and venture capitalist, as well as her training as a physician, provide her with the qualifications and skills to serve as a director of our company.

Kazumi Shiosaki, Ph.D. has served as a director since July 2011 and previously served as our President and Chief Executive Officer and as a director from November 2007 until March 2010. Dr. Shiosaki has also served as Interim President and Chief Executive Officer of Mitokyne, Inc., a biotechnology company, since May 2011. Dr. Shiosaki has served as a Managing Director with MPM Asset Management LLC, or MPM, a venture capital firm, since 2003. Prior to joining MPM, Dr. Shiosaki was Senior Vice President of Drug Discovery at Millennium Pharmaceuticals, Inc., a pharmaceutical company. Previously, she worked on drug discovery programs in a number of therapeutic areas at Abbott, including neuroscience, cardiovascular and infectious disease. Dr. Shiosaki received a B.S. from Whitman College and a Ph.D. in Synthetic Chemistry from the University of California, Berkeley. We believe that Dr. Shiosaki's broad experience in the life sciences industry as a venture capitalist and senior executive and her research knowledge provide her with the qualifications and skills to serve as a director of our company.

Board Composition and Election of Directors

Board Composition

Our board of directors currently consists of seven members, all of whom were elected as directors pursuant to a voting agreement that we entered into with the former holders of our preferred stock prior to our initial public offering. The voting agreement terminated upon the closing of our initial public offering and there are no further contractual obligations regarding the election of our directors. Our directors hold office until their successors have been elected and qualified or until the earlier of their resignation or removal.

Our certificate of incorporation and bylaws provide that the authorized number of directors may be changed only by resolution of our board of directors. Our certificate of incorporation and bylaws also provide that our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in an annual election of directors, and that any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office.

In accordance with the terms of our certificate of incorporation and bylaws, our board of directors is divided into three classes, class I, class II and class III, with members of each class serving staggered three-year terms. The members of the classes are divided as follows:

the class I directors are Drs. Daniel and Shiosaki, and their term will expire at the annual meeting of stockholders to be held in 2014;

the class II directors are Drs. Goldfischer and Seidenberg, and their term will expire at the annual meeting of stockholders to be held in 2015; and

the class III directors are Dr. Gould and Messrs. Mott and Pops, and their term will expire at the annual meeting of stockholders to be held in 2016.

Table of Contents

Upon the expiration of the term of a class of directors, directors in that class will be eligible to be elected for a new three-year term at the annual meeting of stockholders in the year in which their term expires.

We have no formal policy regarding board diversity. Our priority in selection of board members is identification of members who will further the interests of our stockholders through their established record of professional accomplishment, the ability to contribute positively to the collaborative culture among board members, knowledge of our business and understanding of the competitive landscape.

Director Independence

Applicable NASDAQ rules require a majority of a listed company's board of directors to be comprised of independent directors within one year of listing. In addition, the NASDAQ rules require that, subject to specified exceptions, each member of a listed company's audit, compensation and nominating and corporate governance committees be independent and that audit committee members also satisfy independence criteria set forth in Rule 10A-3 under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Under applicable NASDAQ rules, a director will only qualify as an independent director if, in the opinion of the listed company's board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director. In order to be considered independent for purposes of Rule 10A-3, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, the board of directors, or any other board committee, accept, directly or indirectly, any consulting, advisory, or other compensatory fee from the listed company or any of its subsidiaries or otherwise be an affiliated person of the listed company or any of its subsidiaries.

In April 2013, our board of directors undertook a review of the composition of our board of directors and its committees and the independence of each director. Based upon information requested from and provided by each director concerning his or her background, employment and affiliations, including family relationships, our board of directors has determined that each of our directors, with the exception of Drs. Gould and Daniel, is an independent director as defined under applicable NASDAQ rules. In making such determination, our board of directors considered the relationships that each such non-employee director has with our company and all other facts and circumstances that our board of directors deemed relevant in determining his or her independence, including the beneficial ownership of our capital stock by each non-employee director. Dr. Gould is not an independent director under these rules because he is our Chief Executive Officer and Dr. Daniel is not an independent director under these rules because of his affiliation with our collaborator, Celgene.

There are no family relationships among any of our directors or executive officers.

Board Committees

Our board of directors has established an audit committee, a compensation committee and a nominating and corporate governance committee.

Audit Committee

Edgar Filing: Epizyme, Inc. - Form 424B4

The members of our audit committee are Drs. Goldfischer and Shiosaki and Mr. Pops. Dr. Goldfischer is chair of the audit committee. Our audit committee's responsibilities include:

appointing, approving the compensation of, and assessing the independence of our registered public accounting firm;

overseeing the work of our independent registered public accounting firm, including through the receipt and consideration of reports from that firm;

Table of Contents

reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements and related disclosures;

monitoring our internal control over financial reporting, disclosure controls and procedures and code of conduct;

overseeing our internal audit function;

discussing our risk management policies;

establishing policies regarding hiring employees from our independent registered public accounting firm and procedures for the receipt and retention of accounting related complaints and concerns;

meeting independently with our internal auditing staff, if any, our independent registered public accounting firm and management;

reviewing and approving or ratifying any related person transactions; and

preparing the audit committee report required by Securities and Exchange Commission, or SEC, rules.

All audit and non-audit services, other than *de minimis* non-audit services, to be provided to us by our independent registered public accounting firm must be approved in advance by our audit committee.

Our board of directors has determined that Dr. Goldfischer is an audit committee financial expert as defined in applicable SEC rules. We believe that the composition of our audit committee meets the requirements for independence under current NASDAQ and SEC rules and regulations.

In considering the independence of the directors appointed to the audit committee, our board of directors considered that, prior to our initial public offering, entities affiliated with Bay City Capital held 10,476,192 shares of our preferred stock, or approximately 15.5% of our outstanding common stock after giving effect to the automatic conversion of all outstanding shares of our preferred stock into common stock in connection with the closing of our initial public offering. Dr. Goldfischer, a member of our audit committee, is a managing director of Bay City Capital LLC and shares voting and dispositive power with respect to shares held by entities affiliated with Bay City Capital.

Compensation Committee

The members of our compensation committee are Drs. Daniel and Seidenberg and Mr. Mott. Mr. Mott is chair of the compensation committee. Our compensation committee's responsibilities include:

determining our chief executive officer's compensation;

Edgar Filing: Epizyme, Inc. - Form 424B4

reviewing and approving, or making recommendations to our board of directors with respect to, the compensation of our other executive officers;

overseeing an evaluation of our senior executives;

reviewing and making recommendations to our board of directors with respect to management succession planning;

overseeing and administering our cash and equity incentive plans;

reviewing and making recommendations to our board of directors with respect to director compensation;

reviewing and discussing annually with management our Compensation Discussion and Analysis disclosure if and to the extent then required by SEC rules; and

preparing the compensation committee report if and to the extent then required by SEC rules.

Table of Contents

We believe that the composition of our compensation committee meets the requirements for independence under current NASDAQ and SEC rules and regulations. Our board of directors has determined that Dr. Seidenberg and Mr. Mott are independent as currently defined in applicable NASDAQ listing standards. Although the board of directors did not determine that Dr. Daniel is independent, under NASDAQ Marketplace Rule 5615(b)(1), we are permitted to phase in our compliance with the independent compensation committee requirements set forth in NASDAQ Marketplace Rule 5605(d) as follows: (1) one independent member at the time of listing, (2) a majority of independent members within 90 days of listing and (3) all independent members within one year of listing. We expect that by May 31, 2014, the first anniversary of our listing on the NASDAQ Global Market, our compensation committee will comply with the independence requirements under the NASDAQ Marketplace Rules.

Nominating and Corporate Governance Committee

The members of our nominating and corporate governance committee are Drs. Goldfischer, Seidenberg and Shiosaki. Dr. Goldfischer is chair of the nominating and corporate governance committee. Our nominating and corporate governance committee's responsibilities include:

identifying individuals qualified to become members of our board of directors;

recommending to our board of directors the persons to be nominated for election as directors and to each of our board's committees;

developing and recommending to our board of directors corporate governance principles; and

overseeing an annual evaluation of our board of directors.

We believe that the composition of our nominating and corporate governance committee meets the requirements for independence under current NASDAQ and SEC rules and regulations.

Compensation Committee Interlocks and Insider Participation

None of our executive officers serves as a member of the board of directors or compensation committee, or other committee serving an equivalent function, of any other entity that has one or more of its executive officers serving as a member of our board of directors or compensation committee. None of the members of our compensation committee has ever been employed by us.

Table of Contents**EXECUTIVE COMPENSATION**

Our named executive officers for the year ended December 31, 2013 include our principal executive officer and our three other executive officers:

Robert J. Gould, Ph.D., our Chief Executive Officer;

Jason P. Rhodes, our President and Chief Financial Officer;

Robert A. Copeland, Ph.D., our Executive Vice President and Chief Scientific Officer; and

Eric E. Hedrick, M.D., our Chief Medical Officer.

No other individuals served as executive officers of the company at any point during 2013.

Summary Compensation Table

The following table presents the compensation awarded to, earned by or paid to each of our named executive officers for the years ended December 31, 2013 and 2012.

Name and Principal Position	Year	Salary (\$)	Bonus \$(1)	Option Awards \$(2)	All Other Compensation (\$)	Total (\$)
Robert J. Gould, Ph.D. Chief Executive Officer	2013	387,668	177,022	1,699,821	1,995	2,266,506
	2012	381,924	171,866	92,813	1,194	647,797
Jason P. Rhodes President and Chief Financial Officer	2013	364,026	149,166	2,658,467	1,467	3,173,126
	2012	344,793	155,157		949	500,899
Robert A. Copeland, Ph.D. Executive Vice President and Chief Scientific Officer	2013	348,201	139,280	473,666	4,598	965,745
	2012	314,757	125,903	92,813	17,229	550,702
Eric E. Hedrick, M.D. Chief Medical Officer	2013	370,800	92,700		103,415	566,915
	2012	233,308	59,940	511,470	105,674	910,392

- (1) The 2012 amounts reflect the discretionary bonus paid in 2013 for performance during 2012. The bonus paid to Dr. Hedrick was pro-rated based on his May 2012 employment commencement date. The 2013 amounts reflect the discretionary bonus to be paid in 2014 for performance during 2013, as discussed under Narrative to Summary Compensation Table Annual Bonus.
- (2) The amounts reflect the grant date fair value for awards granted during the applicable year. The grant date fair value was computed in accordance with Financial Accounting Standards Board Accounting Standards Codification Topic 718, *Compensation - Stock Compensation*.

Table of Contents**Narrative to Summary Compensation Table**

We review compensation annually for all employees, including our executives. In setting executive base salaries and bonuses and granting equity incentive awards, we consider compensation for comparable positions in the market, the historical compensation levels of our executives, individual performance as compared to our expectations and objectives, our desire to motivate our employees to achieve short- and long-term results that are in the best interests of our stockholders, and a long-term commitment to our company. We do not target a specific competitive position or a specific mix of compensation among base salary, bonus or long-term incentives.

Our board of directors has historically determined our executives' compensation. Our compensation committee typically reviews and discusses management's proposed compensation with the chief executive officer for all executives other than the chief executive officer. Based on those discussions and its discretion, the compensation committee then recommends the compensation for each executive officer. Our board of directors, without members of management present, discusses the compensation committee's recommendations and ultimately approves the compensation of our executive officers. In September 2013, our compensation committee engaged Pearl Meyer & Partners, LLC as its independent compensation consultant to review our executive compensation peer group and program design and assess our executives' compensation relative to comparable companies.

Annual Base Salary. The following table presents the base salaries for each of our named executive officers for the years 2013 and 2014. The 2013 base salaries became effective on January 1, 2013 for all of the named executive officers other than Mr. Rhodes, whose 2013 base salary was increased from \$355,137 to \$372,915 as of July 1, 2013 in connection with his election as President. The 2014 base salaries became effective on January 1, 2014.

Name	2013 Base Salary (\$)	2014 Base Salary (\$)
Robert J. Gould, Ph.D.	387,668	480,000
Jason P. Rhodes	372,915	400,000
Robert A. Copeland, Ph.D.	348,200	400,000
Eric E. Hedrick, M.D.	370,800	382,000

Annual Bonus. Our discretionary bonus plan motivates and rewards our executives for achievements relative to our goals and expectations for each fiscal year. Each named executive officer has a target bonus opportunity, defined as a percentage of his annual salary. Following the end of each year, our board of directors determines bonuses. Material considerations in determining bonuses include our financial performance relative to our plan and achievement of corporate objectives for the year; the executive's handling of unplanned events and opportunities; and the chief executive officer's input with respect to the performance of the company and of our executives. Based on these factors and in the sole discretion of our board of directors, we approved the following bonuses in 2014 for our named executive officers for 2013.

Name	Target Bonus (% of salary)	Actual Bonus (\$)	Actual Bonus (% of salary)
Robert J. Gould, Ph.D.	35	177,022	45
Jason P. Rhodes	40	149,166	40
Robert A. Copeland, Ph.D.	30	139,280	40
Eric E. Hedrick, M.D.	25	92,700	25

Specific achievements and performance considered by our board of directors in determining bonuses for 2013 included:

Edgar Filing: Epizyme, Inc. - Form 424B4

the completion of our initial public offering;

our maintaining budgetary alignment with major research and development milestones and ending the year with significant cash and cash equivalents; and

our clinical trial progress of EPZ-5676 and EPZ-6438.

Table of Contents

To reinforce the importance of integrated and collaborative leadership, our executives' bonuses have historically been solely based on company performance, and we did not include an individual performance component.

Long-Term Incentives. Our 2008 Stock Incentive Plan authorized us to make grants to eligible recipients of non-qualified stock options, incentive stock options, restricted stock awards, restricted stock units and other forms of award, such as stock appreciation rights. While we have made restricted stock awards to our executive officers in the past, our equity grants during 2012 to our executive officers were only in the form of stock options. As of the closing of our initial public offering on June 5, 2013, we ceased granting equity awards under the 2008 Stock Incentive Plan and began granting equity awards under our 2013 Stock Incentive Plan. The 2013 Stock Incentive Plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards, restricted stock units, stock appreciation rights and other stock-based awards.

We typically grant equity incentive awards at the start of employment to each executive and our other employees. Through 2012, we have not maintained a practice of granting additional equity on an annual basis, but we have retained discretion to provide additional targeted grants in certain circumstances.

We award our equity grants on the date our board of directors approves the grant. We set the option exercise price and grant date fair value based on our per-share valuation on the date of grant. Prior to our initial public offering, for grants in connection with initial employment, vesting begins on the initial date of employment. Subsequent to our initial public offering, vesting for all grants begins on the date of grant. Time vested stock option grants to our executives typically vest 25% on the first anniversary of grant or, if earlier, the initial employment date, and 1/48th per month thereafter, are fully vested at the end of four years and have a term of 10 years from the grant date. Our time vested restricted stock grants to executives typically vest 1/48th per month and are fully vested at the end of four years.

In 2013, we awarded time-vested stock options to Dr. Gould, Mr. Rhodes and Dr. Copeland in recognition of achievements and performance during 2012. Also in July 2013, we awarded a time-vested stock option to Mr. Rhodes in connection with his election as President.

Other Compensation. We paid \$102,463 for commercial airfare and other travel-related expenses and lodging in connection with Dr. Hedrick's commuting from his personal residence in New Jersey to our headquarters in Massachusetts on a regular basis. Other amounts shown in the All Other Compensation column in the Summary Compensation Table for each named executive officer relate to premiums paid by us for long-term disability and term life insurance policies and for our fitness benefits, consistent with those provided to all Epizyme employees.

Employment Arrangements. Please see Amended and Restated Employment, Severance and Change of Control Arrangements for information regarding the employment and severance agreements for each of our named executive officers.

Table of Contents**Outstanding Equity Awards at 2013 Fiscal Year End Table**

The following table presents information regarding all outstanding stock options held by each of our named executive officers on December 31, 2013.

Name	Grant Date	Notes	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date
Robert J. Gould, Ph.D.	3/17/2008	(1)	12,535		0.30	3/16/2018
	9/17/2008	(1)	14,131		0.33	9/16/2018
	3/18/2010	(2)	816,147	54,410	0.51	3/17/2020
	10/3/2012	(3)	54,410		2.19	10/2/2022
	1/25/2013	(4)		337,333	3.54	1/24/2023
Jason P. Rhodes	3/18/2010	(5)	306,055	20,404	0.51	3/17/2020
	3/11/2011	(6)	74,813	34,006	0.60	3/10/2021
	1/25/2013	(4)		310,833	3.54	1/24/2023
Robert A. Copeland, Ph.D.	7/1/2013	(7)		50,000	29.95	6/30/2023
	3/18/2010	(2)	56,250	3,750	0.51	3/17/2020
	3/11/2011	(5)	75,463	34,301	0.60	3/10/2021
	10/3/2012	(3)	54,410		2.19	10/2/2022
Eric E. Hedrick, M.D.	1/25/2013	(4)		94,000	3.54	1/24/2023
	6/7/2012	(8)	118,750	181,250	2.19	6/6/2022

- (1) These options were granted in connection with Dr. Gould's service as a non-employee director, prior to his appointment as our President and Chief Executive Officer.
- (2) The unvested shares under this option are scheduled to vest in approximately equal monthly installments through March 18, 2014.
- (3) This option was fully vested as of the grant date.
- (4) The shares under this option are scheduled to vest as to 25% of the unvested shares on January 25, 2014, with the remainder vesting in approximately equal monthly installments through January 25, 2017.
- (5) The unvested shares under these options are scheduled to vest in approximately equal monthly installments through March 12, 2014.
- (6) The unvested shares under this option are scheduled to vest in approximately equal monthly installments through March 11, 2015.
- (7) These options were granted in connection with Mr. Rhodes' election as President and are scheduled to vest as to 25% of the unvested shares on July 1, 2014, with the remainder vesting in approximately equal monthly installments through July 1, 2017.
- (8) The unvested shares under this option are scheduled to vest in approximately equal monthly installments through May 8, 2016.

Amended and Restated Employment, Severance and Change in Control Arrangements

In April 2013, we entered into amended and restated employment offer letters with each of our named executive officers. Each of our executive officers is employed at will.

Each named executive officer has entered into a non-competition and non-solicitation agreement, which will prohibit him from competing with us and soliciting or hiring our employees for a period of one year following the end of his employment with us.

Each named executive officer is also eligible for severance benefits in specified circumstances, as set forth in our Executive Severance and Change in Control Plan. Under the terms of this plan, upon execution and

Table of Contents

effectiveness of a severance agreement and release of claims, each named executive officer will be entitled to severance payments if we:

terminate his employment without cause, prior to or more than 12 months following a change in control; or

terminate his employment without cause or he terminates employment with us for good reason within 12 months following a change in control.

Additionally, Dr. Gould is entitled to severance payments if he terminates his employment with us for good reason prior to or more than 12 months following a change in control.

The following definitions have been adopted in our Executive Severance and Change in Control Plan under which our named executive officers participate:

cause means any of: (a) the executive's conviction of, or plea of guilty or nolo contendere to, any crime involving dishonesty or moral turpitude or any felony; or (b) a good faith finding by us that the executive has (i) engaged in dishonesty, willful misconduct or gross negligence, (ii) breached or threatened to breach the terms of any restrictive covenants or confidentiality agreement or any similar agreement with us, (iii) violated company policies or procedures, or (iv) failed to perform his assigned duties to our satisfaction, following notice of such failure by us and a period of 15 days to cure.

good reason means the occurrence, without the executive's prior written consent, of any of the following events: (i) a material reduction in the executive's authority, duties, or responsibilities; (ii) the relocation of the principal place at which the executive provides services to us by at least 30 miles and to a location such that his daily commuting distance is increased; or (iii) a material reduction of the executive's base salary, other than in connection with, and in an amount substantially proportionate to, reductions made by us to the base salaries of other similarly-situated employees. No resignation will be treated as a resignation for good reason unless (x) the executive has given written notice to us of his intention to terminate his or her employment for good reason, describing the grounds for such action, no later than 90 days after the first occurrence of such circumstances, (y) the executive has provided us with at least 30 days in which to cure the circumstances, and (z) if we are not successful in curing the circumstances, the executive ends his employment within 30 days following the cure period in (y).

change in control means any of the following:

(i) the acquisition by an individual, entity or group within the meaning of Section 13(d)(3) or 14(d)(2) of the Exchange Act, referred to as a Person of beneficial ownership of any of our capital stock if, after such acquisition, such Person beneficially owns more than 50% of either (x) our then-outstanding shares of common stock or (y) the combined voting power of our then-outstanding securities entitled to vote generally in the election of directors; provided, however, that any acquisition directly from us will not be a change in control, nor will any acquisition by any individual, entity, or group pursuant to specified business combinations;

(ii) the consummation of a merger, consolidation, reorganization, recapitalization or share exchange involving us or a sale or other disposition of in excess of 85% of our assets subject to specified exceptions; or

(iii) the liquidation or dissolution of our company;

provided that, where required to avoid additional taxation under Section 409A, the event that occurs must also be a change in the ownership or effective control of a corporation, or a change in the ownership of a substantial portion of the assets of a corporation as defined under applicable regulations.

Table of Contents

The following table summarizes the schedule of severance payments our executive officers would receive in the event of a qualifying termination.

Scenario and Executive Level	Salary Continuation	Bonus	Continuation of Employer Portion of Medical, Dental and Vision Benefit Premiums	Acceleration of Unvested Equity
Prior to a Change in Control				
Chief Executive Officer	12 months	None	12 months	None
President and Executive Vice Presidents	6 months	None	6 months	None
Following a Change in Control				
Chief Executive Officer	18 months	150% of target	18 months	100%
President and Executive Vice Presidents	12 months	100% of target	12 months	100%

Equity Incentive Plans**2008 Stock Incentive Plan**

Our 2008 Stock Incentive Plan, or 2008 Plan, is administered by our board of directors and provided for the grant of incentive stock options within the meaning of Section 422 of the Internal Revenue Code, non-statutory stock options, restricted stock, restricted stock units and other stock-based awards. Our employees, officers, directors, consultants and advisors were eligible to receive awards under our 2008 Plan. However, incentive stock options could only be granted to our employees. The terms of awards are set forth in the applicable award agreements. Upon a merger or other reorganization event, our board of directors, may, in its sole discretion, take any one or more of the following actions pursuant to the 2008 Plan, as to some or all outstanding awards, other than restricted stock awards:

provide that all outstanding awards will be assumed, or substantially equivalent awards shall be substituted, by the acquiring or successor corporation or an affiliate thereof;

upon written notice to a participant, provide that the participant's unexercised options or awards will terminate immediately prior to the consummation of the transaction unless exercised by the participant;

provide that outstanding awards will become exercisable, realizable or deliverable, or restrictions applicable to an award will lapse, in whole or in part, prior to or upon the reorganization event;

in the event of a reorganization event pursuant to which holders of our common stock will receive a cash payment for each share surrendered in the reorganization event, make or provide for a cash payment to the participants with respect to each award held by the participant equal to (1) the number of shares of our common stock subject to the vested portion of the award, after giving effect to any acceleration of vesting that occurs upon or immediately prior to such reorganization event, multiplied by (2) the excess, if any, of the cash payment for each share surrendered in the reorganization event over the exercise, measurement or purchase price of such award and any applicable tax withholdings, in exchange for the termination of such awards; and

provide that, in connection with a liquidation or dissolution, awards convert into the right to receive liquidation proceeds.

Upon the occurrence of a reorganization event other than a liquidation or dissolution, the repurchase and other rights under each outstanding restricted stock award will continue for the benefit of the successor company and will, unless our board of directors may otherwise determine, apply to the cash, securities or other property into which our common stock is converted pursuant to the reorganization event. Upon the occurrence of a reorganization event involving a liquidation or dissolution, all restrictions and conditions on each outstanding

Table of Contents

restricted stock award will automatically be deemed terminated or satisfied, unless otherwise provided in the agreement evidencing the restricted stock award.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2008 Plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part.

As of December 31, 2013, under our 2008 Plan, there were options to purchase an aggregate of 4,460,990 shares of common stock outstanding at a weighted average exercise price of \$1.63 per share, and we had granted 262,192 shares of restricted stock, of which all but 5,555 shares were vested as of December 31, 2013. We no longer grant stock options or other awards under our 2008 Plan. However, any shares of common stock subject to awards under our 2008 Plan that expire, terminate, or are otherwise surrendered, canceled, forfeited or repurchased without having been fully exercised or resulting in any common stock being issued become available for issuance under our 2013 Stock Incentive Plan, or the 2013 Plan, up to a specified number of shares.

2013 Stock Incentive Plan

Our board of directors has adopted and our stockholders have approved the 2013 Plan, which became effective upon the closing of our initial public offering. The 2013 Plan is administered by our board of directors or by a committee appointed by our board of directors. The 2013 Plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards, restricted stock units, stock appreciation rights and other stock-based awards. The number of shares of our common stock that are reserved for issuance under the 2013 Plan is the sum of (i) 1,900,000 shares, plus (ii) the number of shares (up to 4,652,151 shares) equal to the sum of 93,403 shares and the number of shares of our common stock subject to outstanding awards under our 2008 Plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right, plus (iii) an annual increase, to be added on the first day of each fiscal year, equal to the lowest of (x) 2,500,000 shares of our common stock, (y) 5.0% of the number of shares of our common stock outstanding on the first day of the applicable fiscal year and (z) an amount determined by our board of directors.

Our employees, officers, directors, consultants and advisors are eligible to receive awards under the 2013 Plan; however, incentive stock options may only be granted to our employees. The maximum number of shares of common stock with respect to which awards may be granted to any participant under the 2013 Plan is 333,333 per calendar year. For purposes of this limit on the maximum number of shares that may be awarded to any participant, the combination of an option in tandem with a stock appreciation right will be treated as a single award.

Subject to any limitation in the 2013 Plan, our board of directors or any committee or officer to which our board of directors has delegated authority will select the recipients of awards and determine:

the number of shares of common stock covered by options and stock appreciation rights and the dates upon which those awards become exercisable;

the type of options to be granted;

the exercise price of options and measurement price of stock appreciation rights, neither of which may be less than 100% of the fair market value of our common stock on the grant date;

the duration of options and stock appreciation rights which may not be in excess of ten years;

the methods of payment of the exercise price of options; and

the number of shares of common stock subject to any restricted stock awards, restricted stock units or other stock-based awards and the terms and conditions of such awards, including the issue price, conditions for repurchase, repurchase price and performance conditions, if any.

Table of Contents

Our board of directors has delegated authority to our chief executive officer to grant awards other than restricted stock under the 2013 Plan to all of our employees, other than executive officers. Our board of directors has fixed the terms of the awards to be granted by our chief executive officer, including the methods by which the exercise price of such awards is determined and the maximum number of shares subject to awards that he may make.

Upon a merger or other reorganization event, our board of directors, may, in its sole discretion, take any one or more of the following actions pursuant to the 2013 Plan, as to some or all outstanding awards, other than restricted stock:

provide that all outstanding awards will be assumed, or substantially equivalent awards shall be substituted, by the acquiring or successor corporation or an affiliate thereof;

upon written notice to a participant, provide that the participant's unexercised options or awards will terminate immediately prior to the consummation of such transaction unless exercised by the participant;

provide that outstanding awards will become exercisable, realizable or deliverable, or restrictions applicable to an award will lapse, in whole or in part, prior to or upon the reorganization event;

in the event of a reorganization event pursuant to which holders of our common stock will receive a cash payment for each share surrendered in the reorganization event, make or provide for a cash payment to the participants with respect to each award held by the participant equal to (1) the number of shares of our common stock subject to the vested portion of the award, after giving effect to any acceleration of vesting that occurs upon or immediately prior to such reorganization event, multiplied by (2) the excess, if any, of the cash payment for each share surrendered in the reorganization event over the exercise, measurement or purchase price of such award and any applicable tax withholdings, in exchange for the termination of such awards; and

provide that, in connection with a liquidation or dissolution, awards convert into the right to receive liquidation proceeds.

In the case of specified restricted stock units, no assumption or substitution is permitted, and the restricted stock units will instead be settled in accordance with the terms of the applicable restricted stock unit agreement.

Upon the occurrence of a reorganization event other than a liquidation or dissolution, the repurchase and other rights under each outstanding restricted stock award will continue for the benefit of the successor company and will, unless our board of directors may otherwise determine, apply to the cash, securities or other property into which our common stock is converted pursuant to the reorganization event. Upon the occurrence of a reorganization event involving a liquidation or dissolution, all restrictions and conditions on each outstanding restricted stock award will automatically be deemed terminated or satisfied, unless otherwise provided in the agreement evidencing the restricted stock award.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2013 Plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part.

As of December 31, 2013, under our 2013 Plan, there were options to purchase an aggregate of 267,513 shares of common stock outstanding at a weighted average exercise price of \$28.08 per share. There were 1,327,638 shares remaining and available for issuance under the 2013 Plan as of that date, including shares available for grant that have rolled over from the 2008 Plan.

2013 Employee Stock Purchase Plan

Our board of directors has adopted and our stockholders have approved the 2013 Employee Stock Purchase Plan, or the 2013 ESPP, which became effective on May 7, 2013. The 2013 ESPP is administered by our board of directors or by a committee appointed by our board of directors. The 2013 ESPP provides participating

Table of Contents

employees with the opportunity to purchase up to an aggregate of 499,999 shares of our common stock. The number of shares of our common stock reserved for issuance under the 2013 ESPP will automatically increase on the first day of each fiscal year, through January 1, 2023, in an amount equal to the lowest of (1) 233,333 shares of our common stock, (2) 1.0% of the total number of shares of our common stock outstanding on the first day of the applicable year, or (3) an amount determined by our board of directors. The 2013 ESPP provides for six-month offering periods during which eligible employees may elect to have a specified percentage of their compensation withheld through payroll deductions for the purpose of purchasing shares at the end of the period. All of our employees or employees of any designated subsidiary, as defined in the 2013 ESPP, are eligible to participate in the 2013 ESPP, provided that:

such person is customarily employed by us or a designated subsidiary for more than 20 hours a week and for more than five months in a calendar year; and

such person was our employee or an employee of a designated subsidiary on the first day of the applicable offering period under the 2013 ESPP.

No employee is eligible to purchase shares of our common stock that would result in the employee owning 5% or more of the total combined voting power or value of our stock immediately after such purchase. In addition under the 2013 ESPP, no employee may purchase common stock under the plan in excess of \$25,000 for each calendar year, or such lesser amount as determined by our board of directors.

Offering periods under the 2013 ESPP will commence at such time or times as our board of directors may determine. The first offering period under the 2013 ESPP commenced on August 1, 2013 and continued for a six-month period until January 31, 2014. Payroll deductions made during each offering period will be held for the purchase of our common stock at the end of the offering period.

On the commencement date of each offering period, each eligible employee may authorize up to a maximum of 10% of his or her compensation to be deducted by us during the offering period. Each employee who continues to be a participant in the 2013 ESPP on the last business day of the offering period is deemed to have purchased shares, to the extent of accumulated payroll deductions within the 2013 ESPP ownership limits. Under the terms of the 2013 ESPP, the purchase price shall be determined by our board of directors for each offering period and will be at least 85% of the applicable closing price. If our board of directors does not make a determination of the purchase price, the purchase price will be 85% of the lesser of the closing price of our common stock on the first business day of the offering period or the last business day of the offering period. Our board of directors may, in its discretion, choose a different period of twelve months or less for each offering period.

An employee who is not a participant on the last day of the offering period is not entitled to purchase shares under the 2013 ESPP, and the employee's accumulated payroll deductions will be refunded. An employee's rights under the plan terminate upon voluntary withdrawal from the offering plan at any time, or when the employee ceases employment for any reason.

We will be required to make equitable adjustments in connection with the 2013 ESPP and any outstanding awards to reflect stock splits, reverse stock splits, stock dividends, recapitalizations, combination of shares, reclassification of shares, spin-offs and other similar changes in capitalization.

Our board of directors may at any time, and from time to time, amend or suspend the 2013 ESPP. We will obtain stockholder approval for any amendment if such approval is required by Section 423 of the Internal Revenue Code. Further, our board of directors may not make any amendment that would cause the 2013 ESPP to fail to comply with Section 423 of the Internal Revenue Code. Upon termination, we will refund all amounts in the accounts of participating employees that have not been used to purchase shares.

Table of Contents

Health and Welfare Benefits

We maintain a defined contribution employee retirement plan for our employees. Our 401(k) plan is intended to qualify as a tax-qualified plan under Section 401 of the Internal Revenue Code so that contributions to our 401(k) plan, and income earned on such contributions, are not taxable to participants until withdrawn or distributed from the 401(k) plan. Our 401(k) plan provides that each participant may contribute up to 90% of his or her pre-tax compensation, up to a statutory limit, which is \$17,500 for 2013. Participants who are at least 50 years old can also make catch-up contributions, which in 2013 may be up to an additional \$5,500 above the statutory limit. Under our 401(k) plan, each employee is fully vested in his or her deferred salary contributions. Employee contributions are held and invested by the plan's trustee, subject to participants' ability to give investment directions by following certain procedures. We do not currently make discretionary contributions or matching contributions to our 401(k) plan.

Except for the benefits described above under Narrative to Summary Compensation Table Other Compensation, we do not provide perquisites or personal benefits to our named executive officers. We do, however, pay the premiums for term life insurance and long-term disability for all of our employees, including our named executive officers. We do not sponsor and qualified or non-qualified defined benefit plans for any of our employees or executives.

Limitation of Liability and Indemnification

Our certificate of incorporation limits the personal liability of directors for breach of fiduciary duty to the maximum extent permitted by the Delaware General Corporation Law and provides that no director will have personal liability to us or to our stockholders for monetary damages for breach of fiduciary duty or other duty as a director. However, these provisions do not eliminate or limit the liability of any of our directors:

for any breach of the director's duty of loyalty to us or our stockholders;

for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law;

for voting or assenting to unlawful payments of dividends, stock repurchases or other distributions; or

for any transaction from which the director derived an improper personal benefit.

Any amendment to or repeal of these provisions will not eliminate or reduce the effect of these provisions in respect of any act, omission or claim that occurred or arose prior to such amendment or repeal. If the Delaware General Corporation Law is amended to provide for further limitations on the personal liability of directors of corporations, then the personal liability of our directors will be further limited to the greatest extent permitted by the Delaware General Corporation Law.

In addition, our certificate of incorporation provides that we must indemnify our directors and officers and we must advance expenses, including attorneys' fees, to our directors and officers in connection with legal proceedings, subject to very limited exceptions.

Edgar Filing: Epizyme, Inc. - Form 424B4

We maintain a general liability insurance policy that covers specified liabilities of our directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers. In addition, we have entered into indemnification agreements with all of our directors and executive officers. These indemnification agreements may require us, among other things, to indemnify each such director and executive officer for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by him or her in any action or proceeding arising out of his or her service as one of our directors or executive officers.

Some of our non-employee directors may, through their relationships with their employers, be insured or indemnified against specified liabilities incurred in their capacities as members of our board of directors.

Table of Contents

Insofar as indemnification for liabilities arising under the Securities Act of 1933, as amended, or the Securities Act, may be permitted to directors, executive officers or persons controlling us, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Director Compensation

We reimburse our non-employee directors for reasonable travel and other expenses incurred in connection with attending board of director and committee meetings or otherwise in direct service of our company. The table below shows all compensation paid to our non-employee directors during 2013.

Name	Fees Paid		Total (\$)
	In Cash (\$)(1)	Option Awards (\$)(2)(3)	
Thomas O. Daniel, M.D.			
Carl Goldfischer, M.D.	14,304	330,137	344,441
David M. Mott	13,662	330,137	343,799
Richard F. Pops	12,857	330,137	342,994
Beth Seidenberg, M.D.	13,701	330,137	343,838
Kazumi Shiosaki, Ph.D.	14,304	330,137	344,441

- (1) Amounts represent cash compensation for services rendered by each member of the board of directors.
- (2) In 2013, each of Dr. Goldfischer, Mr. Mott, Mr. Pops, Dr. Seidenberg and Dr. Shiosaki was granted an option to purchase 17,666 shares of common stock.
- (3) Amounts shown reflect the grant date fair value of option awards granted during 2013. The grant date fair value was computed in accordance with Accounting Standards Codification Topic 718, *Compensation - Stock Compensation*.

During 2013, we did not provide any cash compensation to Dr. Gould, our Chief Executive Officer, for his service as a director. Dr. Gould's compensation as an executive officer is set forth above under Executive Compensation Summary Compensation Table. During 2013, we did not provide any compensation to Dr. Daniel for his service as a director.

In April 2013, our board of directors approved a director compensation program which became effective upon the closing of our initial public offering on June 5, 2013.

Under this director compensation program, we pay our non-employee directors a cash retainer for service on the board of directors and for service on each committee on which the director is a member. The chairman of each committee receives higher retainers for such service. These fees are payable in arrears in four equal quarterly installments on the last day of each quarter, provided that the amount of such payment is prorated for any portion of such quarter that the director is not serving on our board of directors. The fees paid to non-employee directors for service on the board of directors and for service on each committee of the board of directors on which the director is a member are as follows:

Member Annual Fee	Chairman Additional Annual Fee
-------------------	--------------------------------

Edgar Filing: Epizyme, Inc. - Form 424B4

Board of Directors	\$	35,000	\$
Audit Committee		7,000	8,000
Compensation Committee		5,000	5,000
Nominating and Corporate Governance Committee and any other committee of our board of directors, other than the Audit Committee and Compensation Committee.		2,500	2,500

Table of Contents

We also reimburse our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending our board of director and committee meetings.

In addition, under our director compensation program, each non-employee director serving on our board of directors received, upon the closing of our initial public offering, and each non-employee director that may be elected to our board of directors will receive an option to purchase 17,666 shares of our common stock. Each of the options granted to the non-employee directors on June 5, 2013, vests concurrently with the expiration of initial terms of office for the class in which the director serves, subject to the director's continued service as a director. With respect to each non-employee director that may be elected to our board of directors in the future, each of these options will vest as to 25% of the shares of our common stock underlying such option on the one-year anniversary of the grant date and as to an additional 2.0833% of the shares of our common stock underlying such option at the end of each successive month following the first anniversary of the grant date until the fourth anniversary of the grant date, subject to the non-employee director's continued service as a director. Further, on the date of the first board meeting held after each annual meeting of stockholders, each non-employee director that has served on our board of directors for at least six months will receive an option to purchase 7,333 shares of our common stock. Each of these options will vest in full on the one-year anniversary of the grant date, subject to the non-employee director's continued service as a director. All options issued to our non-employee directors under our director compensation program will become exercisable in full upon a change in control of our company. The exercise price of these options will equal the fair market value of our common stock on the date of grant.

This program is intended to provide a total compensation package that enables us to attract and retain qualified and experienced individuals to serve as directors and to align our directors' interests with those of our stockholders.

Director Equity Outstanding at 2013 Fiscal Year End

The following table provides information about outstanding stock options and stock awards held by each of our non-employee directors as of December 31, 2013. All of these options and awards were granted under our 2013 Plan, except as otherwise noted.

	Option Awards	Option Awards	Stock Awards
	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Options That Have Not Vested (#)	Number of Shares or Units of Stock That Have Not Vested (#)
Thomas O. Daniel, M.D.			
Carl Goldfischer, M.D.		17,666	
David M. Mott		17,666	
Richard F. Pops		17,666	5,555(1)
Beth Seidenberg, M.D.		17,666	
Kazumi Shiosaki, Ph.D.	246,666(2)	17,666	

(1) Represents the unvested portion of the restricted stock granted to Mr. Pops under our 2008 Plan in 2012.

(2) Represents the grant of a nonqualified stock option to Dr. Shiosaki in 2010, in connection with her service as our chief executive officer. The option was granted under our 2008 Plan with a 10-year term and is fully vested.

Table of Contents**TRANSACTIONS WITH RELATED PERSONS**

The following is a description of transactions since January 1, 2011 to which we have been a party, and in which any of our directors, executive officers or beneficial owners of more than 5% of our voting securities, or affiliates or immediate family members of any of our directors, executive officers or beneficial owners of more than 5% of our voting securities, had or will have a direct or indirect material interest. We believe the terms obtained or consideration that we paid or received, as applicable, in connection with the transactions described below were comparable to terms available or the amounts that would be paid or received, as applicable, from unrelated third parties.

Series B Preferred Stock Financing

In September 2011, we issued and sold an aggregate of 18,095,241 shares our series B preferred stock at a price per share of \$1.05 for an aggregate purchase price of \$19.0 million. The following table sets forth the number of shares of our series B preferred stock that we issued to our 5% stockholders and their affiliates in this transaction:

Purchaser	Shares of Series B Preferred Stock (5)	Purchase Price (\$)
Entities affiliated with Bay City Capital(1)	5,238,096	5,500,001
KPCB Holdings, Inc.(2)	3,333,334	3,500,001
Entities affiliated with MPM Capital(3)	3,333,334	3,500,001
New Enterprise Associates 13, L.P.(4)	5,714,286	6,000,000

- (1) Consists of 5,140,144 shares of series B preferred stock purchased by Bay City Capital Fund V., L.P. and 97,952 shares of series B preferred Stock purchased by Bay City Capital Fund V Co-Investment Fund, L.P. Carl Goldfischer, a member of our board of directors, is an Investment Partner and Managing Director of Bay City Capital LLC, serving as a member of Bay City Capital LLC's board of directors and executive committee.
- (2) Beth Seidenberg, M.D., a member of our board of directors, is a partner at Kleiner Perkins Caufield & Byers, an affiliate of KPCB Holdings, Inc.
- (3) Consists of 2,653,297 shares of series B preferred stock purchased by MPM BioVentures IV-QP L.P., 102,220 shares of series B preferred stock purchased by MPM BioVentures IV GmbH & Co. Beteiligungs KG, 75,448 shares purchased by MPM Asset Management BV4 LLC and 502,369 shares of series B preferred Stock purchased by MPM BioVentures IV Strategic Fund, L.P. Kazumi Shiosaki, a member of our board of directors, is a Managing Director of MPM Capital.
- (4) David M. Mott, a member of our board of directors, is a general partner of New Enterprise Associates.
- (5) Each share of our series B preferred stock automatically converted into common stock at a one-for-three ratio upon the closing of our initial public offering in June 2013.

Series C Preferred Stock Financing

In April 2012, in connection with our collaboration and license agreement with Celgene, we issued and sold an aggregate of 9,803,922 shares of our series C preferred stock at a purchase price per share of \$2.55 for an aggregate purchase price of \$25.0 million to Celgene European Investment Company LLC, an affiliate of Celgene, and immediately following such sale, Celgene European Investment Company LLC became a beneficial owner of more than 5% of our voting securities. In connection with the series C financing, Thomas Daniel, an Executive Vice President and President, Research and Early Development of Celgene Corporation, an affiliate of Celgene Investment, was appointed to our

Edgar Filing: Epizyme, Inc. - Form 424B4

board of directors and remains a member of our board of directors. Our collaboration agreement with Celgene contemplates payments by us in excess of \$120,000. See [Business - HMT Collaborations - Therapeutic Collaborations - Celgene](#) for additional information regarding

Table of Contents

this agreement. Each share of our series C preferred stock automatically converted into common stock at a one-for-three ratio upon the closing of our initial public offering in June 2013.

Participation in Initial Public Offering

In our initial public offering, certain of our 5% stockholders and their affiliates purchased an aggregate of 633,332 shares of our common stock. Each of those purchases was made through the underwriters at the initial public offering price. The following table sets forth the aggregate number of shares of our common stock that these 5% stockholders and their affiliates purchased in our initial public offering:

Purchaser	Shares of Common Stock
Entities affiliated with New Enterprise Associates(1)	400,000
Entities affiliated with Bay City Capital(2)	166,666
Celgene European Investment Company LLC(3)	66,666

- (1) Consists of 400,000 shares of common stock purchased by New Enterprise Associates 13, L.P. David Mott, a member of our board of directors, is a general partner of New Enterprise Associates.
- (2) Consists of 166,666 shares of common stock purchased by Bay City Capital Fund V L.P. and Bay City Capital Fund V Co-Investment Fund, L.P. Carl Goldfischer, a member of our board of directors, is an Investment Partner and Managing Director of Bay City Capital LLC, serving as a member of Bay City Capital LLC's board of directors and executive committee.
- (3) Dr. Daniel, a member of our board of directors, is an Executive Vice President and President of Research and Early Development of Celgene Corporation.

Participation in this Offering

CEIC, which is affiliated with one of our collaborators and is an existing investor, has agreed to purchase 340,000 shares of our common stock in this offering at the public offering price. The underwriters will receive the same underwriting discount on any shares purchased by CEIC as they will on any other shares sold to the public in this offering.

Registration Rights

We are a party to an amended and restated investor rights agreement with the former holders of our preferred stock, including some of our 5% stockholders and their affiliates and entities affiliated with our directors. This investor rights agreement provides these holders the right to demand that we file a registration statement or to request that their shares be covered by a registration statement that we are otherwise filing. See Description of Capital Stock Registration Rights for additional information regarding these registration rights.

Indemnification Agreements

Edgar Filing: Epizyme, Inc. - Form 424B4

Our certificate of incorporation provides that we will indemnify our directors and officers to the fullest extent permitted by Delaware law. In addition, we have entered into indemnification agreements with all of our directors and executive officers.

Policies and Procedures for Related Person Transactions

Our board of directors has adopted a written related person transaction policy to set forth policies and procedures for the review and approval or ratification of related person transactions. This policy covers any transaction, arrangement or relationship, or any series of similar transactions, arrangements or relationships, in

Table of Contents

which we were or are to be a participant, the amount involved exceeds \$120,000, and one of our executive officers, directors, director nominees or 5% stockholders, or their immediate family members, each of whom we refer to as a related person, had or will have a direct or indirect material interest, including, without limitation, purchases of goods or services by or from the related person or entities in which the related person has a material interest, indebtedness, guarantees of indebtedness and employment by us of a related person.

If a related person proposes to enter into such a transaction, arrangement or relationship, which we refer to as a related person transaction, the related person must report the proposed related person transaction to our general counsel, or if we do not have a general counsel, our chief financial officer. The policy calls for the proposed related person transaction to be reviewed and, if deemed appropriate, approved by our audit committee. Whenever practicable, the reporting, review and approval will occur prior to entry into the transaction. If advance review and approval is not practicable, the audit committee will review, and, in its discretion, may ratify the related person transaction. The policy also permits the chairman of the audit committee to review and, if deemed appropriate, approve proposed related person transactions that arise between audit committee meetings, subject to ratification by the audit committee at its next meeting. Any related person transactions that are ongoing in nature will be reviewed annually.

A related person transaction reviewed under the policy will be considered approved or ratified if it is authorized by the audit committee after full disclosure of the related person's interest in the transaction. As appropriate for the circumstances, the audit committee will review and consider:

the related person's interest in the related person transaction;

the approximate dollar value of the amount involved in the related person transaction;

the approximate dollar value of the amount of the related person's interest in the transaction without regard to the amount of any profit or loss;

whether the transaction was undertaken in the ordinary course of our business;

whether the terms of the transaction are no less favorable to us than terms that could have been reached with an unrelated third party;

the purpose of, and the potential benefits to us of, the transaction; and

any other information regarding the related person transaction or the related person in the context of the proposed transaction that would be material to investors in light of the circumstances of the particular transaction.

Our audit committee may approve or ratify the transaction only if it determines that, under all of the circumstances, the transaction is in, or is not inconsistent with, our best interests. Our audit committee may impose any conditions on the related person transaction that it deems appropriate.

In addition to the transactions that are excluded by the instructions to the SEC's related person transaction disclosure rule, our board of directors has determined that the following transactions do not create a material direct or indirect interest on behalf of related persons and, therefore, are not related person transactions for purposes of this policy:

interests arising solely from the related person's position as an executive officer of another entity whether or not the person is also a director of the entity, that is a participant in the transaction, where the related person and all other related persons own in the aggregate less than a 10% equity interest in such entity, the related person and his or her immediate family members are not involved in the negotiation of the terms of the transaction and do not receive any special benefits as a result of the transaction and the amount involved in the transaction is less than the greater of \$200,000 or 5% of the annual gross revenues of the company receiving payment under the transaction; and

Table of Contents

a transaction that is specifically contemplated by provisions of our certificate of incorporation or by-laws.

The policy provides that transactions involving compensation of executive officers shall be reviewed and approved by our compensation committee in the manner specified in the compensation committee's charter.

We did not have a written policy regarding the review and approval of related person transactions prior to our initial public offering. Nevertheless, with respect to such transactions, it was the practice of our board of directors to consider the nature of and business reason for such transactions, how the terms of such transactions compared to those which might be obtained from unaffiliated third parties and whether such transactions were otherwise fair to and in the best interests of, or not contrary to, our best interests. In addition, all related person transactions required prior approval, or later ratification, by our board of directors.

Table of Contents**PRINCIPAL AND SELLING STOCKHOLDERS**

The following table sets forth information with respect to the beneficial ownership of our common stock as of December 31, 2013 and on an as adjusted basis to reflect the sale of the common stock offered in this offering by:

each person, or group of affiliated persons, who is known by us to beneficially own more than 5% of our common stock;

each of our directors;

each of our named executive officers;

all of our directors and executive officers as a group; and

each of the selling stockholders.

The column entitled "Shares Beneficially Owned Before Offering" is based on a total of 28,494,447 shares of our common stock outstanding as of December 31, 2013. The column entitled "Shares Beneficially Owned After Offering" is based on shares of our common stock to be outstanding after this offering, including the 3,000,000 shares of our common stock that we are selling in this offering and the 1,492,679 shares of our common stock that the selling stockholders are selling in this offering, and reflects the exercise by certain selling stockholders of options to purchase 123,500 shares being sold in this offering, but not including any additional shares issuable upon exercise of the underwriters' option to purchase additional shares or other outstanding options.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC and includes voting or investment power with respect to our common stock. Shares of our common stock subject to options that are currently exercisable or exercisable within 60 days after December 31, 2013 are considered outstanding and beneficially owned by the person holding the options for the purpose of calculating the percentage ownership of that person but not for the purpose of calculating the percentage ownership of any other person. Except as otherwise noted, the persons and entities in this table have sole voting and investing power with respect to all of the shares of our common stock beneficially owned by them, subject to community property laws, where applicable. Except as otherwise set forth below, the address of each beneficial owner is c/o Epizyme, Inc., 400 Technology Square, Cambridge, Massachusetts 02139.

Celgene European Investment Company LLC, or CEIC, which is affiliated with one of our collaborators and is an existing investor, has agreed to purchase 340,000 shares of our common stock in this offering at the public offering price.

Name of Beneficial Owner	Shares Beneficially Owned Before Offering		Number of Shares Offered	Shares Beneficially Owned After Offering	
	Number	%		Number	%
5% Stockholders:					
Entities affiliated with New Enterprise Associates(1)	6,446,089	22.6%		6,446,089	20.4%
Entities affiliated with Kleiner, Perkins, Caufield & Byers(2)	4,532,222	15.9	416,667	4,115,555	13.0

Edgar Filing: Epizyme, Inc. - Form 424B4

Entities affiliated with Bay City Capital(3)	3,658,729	12.8	466,667	3,192,062	10.1
Celgene European Investment Company LLC(4)	3,334,640	11.7		3,674,640	11.6
Entities affiliated with MPM Capital(5)	2,880,485	10.1	466,666	2,413,819	7.6

Table of Contents

Name of Beneficial Owner	Shares Beneficially Owned Before Offering		Number of Shares Offered	Shares Beneficially Owned After Offering	
	Number	%		Number	%
Directors and Named Executive Officers:					
David M. Mott(6)	6,446,089	22.6%		6,446,089	20.4%
Beth Seidenberg, M.D.(7)	4,532,222	15.9	416,667	4,115,555	13.0
Carl Goldfischer, M.D.(8)	3,658,729	12.8	466,667	3,192,062	10.1
Thomas O. Daniel, M.D.(9)					
Kazumi Shiosaki, Ph.D.(10)	493,332	1.7		493,332	1.5
Richard F. Pops	60,000	*		60,000	*
Robert J. Gould, Ph.D.(11)	1,024,856	3.5	60,000	964,856	3.0
Jason P. Rhodes(12)	483,188	1.7	50,000	433,188	1.4
Robert A. Copeland, Ph.D.(13)	303,680	1.1	19,179	284,501	*
Eric E. Hedrick, M.D.(14)	131,249	*	13,500	117,749	*
All current executive officers and directors as a group (10 persons)(15)	17,133,345	56.0	1,026,013	16,107,332	47.9
All selling stockholders	13,348,535	44.0%	1,492,679	11,855,856	35.5%

* Represents beneficial ownership of less than one percent of our outstanding common stock.

- (1) Consists of 6,439,740 shares of common stock held of record by New Enterprise Associates 13, L.P. (NEA13) and 6,349 shares of common stock held of record by NEA Ventures 2009, L.P. (Ven 2009). NEA Partners 13, L.P. (NEA Partners 13) is the sole General Partner of NEA 13 and NEA 13 GP, LTD (NEA 13 LTD) is the sole General Partner of NEA Partners 13. The individual Directors (collectively, the NEA 13 Directors) of NEA 13 LTD are M. James Barrett, Peter J. Barris, Forest Baskett, Ryan D. Drant, Patrick J. Kerins, Krishna Kittu Kolluri, David M. Mott, a member of our board of directors, Scott D. Sandell, Ravi Viswanathan and Harry R. Weller. The NEA 13 Directors share voting and dispositive power with regard to the shares directly held by NEA 13. Karen P. Welsh, the General Partner of Ven 2009, shares voting and dispositive power with regard to the shares directly held by Ven 2009. The principal business address of New Enterprise Associates, Inc. is 1954 Greenspring Drive, Suite 600, Timonium, MD 21093.
- (2) Consists of 4,226,751 shares of common stock held by Kleiner Perkins Caufield & Byers XIII, LLC (KPCB XIII), of which 388,584 are being sold in this offering, 60,960 shares of common stock held by Raymond J. Lane, of which 5,604 are being sold in this offering, and 244,511 shares of common stock beneficially owned by individuals and entities associated with Kleiner Perkins Caufield & Byers (collectively, KPCB Direct), of which 22,479 are being sold in this offering. All shares are held for convenience in the name of KPCB Holdings, Inc. as nominee, for the accounts of such individuals and entities who each exercise their own voting and dispositive control over such shares. The managing member of KPCB XIII is KPCB XIII Associates, LLC (KPCB XIII Associates). Brook H. Byers, L. John Doerr, Joseph Lacob, Raymond J. Lane and Theodore E. Schlein, the managing directors of KPCB XIII Associates, LLC, and Dr. Seidenberg, a member of our board of directors and of KPCB XIII Associates, exercise shared voting and dispositive control over the shares directly held by KPCB XIII. Dr. Seidenberg disclaims beneficial ownership of all shares held by KPCB XIII except to the extent of her pecuniary interest therein. The principal business address for all entities and individuals affiliated with Kleiner Perkins Caufield & Byers is 2750 Sand Hill Road, Menlo Park, CA 94025.
- (3) Consists of 3,590,311 shares of common stock held by Bay City Capital Fund V, L.P., of which 457,940 are being sold in this offering, and 68,418 shares of common stock held by Bay City Capital Fund V Co-Investment Fund, L.P., of which 8,727 are being sold in this offering. Bay City Capital Management V LLC (GP V) is the general partner of Bay City Capital Fund V, L.P. and Bay City Capital Fund V Co-Investment Fund, L.P. (collectively, BCC V). Bay City Capital LLC (BCC LLC) is the manager of GP V. BCC V has shared voting and dispositive power with respect to the shares held by BCC V. GP V has sole voting and dispositive power with respect to the shares held by BCC V. GP V disclaims beneficial ownership of these shares, except to the extent of its pecuniary interest therein. BCC LLC has sole voting and dispositive power with respect to the shares held by BCC V. BCC LLC disclaims beneficial ownership

Table of Contents

- of these shares, except to the extent of its pecuniary interest therein. Dr. Carl Goldfischer, a member of our board of directors, is a managing director of Bay City Capital LLC and shares voting and dispositive power with respect to shares held by BCC V. Dr. Goldfischer disclaims beneficial ownership of these shares, except to the extent of its pecuniary interest therein. The principal business address of Bay City Capital Management V LLC is 750 Battery Street Suite 400, San Francisco, CA 94111.
- (4) Shares beneficially owned before this offering consists of 3,334,640 shares of common stock. The principal business address of Celgene European Investment Company LLC is 86 Morris Avenue, Summit, NJ 07901. The percentage of shares beneficially owned by CEIC after this offering reflects the purchase by CEIC of 340,000 shares in this offering.
- (5) Consists of (i) 2,328,958 shares of common stock held by MPM BioVentures IV-QP, L.P., of which 377,313 are being sold in this offering, (ii) 89,724 shares of common stock held by MPM BioVentures IV GmbH & Co. Beteiligungs KG, of which 14,536 are being sold in this offering, (iii) 66,224 shares of common stock held by MPM Asset Management Investors BV4 LLC, of which 10,729 are being sold in this offering, and (iv) 395,579 shares of common stock held by MPM BioVentures IV Strategic Fund, L.P., of which 64,088 are being sold in this offering. MPM Asset Management LLC is the Management Company of MPM BioVentures IV LLC. MPM BioVentures IV LLC is the Managing Member of MPM BioVentures IV GP LLC, which is the General Partner of MPM BioVentures IV-QP, L.P. and MPM BioVentures IV Strategic Fund, L.P. and the Managing Limited Partner of MPM BioVentures IV GmbH & Co. Beteiligungs KG. MPM BioVentures IV LLC is the Manager of MPM Asset Management Investors BV4 LLC. Ansbert Gadick, Luke Evnin, Todd Foley, John Vander Vort, James P. Scopa and Vaughn M. Kailian are the Members of MPM BioVentures IV LLC. All members share all power to vote, acquire, hold and dispose of all shares. Each member disclaims beneficial ownership of the securities except to the extent of their pecuniary interest therein. In addition, Dr. Kazumi Shiosaki, a member of our board of directors and our former Chief Executive Officer, is a Managing Director of MPM Asset Management LLC but does not share voting or dispositive power over these shares. The address for the funds managed by MPM Capital is 200 Clarendon St., 54th Floor, Boston, MA 02116.
- (6) Consists of the shares described in note (1) above. Mr. Mott is a General Partner of New Enterprise Associates a member of the board of directors of NEA Management Company, LLC and a director of both NEA 13 LTD, the General Partner of NEA Partners 13, the General Partner of NEA 13, and as such Mr. Mott may be deemed to share voting and dispositive power with respect to all shares held by these entities. Mr. Mott disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. Mr. Mott's business address is 5425 Wisconsin Avenue, Suite 800, Chevy Chase, MD 20815.
- (7) Consists of the shares described in note (2) above. Dr. Seidenberg is a partner at Kleiner Perkins Caufield & Byers, and as such Dr. Seidenberg may be deemed to share voting and dispositive power with respect to all shares held by these entities. Dr. Seidenberg disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. Dr. Seidenberg's business address is 2750 Sand Hill Road, Menlo Park, California 94025.
- (8) Consists of the shares described in note (3) above. Dr. Goldfischer is an Investment Partner and Managing Director of BCC LLC and shares voting and dispositive power with respect to shares held by BCC V. Dr. Goldfischer disclaims beneficial ownership of these shares, except to the extent of any pecuniary interest therein. Dr. Goldfischer's business address is 750 Battery Street Suite 400, San Francisco, CA 94111.
- (9) Dr. Daniel, a member of our board of directors, is an Executive Vice President and President of Research and Early Development of Celgene Corporation but does not share voting or dispositive power over shares held by Celgene. Dr. Daniel's business address is 86 Morris Avenue, Summit, NJ 07901.
- (10) Consists of (i) 246,666 shares of common stock and (ii) 246,666 shares of common stock issuable upon the exercise of options exercisable within 60 days after December 31, 2013.
- (11) Consists of shares of common stock issuable upon the exercise of options exercisable within 60 days after December 31, 2013, of which 60,000 are being sold in this offering.
- (12) Consists of shares of common stock issuable upon the exercise of options exercisable within 60 days after December 31, 2013, of which 50,000 are being sold in this offering.

Table of Contents

- (13) Consists of (i) 31,483 shares of common stock held by Dr. Copeland's spouse, (ii) 53,544 shares of common stock held by Dr. Copeland, of which 19,179 are being sold in this offering, and (iii) 218,653 shares of common stock issuable upon the exercise of options held by Dr. Copeland and exercisable within 60 days after December 31, 2013.
- (14) Consists of shares of common stock issuable upon the exercise of options exercisable within 60 days after December 31, 2013, of which 13,500 are being sold in this offering.
- (15) Shares beneficially owned before this offering consists of 15,028,733 shares of common stock and 2,104,612 shares of common stock issuable upon the exercise of options exercisable within 60 days after December 31, 2013 of which 123,500 are being sold in this offering.

Table of Contents

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our amended and restated certificate of incorporation and bylaws are summaries and are qualified by reference to our certificate of incorporation and bylaws.

Our authorized capital stock consists of 125,000,000 shares of our common stock, par value \$0.0001 per share, and 5,000,000 shares of our preferred stock, par value \$0.0001 per share, all of which preferred stock is undesignated.

As of December 31, 2013, we had issued and outstanding 28,494,477 shares of our common stock held by approximately 31 stockholders of record.

Common Stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Subject to the supermajority votes for some matters, other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter. Our amended and restated certificate of incorporation and amended and restated bylaws also provide that our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our certificate of incorporation described below under **Anti-Takeover Effects of Delaware Law and Our Charter and Bylaws** **Removal of Directors** and **Stockholder Action by Written Consent; Special Meetings**. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of any outstanding preferred stock.

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred Stock

Under the terms of our certificate of incorporation, our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

Edgar Filing: Epizyme, Inc. - Form 424B4

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. As of December 31, 2013, there were no shares of preferred stock outstanding, and we have no present plans to issue any shares of preferred stock.

Table of Contents

Options

As of December 31, 2013, options to purchase an aggregate of 4,728,503 shares of our common stock at a weighted average exercise price of \$3.13 per share were outstanding.

Anti-Takeover Effects of Delaware Law and Our Charter and Bylaws

Delaware law contains, and our certificate of incorporation and our bylaws contain, provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

Removal of Directors

A director may be removed only for cause and only by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in an annual election of directors. Any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office.

Stockholder Action by Written Consent; Special Meetings

Our certificate of incorporation provides that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of such holders and may not be effected by any consent in writing by such holders. Our certificate of incorporation and bylaws also provide that, except as otherwise required by law, special meetings of our stockholders can only be called by our chairman of the board, our chief executive officer or our board of directors.

Advance Notice Requirements for Stockholder Proposals

Our bylaws have established an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of persons for election to our board of directors. Stockholders at an annual meeting will only be able to consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors or by a stockholder of record on the record date for the meeting who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder's intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities.

Delaware Business Combination Statute

We are subject to Section 203 of the Delaware General Corporation Law. Subject to specified exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a business combination with any interested stockholder for three years following the date that the person became an interested stockholder, unless the interested stockholder attained that status with the approval of our board of directors or unless the business combination is approved in a prescribed manner. A business combination includes, among other things, a merger or consolidation involving us and the interested stockholder and the sale of more than 10% of our assets. In general, an interested stockholder is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Table of Contents

Amendment of Certificate of Incorporation and Bylaws

The Delaware General Corporation Law provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws, unless a corporation's certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our bylaws may be amended or repealed by a majority vote of our board of directors or by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our certificate of incorporation described above under **Removal of Directors** and **Stockholder Action by Written Consent; Special Meetings**.

Right of First Negotiation with Celgene

Under our collaboration agreement with Celgene, we granted to Celgene a right of first negotiation with respect to business combination transactions that we may desire to pursue with third parties during an option period that Celgene has the right to extend from July 2015 to July 2016. During the option period, we are required to notify Celgene if we desire to pursue a specified business combination transaction with a third party prior to negotiating terms with the third party, and after so notifying Celgene we have agreed not to, directly or indirectly, solicit, initiate or encourage proposals from, discuss or negotiate with, or provide any information to, any third party related to the proposed transaction for a specified period from the date we first notify Celgene of such proposed transaction, or the Celgene negotiation period. If Celgene notifies us that it is interested in entering into the proposed transaction, we have agreed to negotiate in good faith with Celgene during the Celgene negotiation period. Following the Celgene negotiation period, if we have not entered into the proposed transaction with Celgene, or if Celgene does not notify us that it is interested in entering into the proposed transaction, we are free to enter into the proposed transaction with a third party for a period of 225 days following the expiration of the Celgene negotiation period, but we are obligated to re-offer the proposed transaction to Celgene if during the option term we propose to enter into the proposed transaction with a third party on terms that, in specified respects, are less favorable to us than the terms last offered by Celgene.

Registration Rights

We are party to an amended and restated investor rights agreement dated April 2, 2012, which we refer to as the investor rights agreement, pursuant to which holders of an aggregate of 18,462,333 shares of our common stock will have the right to require us to register these shares under the Securities Act under specified circumstances. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act. If not otherwise exercised, the rights described below will expire in June 2020, which is seven years after the closing of our initial public offering.

Demand and Form S-3 Registration Rights

Subject to specified limitations set forth in the investor rights agreement, at any time, the holders of at least 50.1% of the then outstanding shares having rights under the investor rights agreement, which we refer to as registrable securities, may demand that we register all or a portion of the registrable securities under the Securities Act for purposes of a public offering having an aggregate offering price to the public of not less than \$5,000,000. We are not obligated to file a registration statement pursuant to this provision on more than two occasions.

Edgar Filing: Epizyme, Inc. - Form 424B4

In addition, subject to specified limitations set forth in the investor rights agreement, at any time after we become eligible to file a registration statement on Form S-3, holders of at least 50.1% of the registrable securities then outstanding may request that we register their registrable securities on Form S-3 for purposes of a public offering for which the reasonably anticipated price to the public would exceed \$3,000,000. We are not obligated to file a registration statement pursuant to this provision on more than two occasions in any 12-month period.

Table of Contents

Incidental Registration Rights

If we propose to register for our own account any of our securities under the Securities Act, the holders of registrable securities will be entitled to notice of the registration and, subject to specified exceptions, have the right to require us to use our best efforts to register all or a portion of the registrable securities then held by them in that registration.

In the event that any registration in which the holders of registrable shares participate pursuant to our investor rights agreement is an underwritten public offering, we have agreed to enter into an underwriting agreement containing customary representations and warranties and covenants, including without limitation customary provisions with respect to indemnification of the underwriters of such offering.

In the event that any registration in which the holders of registrable shares participate pursuant to our investor rights agreement is an underwritten public offering, we will use our best efforts to include the requested registrable shares to be included, but such inclusions may be limited by market conditions to the extent set forth in the investor rights agreement.

In connection with this offering, the holders of registrable securities were entitled to, and the necessary percentage of holders waived, their rights to include their registrable securities in this offering.

Expenses

Pursuant to the investor rights agreement, we are required to pay all registration expenses, including the fees and expenses of one counsel to represent the selling stockholders, other than any underwriting discounts, selling commissions and fees and expenses of a selling stockholder's own counsel, except for the one counsel selected to represent all selling stockholders, related to any demand, Form S-3 or incidental registration. We are not required to pay registration expenses if the registration request under the investor rights agreement is withdrawn at the request of holders initiating such registration request, unless the withdrawal is due to discovery of a materially adverse change in our business after the initiation of such registration request.

The investor rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us or any violation or alleged violation whether by action or inaction by us under the Securities Act, the Exchange Act, any state securities or Blue Sky law or any rule or regulation promulgated under the Securities Act, the Exchange Act or any state securities or Blue Sky law in connection with such registration statement or the qualification or compliance of the offering, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, Inc.

NASDAQ Global Market

Our common stock is listed on The NASDAQ Global Market under the symbol EPZM .

Table of Contents

SHARES ELIGIBLE FOR FUTURE SALE

Future sales of substantial amounts of our common stock, including shares issued upon exercise of outstanding options or in the public market after this offering, or the anticipation of these sales, could adversely affect market prices prevailing from time to time and could impair our ability to raise capital through sales of equity securities. Our common stock is listed on The NASDAQ Global Market under the symbol EPZM.

Upon the closing of this offering, we will have outstanding 31,617,947 shares of our common stock based on 28,494,447 shares of our common stock outstanding as of December 31, 2013 and reflecting the exercise by certain selling shareholders of options to purchase 123,500 shares being sold in this offering, but assuming no exercise by the underwriters of their option to purchase additional shares.

Of the shares to be outstanding immediately after the closing of this offering, 11,418,274 shares of common stock, including the shares being sold in this offering, including both the shares sold by us and the shares sold by the selling stockholders, and the 5,913,300 shares sold in our initial public offering, will be freely tradable without restriction under the Securities Act unless purchased by our affiliates, as that term is defined in Rule 144 under the Securities Act.

The remaining 20,199,673 shares of our common stock are restricted securities under Rule 144. Of these shares, 19,859,673 shares are subject to lock-up agreements entered into in connection with this offering, which expire 60 days after the date of this prospectus. After the lock-up period, these restricted securities may be sold in the public market only if registered or if they qualify for an exemption from registration under Rule 144 or 701 under the Securities Act or any other exemption.

Rule 144

In general, under Rule 144, any person who is not our affiliate and has held their shares for at least six months, including the holding period of any prior owner other than one of our affiliates, may sell those shares without restriction, subject to the availability of current public information about us. In addition, under Rule 144, any person who is not our affiliate and has not been our affiliate at any time during the preceding three months and has held their shares for at least one year, including the holding period of any prior owner other than one of our affiliates, would be entitled to sell an unlimited number of shares immediately upon the closing of this offering without regard to whether current public information about us is available.

A person who is our affiliate or who was our affiliate at any time during the preceding three months and who has beneficially owned restricted securities for at least six months, including the holding period of any prior owner other than one of our affiliates, is entitled to sell a number of shares within any three-month period that does not exceed the greater of:

1% of the number of shares of our common stock then outstanding, which will equal 316,179 shares immediately after this offering assuming no exercise by the underwriters of their option to purchase additional shares and no exercise of options outstanding as of December 31, 2013; and

the average weekly trading volume in our common stock on The NASDAQ Global Market during the four calendar weeks preceding the date of filing of a Notice of Proposed Sale of Securities Pursuant to Rule 144 with respect to the sale.

Edgar Filing: Epizyme, Inc. - Form 424B4

Sales under Rule 144 by our affiliates are also subject to manner of sale provisions and notice requirements and to the availability of current public information about us.

Upon the expiration of the 60-day lock-up agreements entered into in connection with this offering, as described below, shares of our common stock will be eligible for sale under Rule 144. We cannot estimate the number of shares of our common stock that our existing stockholders will elect to sell under Rule 144.

Table of Contents

Rule 701

In general, under Rule 701 of the Securities Act, any of our employees, consultants or advisors, other than our affiliates, who purchased shares from us in connection with a qualified compensatory stock plan or other written agreement before our initial public offering is eligible to resell these shares in reliance on Rule 144, but without compliance with the various restrictions, including the availability of public information about us, holding period and volume limitations, contained in Rule 144.

Lock-up Agreements

We and each of our directors and executive officers and their affiliated entities, as well as the selling stockholders, have agreed that, without the prior written consent of Citigroup on behalf of the underwriters for this offering, we and they will not, subject to limited exceptions, during the period ending 60 days after the date of this prospectus:

offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock, except for the shares made available by our selling stockholders as part of this prospectus; or

enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock.

After giving effect to the sale of shares by the selling stockholders in this offering, a total of 19,859,673 outstanding shares of common stock will be subject to these lock-up arrangements.

See **Underwriting** for a further description of the lock-up arrangements applicable to our common stock.

Registration Rights

Subject to the lock-up agreements described above and assuming that the underwriters do not exercise their option to purchase additional shares of common stock, the holders of an aggregate of 18,462,333 shares of our common stock will have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act. See **Description of Capital Stock Registration Rights** for additional information regarding these registration rights.

Stock Options and Form S-8 Registration Statement

Edgar Filing: Epizyme, Inc. - Form 424B4

As of December 31, 2013, we had outstanding options to purchase an aggregate of 4,728,503 shares of our common stock, of which options to purchase 2,646,881 shares were vested. We have filed a registration statement on Form S-8 under the Securities Act to register all of the shares of our common stock subject to outstanding options and options and other awards issuable pursuant to our 2008 Plan and our 2013 Plan. See Executive Compensation Stock Option and Other Compensation Plans for additional information regarding these plans. Accordingly, shares of our common stock registered under the registration statements will be available for sale in the open market, subject to Rule 144 volume limitations applicable to affiliates, and subject to any vesting restrictions and lock-up agreements applicable to these shares.

Table of Contents

MATERIAL U.S. TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF COMMON STOCK

The following is a general discussion of material U.S. federal income and estate tax considerations relating to ownership and disposition of our common stock by a non-U.S. holder. For purposes of this discussion, the term "non-U.S. holder" means a beneficial owner of our common stock that is not, for U.S. federal income tax purposes:

an individual who is a citizen or resident of the United States;

a corporation, or other entity treated as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States or of any political subdivision of the United States;

an estate the income of which is subject to U.S. federal income taxation regardless of its source; or

a trust, if a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or if the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury regulations.

An individual may be treated as a resident instead of a nonresident of the United States in any calendar year for U.S. federal income tax purposes if the individual was present in the United States for at least 31 days in that calendar year and for an aggregate of at least 183 days during the three-year period ending with the current calendar year. For purposes of this calculation, all of the days present in the current year, one-third of the days present in the immediately preceding year and one-sixth of the days present in the second preceding year are counted. Residents are taxed for U.S. federal income tax purposes as if they were U.S. citizens.

This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus and all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change could alter the tax consequences to non-U.S. holders described in this prospectus. In addition, the Internal Revenue Service, or the IRS, could challenge one or more of the tax consequences described in this prospectus.

We assume in this discussion that each non-U.S. holder holds shares of our common stock as a capital asset (generally, property held for investment). This discussion does not address all aspects of U.S. federal income and estate taxation that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder's individual circumstances nor does it address any aspects of U.S. state, local or non-U.S. taxes. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as:

insurance companies;

tax-exempt organizations;

financial institutions;

brokers or dealers in securities;

regulated investment companies;

pension plans;

controlled foreign corporations;

passive foreign investment companies;

owners that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment; and

certain U.S. expatriates.

Table of Contents

In addition, this discussion does not address the tax treatment of partnerships or persons who hold their common stock through partnerships or other entities which are pass-through entities for U.S. federal income tax purposes. A partner in a partnership or other pass-through entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

Prospective investors should consult their own tax advisors regarding the U.S. federal, state, local and non-U.S. income and other tax considerations of acquiring, holding and disposing of our common stock.

Dividends

If we pay distributions on our common stock, those distributions generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such holder's tax basis in the common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below under the heading **Gain on Disposition of Common Stock**.

Dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States, and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. However, such U.S. effectively connected income, net of specified deductions and credits, is taxed at the same graduated U.S. federal income tax rates applicable to U.S. persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional **branch profits tax** at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty between the United States and such holder's country of residence generally will be required to provide a properly executed IRS Form W-8BEN (or successor form) and satisfy applicable certification and other requirements. Non-U.S. holders are urged to consult their own tax advisors regarding their entitlement to benefits under a relevant income tax treaty.

A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim with the IRS.

Gain on Disposition of Common Stock

Edgar Filing: Epizyme, Inc. - Form 424B4

A non-U.S. holder generally will not be subject to U.S. federal income tax on gain recognized on a disposition of our common stock unless:

the gain is effectively connected with the non-U.S. holder's conduct of a trade or business in the United States, and, if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the United States; in these cases, the non-U.S. holder will be taxed on a net income basis at the regular graduated rates and in the manner applicable to U.S. persons, and, if the non-U.S. holder is a foreign corporation, an additional branch profits tax at a rate of 30%, or a lower rate as may be specified by an applicable income tax treaty, may also apply;

Table of Contents

the non-U.S. holder is a non-resident alien present in the United States for 183 days or more in the taxable year of the disposition and certain other requirements are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty) on the net gain derived from the disposition, which may be offset by U.S.-source capital losses of the non-U.S. holder, if any; or

we are or have been, at any time during the five-year period preceding such disposition (or the non-U.S. holder's holding period, if shorter) a U.S. real property holding corporation unless our common stock is regularly traded on an established securities market and the non-U.S. holder held no more than 5% of our outstanding common stock, directly or indirectly, during the shorter of the five-year period ending on the date of the disposition or the period that the non-U.S. holder held our common stock. Generally, a corporation is a U.S. real property holding corporation if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we believe that we are not currently, and we do not anticipate becoming, a U.S. real property holding corporation for U.S. federal income tax purposes. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rule described above.

Information Reporting and Backup Withholding Tax

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a U.S. person (as defined in the Code) in order to avoid backup withholding at the applicable rate, currently 28%, with respect to dividends on our common stock. Generally, a holder will comply with such procedures if it provides a properly executed IRS Form W-8BEN (or other applicable Form W-8) or otherwise meets documentary evidence requirements for establishing that it is a non-U.S. holder, or otherwise establishes an exemption. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above under Dividends, will generally be exempt from U.S. backup withholding.

Information reporting and backup withholding generally will apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder can be refunded or credited against the non-U.S. holder's U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

Federal Estate Tax

Edgar Filing: Epizyme, Inc. - Form 424B4

Common stock owned or treated as owned by an individual who is a non-U.S. holder (as specially defined for U.S. federal estate tax purposes) at the time of death will be included in the individual's gross estate for U.S. federal estate tax purposes and, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise.

Table of Contents

Recently Enacted Legislation Relating to Foreign Accounts

The Foreign Account Tax Compliance Act, or FATCA, was enacted in March 2010. Generally, FATCA imposes a 30% withholding tax on dividends of, and gross proceeds from the sale or disposition, of our common stock if paid to a foreign entity unless (i) if the foreign entity is a foreign financial institution, the foreign entity undertakes certain due diligence, reporting, withholding, and certification obligations, (ii) if the foreign entity is not a foreign financial institution, the foreign entity identifies certain of its U.S. investors, or (iii) the foreign entity is otherwise exempt under FATCA.

Although this legislation is effective with regards to amounts paid after December 31, 2012, (1) under IRS Notice 2013-43 issued on July 7, 2013, withholding under FATCA will only apply to payments of dividends on our common stock made after June 30, 2014 and (2) under final regulations issued by the U.S. Department of Treasury on January 17, 2013, withholding under FATCA will only apply to payments of gross proceeds from a sale or other disposition of our common stock made after December 31, 2016.

The preceding discussion of material U.S. federal tax considerations is for general information only. It is not tax advice. Prospective investors should consult their own tax advisors regarding the particular U.S. federal, state, local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed changes in applicable laws.

Table of Contents**UNDERWRITING**

Citigroup Global Markets Inc., Cowen and Company, LLC and Leerink Partners LLC are acting as joint book-running managers of the offering and as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus, each underwriter named below has severally agreed to purchase, and we and the selling stockholders have agreed to sell to that underwriter, severally, the number of shares set forth opposite the underwriter's name.

Underwriter	Number of Shares
Citigroup Global Markets Inc.	1,752,145
Cowen and Company, LLC	853,609
Leerink Partners LLC	853,609
JMP Securities LLC	404,341
Wedbush Securities Inc.	404,341
BTIG LLC.	224,634
Total	4,492,679

The underwriting agreement provides that the obligations of the underwriters to purchase the shares included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the shares (other than those covered by the option to purchase additional shares described below) if they purchase any of the shares.

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount from the public offering price not to exceed \$1.009125 per share. If all the shares are not sold at the offering price, the underwriters may change the offering price and the other selling terms. The representatives have advised us that the underwriters do not intend to make sales to discretionary accounts.

If the underwriters sell more shares than the total number set forth in the table above, the underwriters have been granted an option, exercisable for 30 days from the date of this prospectus, to purchase up to 673,901 additional shares from us at the public offering price less the underwriting discount. To the extent the option is exercised, each underwriter must purchase a number of additional shares approximately proportionate to that underwriter's initial purchase commitment. Any shares issued or sold under the option will be issued and sold on the same terms and conditions as the other shares that are the subject of this offering.

We, our officers and directors and their affiliates and the selling stockholders have agreed that, subject to specified limited exceptions, for a period of 60 days from the date of this prospectus, we and they will not, without the prior written consent of Citigroup, dispose of or hedge any shares of our common stock or any securities convertible into or exchangeable for our common stock. Citigroup in its sole discretion may release any of the securities subject to these lock-up agreements at any time, which, in the case of officers and directors, shall be with notice.

Our common stock is listed on The NASDAQ Global Market under the symbol EPZM.

Edgar Filing: Epizyme, Inc. - Form 424B4

The following table shows the underwriting discounts and commissions that we and the selling stockholders are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Paid by Epizyme, Inc.		Paid by Selling Stockholders.	
	No Exercise	Full Exercise	No Exercise	Full Exercise
Per share	\$ 1.681875	\$ 1.681875	\$ 1.608750	\$ 1.608750
Total	\$ 5,045,625	\$ 6,179,042	\$ 2,401,347	\$ 2,401,347

Table of Contents

In addition, we estimate that the expenses of this offering, other than underwriting discounts and commissions, payable by us will be \$0.7 million. We have also agreed to reimburse the underwriters for certain of their expenses as set forth in the underwriting agreement, and the underwriters have agreed to reimburse us for certain of our expenses incurred in connection with this offering.

In connection with the offering, the underwriters may purchase and sell shares in the open market. Purchases and sales in the open market may include short sales, purchases to cover short positions, which may include purchases pursuant to their option to purchase additional shares, and stabilizing purchases.

Short sales involve secondary market sales by the underwriters of a greater number of shares than they are required to purchase in the offering.

Covered short sales are sales of shares in an amount up to the number of shares represented by the underwriters' option to purchase additional shares.

Naked short sales are sales of shares in an amount in excess of the number of shares represented by the underwriters' option to purchase additional shares.

Covering transactions involve purchases of shares either pursuant to the underwriters' option to purchase additional shares or in the open market in order to cover short positions.

To close a naked short position, the underwriters must purchase shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchase in the offering.

To close a covered short position, the underwriters must purchase shares in the open market or must exercise the option to purchase additional shares. In determining the source of shares to close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares.

Stabilizing transactions involve bids to purchase shares so long as the stabilizing bids do not exceed a specified maximum.

Purchases to cover short positions and stabilizing purchases, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the shares. They may also cause the price of the shares to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on The NASDAQ Global Market, in the over-the-counter market or otherwise. If the underwriters commence any of these transactions, they may discontinue them at any time.

Conflicts of Interest

The underwriters are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, principal investment, hedging, financing and brokerage activities. The

Edgar Filing: Epizyme, Inc. - Form 424B4

underwriters and their respective affiliates may, from time to time, engage in transactions with and perform services for us in the ordinary course of their business for which they may receive customary fees and reimbursement of expenses. In the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (which may include bank loans and/or credit default swaps) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Table of Contents

We and the selling stockholders have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make because of any of those liabilities.

Notice to Prospective Investors in the European Economic Area

In relation to each member state of the European Economic Area that has implemented the Prospectus Directive (each, a relevant member state), with effect from and including the date on which the Prospectus Directive is implemented in that relevant member state (the relevant implementation date), an offer of shares described in this prospectus may not be made to the public in that relevant member state other than:

to any legal entity which is a qualified investor as defined in the Prospectus Directive;

to fewer than 100 or, if the relevant member state has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the relevant Dealer or Dealers nominated by us for any such offer; or

in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For purposes of this provision, the expression an offer of securities to the public in any relevant member state means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe for the shares, as the expression may be varied in that member state by any measure implementing the Prospectus Directive in that member state, and the expression Prospectus Directive means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the relevant member state) and includes any relevant implementing measure in the relevant member state. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

The sellers of the shares have not authorized and do not authorize the making of any offer of shares through any financial intermediary on their behalf, other than offers made by the underwriters with a view to the final placement of the shares as contemplated in this prospectus. Accordingly, no purchaser of the shares, other than the underwriters, is authorized to make any further offer of the shares on behalf of the sellers or the underwriters.

Notice to Prospective Investors in the United Kingdom

This prospectus is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order) or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (each such person being referred to as a relevant person). This prospectus and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients

Edgar Filing: Epizyme, Inc. - Form 424B4

to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Notice to Prospective Investors in Australia

No prospectus or other disclosure document (as defined in the Corporations Act 2001 (Cth) of Australia (**Corporations Act**)) in relation to the common stock has been or will be lodged with the Australian

Table of Contents

Securities & Investments Commission (ASIC). This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

you confirm and warrant that you are either:

- a sophisticated investor under section 708(8)(a) or (b) of the Corporations Act;

- a sophisticated investor under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to us which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;

- a person associated with the company under section 708(12) of the Corporations Act; or

- a professional investor within the meaning of section 708(11)(a) or (b) of the Corporations Act, and to the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act any offer made to you under this document is void and incapable of acceptance; and

you warrant and agree that you will not offer any of the common stock for resale in Australia within 12 months of that common stock being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Notice to Prospective Investors in France

Neither this prospectus nor any other offering material relating to the shares described in this prospectus has been submitted to the clearance procedures of the *Autorité des Marchés Financiers* or of the competent authority of another member state of the European Economic Area and notified to the *Autorité des Marchés Financiers*. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus nor any other offering material relating to the shares has been or will be:

released, issued, distributed or caused to be released, issued or distributed to the public in France; or

used in connection with any offer for subscription or sale of the shares to the public in France.

Such offers, sales and distributions will be made in France only:

to qualified investors (*investisseurs qualifiés*) and/or to a restricted circle of investors (*cercle restreint d'investisseurs*), in each case investing for their own account, all as defined in, and in accordance with articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French *Code monétaire et financier*;

Edgar Filing: Epizyme, Inc. - Form 424B4

to investment services providers authorized to engage in portfolio management on behalf of third parties; or

in a transaction that, in accordance with article L.411-2-II-1^o-or-2^o-or 3^o of the French *Code monétaire et financier* and article 211-2 of the General Regulations (*Règlement Général*) of the *Autorité des Marchés Financiers*, does not constitute a public offer (*appel public à l'épargne*).

The shares may be resold directly or indirectly, only in compliance with articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French *Code monétaire et financier*.

Notice to Prospective Investors in Hong Kong

The shares may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), or (ii) to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances

Table of Contents

which do not result in the document being a prospectus within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong) and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Notice to Prospective Investors in Japan

The shares offered in this prospectus have not been and will not be registered under the Financial Instruments and Exchange Law of Japan. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan (including any corporation or other entity organized under the laws of Japan), except (i) pursuant to an exemption from the registration requirements of the Financial Instruments and Exchange Law and (ii) in compliance with any other applicable requirements of Japanese law.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to compliance with conditions set forth in the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

to an institutional investor (for corporations, under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than S\$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and

Edgar Filing: Epizyme, Inc. - Form 424B4

further for corporations, in accordance with the conditions specified in Section 275 of the SFA;

where no consideration is or will be given for the transfer; or

where the transfer is by operation of law.

Table of Contents

LEGAL MATTERS

The validity of the shares of common stock offered hereby is being passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Cooley LLP, San Francisco, California, is acting as counsel for the underwriters in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements as of December 31, 2011 and 2012, and for the years then ended, as set forth in their report. We have included our consolidated financial statements in the prospectus and elsewhere in this registration statement in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-1 under the Securities Act with respect to the shares of common stock we are offering to sell. This prospectus, which constitutes part of the registration statement, does not include all of the information contained in the registration statement and the exhibits, schedules and amendments to the registration statement. For further information with respect to us and our common stock, we refer you to the registration statement and to the exhibits and schedules to the registration statement. Statements contained in this prospectus about the contents of any contract, agreement or other document are not necessarily complete, and, in each instance, we refer you to the copy of the contract, agreement or other document filed as an exhibit to the registration statement. Each of these statements is qualified in all respects by this reference.

You may read and copy the registration statement of which this prospectus is a part at the SEC's public reference room, which is located at 100 F Street, N.E., Room 1580, Washington, DC 20549. You can request copies of the registration statement by writing to the Securities and Exchange Commission and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the SEC's public reference room. In addition, the SEC maintains an Internet website, which is located at <http://www.sec.gov>, that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. You may access the registration statement of which this prospectus is a part at the SEC's Internet website.

We are subject to the reporting and information requirements of the Exchange Act and, as a result, file periodic reports, proxy statements and other information with the SEC. These periodic reports and other information are available for inspection and copying at the SEC's public reference room and the website of the SEC, in each case, referred to above. We also maintain a website at <http://www.epizyme.com>. You may access our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act with the SEC free of charge at our website as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC. The information contained in, or that can be accessed through, our website is not part of this prospectus. The reference to our web address does not constitute incorporate by reference of the information contained at or accessible through such site.

Table of Contents

EPIZYME, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

<u>Report of Independent Registered Public Accounting Firm</u>	F-2
<u>Consolidated Balance Sheets</u>	F-3
<u>Consolidated Statements of Operations and Comprehensive (Loss) Income</u>	F-4
<u>Consolidated Statements of Cash Flows</u>	F-5
<u>Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' (Deficit) Equity</u>	F-6
<u>Notes to Consolidated Financial Statements</u>	F-7

F-1

Table of Contents

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders

Epizyme, Inc.

We have audited the accompanying consolidated balance sheets of Epizyme, Inc. (the Company) as of December 31, 2011 and 2012, and the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred stock and stockholders' deficit, and cash flows for the years then ended. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Epizyme, Inc. at December 31, 2011 and 2012, and the consolidated results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts

March 22, 2013, except for Note 13,

as to which the date is May 13, 2013

Table of Contents**EPIZYME, INC.****CONSOLIDATED BALANCE SHEETS**

(amounts in thousands except share and per share data)

	December 31, 2011	December 31, 2012	September 30, 2013 (unaudited)
ASSETS			
Current assets:			
Cash and cash equivalents	\$ 33,341	\$ 97,981	\$ 139,575
Accounts receivable	1,873	1,829	2,155
Prepaid expenses and other current assets	208	815	2,130
Total current assets	35,422	100,625	143,860
Property and equipment, net	1,577	2,140	2,028
Restricted cash and other assets	331	746	1,462
Deferred income taxes, net	30		
Total assets	\$ 37,360	\$ 103,511	\$ 147,350
LIABILITIES AND STOCKHOLDERS (DEFICIT) EQUITY			
Current liabilities:			
Accounts payable	\$ 2,498	\$ 2,967	\$ 3,525
Accrued expenses	1,700	4,328	5,384
Current portion of deferred revenue	7,096	28,208	21,556
Current portion of deferred rent	54		
Total current liabilities	11,348	35,503	30,465
Deferred revenue, net of current portion	22,721	41,237	29,150
Deferred rent, net of current portion	188	9	95
Other long-term liabilities		1,732	357
Commitments and contingencies			
Redeemable convertible preferred stock, \$0.0001 par value; 52,096,000 (Series A and B), 61,899,922 (Series A, B and C) and 5,000,000 (unaudited) shares authorized, respectively; 52,095,243, 61,899,165 and 0 (unaudited) shares issued and outstanding, respectively; aggregate liquidation preference of \$54,000, \$79,000 and \$0 (unaudited) respectively			
	53,747	76,156	
Stockholders (deficit) equity:			
Common stock, \$0.0001 par value; 80,000,000, 90,000,000 and 125,000,000 (unaudited) shares authorized, respectively; 1,645,729, 1,694,862 and 28,418,420 (unaudited) shares issued, respectively; and 1,614,091, 1,672,639 and 28,408,698 (unaudited) shares outstanding, respectively			
	0	0	3
Treasury stock, at cost; 11,544, 11,544 and 0 shares, respectively	0	0	
Additional paid-in capital	1,251	1,471	159,290
Accumulated deficit	(51,895)	(52,597)	(72,010)
Total stockholders (deficit) equity	(50,644)	(51,126)	87,283
Total liabilities and stockholders (deficit) equity	\$ 37,360	\$ 103,511	\$ 147,350

Edgar Filing: Epizyme, Inc. - Form 424B4

See notes to consolidated financial statements.

F-3

Table of Contents**EPIZYME, INC.****CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE (LOSS) INCOME**

(amounts in thousands except per share data)

	Year Ended December 31,		Nine Months Ended September 30,	
	2011	2012	2012	2013
			(unaudited)	(unaudited)
Collaboration revenue	\$ 6,944	\$ 45,222	\$ 36,327	\$ 32,165
Operating expenses:				
Research and development	22,911	38,482	27,385	41,882
General and administrative	5,000	7,508	5,175	9,664
Total operating expenses	27,911	45,990	32,560	51,546
Operating (loss) income	(20,967)	(768)	3,767	(19,381)
Other income (expense):				
Interest income	33	145	108	54
Other expense, net	(23)	(78)	(39)	(86)
Other income (expense), net	10	67	69	(32)
(Loss) income before income taxes	(20,957)	(701)	3,836	(19,413)
Income tax expense		1		
Net (loss) income	\$ (20,957)	\$ (702)	\$ 3,836	\$ (19,413)
Less: accretion of redeemable convertible preferred stock to redemption value	45	486	326	264
Less: income allocable to participating securities			3,239	
(Loss) income allocable to common stockholders basic	(21,002)	(1,188)	271	(19,677)
Undistributed income re-allocated to common stockholders			147	
(Loss) income allocable to common stockholders diluted	\$ (21,002)	\$ (1,188)	\$ 418	\$ (19,677)
(Loss) earnings per share allocable to common stockholders:				
Basic	\$ (14.65)	\$ (0.72)	\$ 0.17	\$ (1.49)
Diluted	\$ (14.65)	\$ (0.72)	\$ 0.16	\$ (1.49)
Weighted average shares outstanding:				
Basic	1,434	1,645	1,637	13,212
Diluted	1,434	1,645	2,641	13,212
Comprehensive (loss) income	\$ (20,957)	\$ (702)	\$ 3,836	\$ (19,413)

See notes to consolidated financial statements.

Table of Contents**EPIZYME, INC.****CONSOLIDATED STATEMENTS OF CASH FLOWS**

(amounts in thousands)

	Year Ended December 31,		Nine Months Ended September 30,	
	2011	2012	2012 (unaudited)	2013 (unaudited)
CASH FLOWS FROM OPERATING ACTIVITIES:				
Net (loss) income	\$ (20,957)	\$ (702)	\$ 3,836	\$ (19,413)
Adjustments to reconcile net (loss) income to net cash provided by (used in) operating activities:				
Depreciation and amortization	479	847	440	534
Stock-based compensation	305	689	210	1,819
Loss on disposal of property and equipment	24	35	20	
Changes in operating assets and liabilities:				
Accounts receivable	(1,872)	44	(3,663)	(326)
Prepaid expenses and other current assets	191	(607)	(553)	(1,315)
Accounts payable	1,284	469	(517)	364
Accrued expenses	769	2,667	1,933	1,052
Deferred revenue	29,817	39,628	45,952	(18,739)
Deferred rent	242	(233)	31	86
Restricted cash and other assets	(282)	(415)	(495)	(716)
Other long-term liabilities		1,732	1,159	(1,375)
Net cash provided by (used in) operating activities	10,000	44,154	48,353	(38,029)
CASH FLOWS FROM INVESTING ACTIVITIES:				
Purchases of property and equipment	(918)	(1,482)	(239)	(230)
Proceeds from property insurance claim		37		
Net cash used in investing activities	(918)	(1,445)	(239)	(230)
CASH FLOWS FROM FINANCING ACTIVITIES:				
Proceeds from sale of redeemable convertible preferred stock	19,000	21,961	21,961	
Proceeds from initial public offering, net of commissions				82,491
Proceeds from stock options exercised	104	8	3	171
Payment of redeemable convertible preferred stock issuance costs	(21)	(38)	(38)	
Payment of initial public offering costs				(2,809)
Net cash provided by financing activities	19,083	21,931	21,926	79,853
Net increase in cash and cash equivalents	28,165	64,640	70,040	41,594
Cash and cash equivalents at beginning of year	5,176	33,341	33,341	97,981
Cash and cash equivalents at end of year	\$ 33,341	\$ 97,981	\$ 103,381	\$ 139,575

SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:

Purchases of property and equipment unpaid at period end	192
--	-----

Edgar Filing: Epizyme, Inc. - Form 424B4

Conversion of redeemable convertible preferred stock to common stock				76,420
Accretion of redeemable convertible preferred stock to redemption value	45	486	326	264
Vesting of restricted stock liability	13	9	9	
Initial public offering costs incurred but unpaid at period end				6

See notes to consolidated financial statements.

F-5

Table of Contents**EPIZYME, INC.****CONSOLIDATED STATEMENTS OF REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS (DEFICIT) EQUITY**

(amounts in thousands except share data)

	Common Stock		Treasury Stock	Additional Paid-In Capital	Accumulated Deficit	Total Stockholders (Deficit) Equity	Redeemable Convertible Preferred Stock Carrying Value	
	Shares	Amount					Shares	Amount
Balance at December 31, 2010	1,443,388	\$ 0	\$ 0	\$ 874	\$ (30,938)	\$ (30,064)	34,000,002	\$ 34,723
Issuance of Series B redeemable convertible preferred stock (net of issuance costs of \$21)							18,095,241	18,979
Exercise of stock options	202,341	0		104		104		
Vesting of restricted common stock issued to non-employees				13		13		
Stock-based compensation				305		305		
Accretion of redeemable convertible preferred stock to redemption value				(45)		(45)		45
Net loss					(20,957)	(20,957)		
Balance at December 31, 2011	1,645,729	0	0	1,251	(51,895)	(50,644)	52,095,243	53,747
Issuance of Series C redeemable convertible preferred stock (net of issuance costs of \$38)							9,803,922	21,923
Exercise of stock options	15,800	0		8		8		
Vesting of restricted common stock issued to non-employees				9		9		
Stock-based compensation	33,333	0		689		689		
Accretion of redeemable convertible preferred stock to redemption value				(486)		(486)		486
Net loss					(702)	(702)		
Balance at December 31, 2012	1,694,862	\$ 0	\$ 0	\$ 1,471	\$ (52,597)	\$ (51,126)	61,899,165	\$ 76,156
Exercise of stock options (unaudited)	177,212	0		171		171		
Stock-based compensation (unaudited)				1,819		1,819		
Accretion of redeemable convertible preferred stock to redemption value (unaudited)				(264)		(264)		264
Issuance of common stock, net of commissions and offering costs (unaudited)	5,913,300	1		79,675		79,676		
Conversion of redeemable convertible preferred stock to common stock (unaudited)	20,633,046	2		76,418		76,420	(61,899,165)	(76,420)
Retirement of treasury stock (unaudited)			(0)	(0)				
Net loss (unaudited)					(19,413)	(19,413)		
Balance at September 30, 2013 (unaudited)	28,418,420	\$ 3	\$	\$ 159,290	\$ (72,010)	\$ 87,283		

Edgar Filing: Epizyme, Inc. - Form 424B4

See notes to consolidated financial statements.

F-6

Table of Contents

EPIZYME, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. The Company

Epizyme, Inc. is a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize innovative personalized therapeutics for patients with genetically defined cancers. The Company has built a proprietary product platform that it uses to create small molecule inhibitors of a 96-member class of enzymes known as histone methyltransferases (HMTs). Genetic alterations can result in changes to the activity of HMTs, making them oncogenic. The Company's therapeutic strategy is to inhibit oncogenic HMTs to treat the underlying causes of the associated genetically defined cancers. As used in this prospectus, unless the context indicates otherwise, all references herein to Epizyme or the Company refer to Epizyme, Inc. and its wholly owned subsidiary.

On June 5, 2013, the Company completed an initial public offering (IPO) of its common stock, which resulted in the sale of 5,913,300 shares, including all additional shares available to cover over-allotments, at a price of \$15.00 per share. The Company received net proceeds before expenses from the IPO of \$82.5 million after deducting underwriting discounts and commissions paid by the Company. In preparation for the IPO, the Company's Board of Directors and stockholders approved a one-for-three reverse stock split of the Company's common stock effective May 13, 2013. All share and per share amounts in the consolidated financial statements and notes thereto have been retroactively adjusted, where necessary, to give effect to this reverse stock split. In connection with the closing of the IPO, all of the Company's outstanding redeemable convertible preferred stock automatically converted to common stock at a one-for-three ratio as of June 5, 2013, resulting in an additional 20,633,046 shares of common stock of the Company becoming outstanding. Following these transactions, the Company's total issued common stock as of September 30, 2013 was 28,418,420 shares. The significant increase in shares outstanding in June 2013 is expected to impact the year-over-year comparability of the Company's (loss) earnings per share calculations through 2014.

2. Summary of Significant Accounting Policies

Principles of Consolidation

The consolidated financial statements include the accounts of the Company and its wholly owned, controlled subsidiary, Epizyme Securities Corporation. All intercompany balances and transactions have been eliminated in consolidation.

Unaudited Interim Financial Statements

The accompanying consolidated interim financial statements as of September 30, 2013 and for the nine months ended September 30, 2012 and 2013 and the related interim information contained within the notes to the consolidated financial statements are unaudited. The unaudited interim consolidated financial statements have been prepared on the same basis as the audited consolidated financial statements. In the opinion of the Company's management, the accompanying unaudited interim consolidated financial statements contain all adjustments which are necessary to

Edgar Filing: Epizyme, Inc. - Form 424B4

present fairly the Company's financial position as of September 30, 2013 and the results of its operations and cash flows for the nine months ended September 30, 2012 and 2013. Such adjustments are of a normal and recurring nature. The results for the nine months ended September 30, 2013 are not indicative of the results for the year ending December 31, 2013, or for any future period.

Use of Estimates

The preparation of these consolidated financial statements in accordance with accounting principles generally accepted in the United States of America requires management to make estimates, judgments and

F-7

Table of Contents

assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities, as of the date of the consolidated financial statements, and the reported amounts of collaboration revenue and expenses during the reporting period. Actual results and outcomes may differ materially from management's estimates, judgments and assumptions.

Subsequent Events

The Company considers events or transactions that occur after the balance sheet date but before the consolidated financial statements are issued to provide additional evidence relative to certain estimates or to identify matters that require additional disclosure. The Company evaluated all events and transactions through the date the consolidated financial statements as of December 31, 2012 were issued, except for Note 13, *Subsequent Events*, as to which the date is May 13, 2013. For the financial statements as of September 30, 2013, the Company further evaluated all events and transactions through the date those financial statements were issued.

Fair Value Measurements

The Company classifies fair value based measurements using a three-level hierarchy that prioritizes the inputs used to measure fair value. This hierarchy requires entities to maximize the use of observable inputs and minimize the use of unobservable inputs. The three levels of inputs used to measure fair value are as follows: Level 1, quoted market prices in active markets for identical assets or liabilities; Level 2, observable inputs other than quoted market prices included in Level 1 such as quoted market prices for markets that are not active or other inputs that are observable or can be corroborated by observable market data; and Level 3, unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities, including certain pricing models, discounted cash flow methodologies and similar techniques that use significant unobservable inputs.

The Company's financial instruments as of December 31, 2011 and 2012 and September 30, 2013 consisted primarily of cash and cash equivalents, accounts receivable and accounts payable. The Company believes the carrying values of its cash, accounts receivable and accounts payable approximate their respective fair values due to the short-term nature of these instruments. As of December 31, 2011 and 2012 and September 30, 2013, the Company's financial assets recognized at fair value consisted of the following:

	Fair Value as of December 31, 2011			
	Total	Level 1	Level 2	Level 3
	(in thousands)			
Cash equivalents	\$ 32,233	\$ 32,233	\$	\$
Total	\$ 32,233	\$ 32,233	\$	\$

	Fair Value as of December 31, 2012			
	Total	Level 1	Level 2	Level 3
	(in thousands)			
Cash equivalents	\$ 97,375	\$ 97,375	\$	\$
Total	\$ 97,375	\$ 97,375	\$	\$

Edgar Filing: Epizyme, Inc. - Form 424B4

	Fair Value as of September 30, 2013			
	Total	Level 1 (unaudited) (in thousands)	Level 2	Level 3
Cash equivalents	\$ 121,409	\$ 121,409	\$	\$
Total	\$ 121,409	\$ 121,409	\$	\$

F-8

Table of Contents
Cash Equivalents

The Company considers all highly liquid investments with maturities of three months or less when purchased to be cash equivalents. As of December 31, 2011 and 2012 and September 30, 2013, cash equivalents consisted of interest-bearing money market accounts and prime money market funds.

Accounts Receivable

Accounts receivable are amounts due from collaboration partners as a result of research and development services provided, reimbursement under equally co-funded global development arrangements or milestones achieved but not yet paid. The Company considered the need for an allowance for doubtful accounts and has concluded that no allowance was needed as of December 31, 2011 or 2012 or September 30, 2013, as the estimated risk of loss on its accounts receivable was determined to be minimal.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to concentrations of credit risk include cash and cash equivalents and accounts receivable. The Company attempts to minimize the risks related to cash and cash equivalents by working with highly rated financial institutions that invest in a broad and diverse range of financial instruments as defined by the Company. The Company has established guidelines relative to credit ratings and maturities intended to safeguard principal balances and maintain liquidity. The Company maintains its funds in accordance with its investment policy, which defines allowable investments, specifies credit quality standards and is designed to limit the Company's credit exposure to any single issuer.

Accounts receivable represent amounts due from collaboration partners. The Company monitors economic conditions to identify facts or circumstances that may indicate that any of its accounts receivable are at risk.

As of December 31, 2011 and 2012 and September 30, 2013, two collaboration partners, Eisai Co. Ltd. (Eisai) and Celgene Corporation (Celgene), accounted for all of the Company's accounts receivable. Refer to Note 9, *Collaborations*, for additional information regarding the Company's collaboration agreements with Eisai and Celgene.

Property and Equipment

The Company records property and equipment at cost. The Company calculates depreciation and amortization using the straight-line method over the following estimated useful lives:

Asset Category	Useful Lives
----------------	--------------

Edgar Filing: Epizyme, Inc. - Form 424B4

Laboratory equipment	5 - 20 years
Office furniture and equipment	3 - 10 years
Leasehold improvements	3 - 10 years or the remaining term of respective lease, if shorter

The Company capitalizes expenditures for new property and equipment and improvements to existing facilities and charges the cost of maintenance to expense. The Company eliminates the cost of property retired or otherwise disposed of, along with the corresponding accumulated depreciation, from the related accounts, and the resulting gain or loss is reflected in the results of operations.

Impairment of Long-Lived Assets

The Company reviews long-lived assets to be held and used, including property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying amount of the assets or asset group may not be recoverable. No such impairments were recorded during 2011, 2012 or the nine months ended September 30, 2013.

Table of Contents

Evaluation of recoverability is based on an estimate of undiscounted future cash flows resulting from the use of the asset or asset group and its eventual disposition. In the event that such cash flows are not expected to be sufficient to recover the carrying amount of the asset or asset group, the assets are written down to their estimated fair values.

Income Taxes

The Company records deferred income taxes to recognize the effect of temporary differences between tax and financial statement reporting. The Company calculates the deferred taxes using enacted tax rates expected to be in place when the temporary differences are realized and records a valuation allowance to reduce deferred tax assets if it is determined that it is more likely than not that all or a portion of the deferred tax asset will not be realized. The Company considers many factors when assessing the likelihood of future realization of deferred tax assets, including recent earnings results, expectations of future taxable income, carryforward periods available and other relevant factors. The Company records changes in the required valuation allowance in the period that the determination is made.

The Company assesses its income tax positions and records tax benefits for all years subject to examination based upon management's evaluation of the facts, circumstances and information available as of the reporting date. For those tax positions where it is more likely than not that a tax benefit will be sustained, the Company records the largest amount of tax benefit with a greater than 50.0% likelihood of being realized upon ultimate settlement with a taxing authority having full knowledge of all relevant information. For those income tax positions where it is not more likely than not that a tax benefit will be sustained, the Company does not recognize a tax benefit in the financial statements. The Company records interest and penalties related to uncertain tax positions, if applicable, as a component of income tax expense. Refer to Note 5, *Income Taxes*, for additional information regarding the Company's income taxes.

Redeemable Convertible Preferred Stock

The Company initially records preferred stock that may be redeemed at the option of the holder or based on the occurrence of events not under the Company's control outside of stockholders' (deficit) equity at the value of the proceeds received or fair value, if lower, net of issuance costs. Subsequently, if it is probable that the preferred stock will become redeemable, the Company adjusts the carrying value to the redemption value over the period from the issuance date to the earliest possible redemption date using the effective interest method. If it is not probable that the preferred stock will become redeemable, the Company does not adjust the carrying value.

Common Stock Valuation

Prior to the completion of the Company's IPO, due to the absence of an active market for the Company's common stock, the Company utilized methodologies in accordance with the framework of the American Institute of Certified Public Accountants Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its common stock. The Company utilized a probability weighted expected return methodology for its common stock valuations as of February 11, 2011, April 30, 2012, November 30, 2012, February 28, 2013, April 18, 2013 and April 30, 2013 based upon an assessment of the probability of the occurrence of specific scenarios. Each valuation includes estimates and assumptions that require the Company's judgment. These estimates include assumptions regarding future performance, including the probability of successful completion of preclinical studies and clinical trials and the probability and estimated time to completion of an initial public offering or sale. Significant changes to the key assumptions used in the valuations could result in different fair values of common stock at each valuation date. Subsequent to the completion of the Company's IPO, which occurred on June 5, 2013, the fair value of the Company's common stock is based on observable market prices.

Table of Contents**Revenue Recognition**

The Company recognizes revenue when all of the following criteria are met: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the Company's price to the customer is fixed or determinable and collectability is reasonably assured.

The Company has entered into collaboration and license agreements to discover, develop, manufacture and commercialize compounds directed to specific histone methyltransferase (HMT) targets. The terms of these agreements typically contain multiple deliverables, which may include: (i) licenses, or options to obtain licenses, to compounds directed to specific HMT targets (referred to as exclusive licenses) and (ii) research and development activities to be performed on behalf of the collaboration partner related to the licensed HMT targets. Payments to the Company under these agreements may include non-refundable license fees, option fees, exercise fees, payments for research activities, payments based upon the achievement of certain milestones and royalties on any resulting net product sales.

Multiple-Element Revenue Arrangements. The Company's collaborations primarily represent multiple-element revenue arrangements. To account for these transactions, the Company determines the elements, or deliverables, included in the arrangement and allocates arrangement consideration to the various elements based on each element's relative selling price. The identification of individual elements in a multiple-element arrangement and the estimation of the selling price of each element involves significant judgment, including consideration as to whether each delivered element has standalone value to the collaborator. The Company determines the estimated selling price for deliverables within each agreement using vendor-specific objective evidence (VSOE) of selling price, if available, or third party evidence of selling price if VSOE is not available, or the Company's best estimate of selling price, if neither VSOE nor third party evidence is available. Determining the best estimate of selling price for a deliverable requires significant judgment. The Company typically uses its best estimate of a selling price to estimate the selling price for licenses to its proprietary technology, since it often does not have VSOE or third party evidence of selling price for these deliverables. In those circumstances where the Company applies its best estimate of selling price to determine the estimated selling price of a license to its proprietary technology, it considers market conditions as well as entity-specific factors, including those factors contemplated in negotiating the agreements as well as internally developed estimates that include assumptions related to the market opportunity, estimated development costs, probability of success and the time needed to commercialize a product candidate pursuant to the license. In validating its best estimate of selling price, the Company evaluates whether changes in the key assumptions used to determine its best estimate of selling price will have a significant effect on the allocation of arrangement consideration between deliverables. The Company recognizes consideration allocated to an individual element when all other revenue recognition criteria are met for that element.

The Company's multiple-element revenue arrangements generally include the following:

Exclusive Licenses The deliverables under the Company's collaboration agreements generally include exclusive licenses to discover, develop, manufacture and commercialize compounds with respect to one or more specified HMT targets. To account for this element of the arrangement, management evaluates whether the exclusive license has standalone value from the undelivered elements to the collaboration partner based on the consideration of the relevant facts and circumstances of each arrangement, including the research and development capabilities of the collaboration partner. The Company may recognize arrangement consideration allocated to licenses upon delivery of the license if facts and circumstances indicate that the license has standalone value from the undelivered elements, which generally include research and development services. The Company defers arrangement consideration allocated to licenses if facts and circumstances indicate that the delivered license does not have standalone value from the undelivered elements.

The Company has determined that certain of its exclusive licenses lack standalone value apart from the related research and development services and is therefore recognizing collaboration revenue from non-

Table of Contents

refundable exclusive license fees on a straight-line basis over the contracted or estimated period of performance, which is generally the period over which the research and development services are to be provided.

Research and Development Services The deliverables under the Company's collaboration and license agreements generally include deliverables related to research and development services to be performed by the Company on behalf of the collaboration partner. As the provision of research and development services is a part of the Company's central operations, when the Company is principally responsible for the performance of these services under the agreements, the Company recognizes revenue on a gross basis for research and development services as those services are performed.

Option Arrangements The Company's arrangements may provide a collaborator with the right to select a target for licensing either at the inception of the arrangement or within an initial pre-defined selection period, which may, in certain cases, include the right of the collaborator to extend the selection period. Under these agreements, fees may be due to the Company (i) at the inception of the arrangement as an upfront fee or payment, (ii) upon the exercise of an option to acquire a license or (iii) upon extending the selection period as an extension fee or payment.

The accounting for option arrangements is dependent on the nature of the options granted to the collaboration partner. Options are considered substantive if, at the inception of the arrangement, the Company is at risk as to whether the collaboration partner will choose to exercise the options to secure exclusive licenses. Factors that the Company considers in evaluating whether options are substantive include the overall objective of the arrangement, the benefit the collaborator might obtain from the arrangement without exercising the options, the cost to exercise the options relative to the total upfront consideration and the additional financial commitments or economic penalties imposed on the collaborator as a result of exercising the options. For arrangements under which the option to secure licenses is considered substantive, the Company does not consider the licenses to be deliverables at the inception of the arrangement. For arrangements under which the option to secure licenses is not considered substantive, the Company considers the license to be a deliverable at the inception of the arrangement and, upon delivery of the license, would apply the multiple-element revenue arrangement criteria to the license and any other deliverables to determine the appropriate revenue recognition. None of the options to secure exclusive licenses included in the Company's collaborative arrangements have been determined to be substantive.

Milestone Revenue. The Company's collaboration and license agreements generally include contingent milestone payments related to specified preclinical research and development milestones, clinical development milestones, regulatory milestones and sales-based milestones. Preclinical research and development milestones are typically payable upon the selection of a compound candidate for the next stage of research and development. Clinical development milestones are typically payable when a product candidate initiates or advances in clinical trial phases or achieves defined clinical events such as proof-of-concept. Regulatory milestones are typically payable upon submission for marketing approval with regulatory authorities or upon receipt of actual marketing approvals for a compound, approvals for additional indications, or upon the first commercial sale. Sales-based milestones are typically payable when annual sales reach specified levels.

At the inception of each arrangement that includes milestone payments, the Company evaluates whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether (a) the consideration is commensurate with either (i) the entity's performance to achieve the milestone or (ii) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone; (b) the consideration relates solely to past performance; and (c) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. The Company evaluates factors such as the scientific, regulatory, commercial and other risks that must be overcome to achieve the respective milestone, the level of effort and investment required to achieve the respective milestone and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement in making this assessment.

Table of Contents

The Company generally considers non-refundable preclinical research and development, clinical development and regulatory milestones that the Company expects to be achieved as a result of the Company's efforts during the period of the Company's performance obligations under the collaboration and license agreements to be substantive and recognizes them as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. If not considered to be substantive, the Company initially defers milestones and recognizes them over the remaining term of the Company's performance obligations. Milestones that are not considered substantive because the Company does not contribute effort to the achievement of such milestones are generally achieved after the period of the Company's performance obligations and are recognized as revenue upon achievement, assuming all other revenue recognition criteria are met, as there are no undelivered elements remaining and no continuing performance obligations.

Research and Development Expenses

Research and development expenses consist of expenses incurred in performing research and development activities, including compensation and benefits, facilities expenses, overhead expenses, clinical trial and related clinical manufacturing expenses, fees paid to clinical research organizations and other outside expenses. The Company expenses research and development expenses as incurred. The Company records payments made for research and development services prior to the services being rendered as prepaid expenses on the consolidated balance sheets and expenses them as the services are provided. In circumstances where the Company's collaboration and license agreements provide for equally co-funded global development, amounts received from collaboration partners for such co-funding are recorded as a reduction to research and development expense.

Stock-Based Compensation

The Company measures employee stock-based compensation based on the grant date fair value of the stock-based compensation award. Historically, the Company has generally granted stock options at exercise prices equal to the fair value of the Company's common stock on the date of grant. Refer to *Common Stock Valuation* for further information regarding the Company's policy for determining the fair value of its common stock.

The Company recognizes employee stock-based compensation expense, less estimated forfeitures, on a straight-line basis over the requisite service period of the awards. The Company estimates forfeitures at the time of grant and revises those estimates in subsequent periods if actual forfeitures differ from those estimates.

Refer to Note 10, *Employee Benefit Plans*, for additional information regarding the measurement and recognition of expense related to the Company's stock-based compensation awards.

Earnings (Loss) per Share

The Company computes basic earnings (loss) per share by dividing income (loss) allocable to common stockholders by the weighted average number of common shares outstanding. During periods of income, the Company allocates participating securities a proportional share of income determined by dividing total weighted average participating securities by the sum of the total weighted average common shares and participating securities (the two-class method). The Company's restricted stock and, prior to its automatic conversion, redeemable convertible preferred stock participate in any dividends declared by the Company and are therefore considered to be participating securities. Participating securities have the

Edgar Filing: Epizyme, Inc. - Form 424B4

effect of diluting both basic and diluted earnings per share during periods of income. During periods of loss, the Company allocates no loss to participating securities because they have no contractual obligation to share in the losses of the Company. The Company computes diluted earnings (loss) per share after giving consideration to the dilutive effect of stock options that are outstanding during the period, except where such non-participating securities would be anti-dilutive. Refer to Note 11, *Loss per Share*, for the Company's calculation of loss per share for the periods presented.

F-13

Table of Contents**Segment Information**

The Company operates as one reportable business segment: the discovery and development of personalized therapeutics for patients with genetically defined cancers.

Recent Accounting Pronouncements

In July 2013, the Financial Accounting Standards Board issued Accounting Standards Update (ASU) No. 2013-11, *Presentation of an Unrecognized Tax Benefit When a Net Operating Loss Carryforward, a Similar Tax Loss, or a Tax Credit Carryforward Exists*. ASU 2013-11 amends Accounting Standards Codification (ASC) 740, *Income Taxes*, by providing guidance on the financial statement presentation of an unrecognized benefit when a net operating loss carryforward, a similar tax loss, or a tax credit carryforward exists. The ASU does not affect the recognition or measurement of uncertain tax positions under ASC 740. ASU 2013-11 will be effective for the Company for interim and annual periods beginning after December 15, 2013, with early adoption permitted. The Company does not expect the adoption of this ASU to have any impact on its consolidated financial statements.

3. Property and Equipment, net

Property and equipment, net consists of the following:

	December 31,	
	2011	2012
	(in thousands)	
Laboratory equipment	\$ 1,866	\$ 2,549
Office furniture and equipment	566	1,025
Leasehold improvements	213	410
Property and equipment	2,645	3,984
Less: accumulated depreciation and amortization	(1,068)	(1,844)
Property and equipment, net	\$ 1,577	\$ 2,140

Depreciation and amortization expense was \$0.5 million and \$0.8 million for the years ended December 31, 2011 and 2012, respectively.

4. Accrued Expenses

Accrued expenses consisted of the following:

Edgar Filing: Epizyme, Inc. - Form 424B4

	December 31, 2011	December 31, 2012	September 30, 2013 (unaudited)
	(in thousands)		
Employee compensation and benefits	\$ 1,274	\$ 1,880	\$ 1,882
Current portion of contract termination obligations		1,274	538
Research and development and professional expenses	396	1,174	2,964
Deferred income taxes, net	30		
Accrued expenses	\$ 1,700	\$ 4,328	\$ 5,384

Contract termination obligations include estimated repayments due to the termination of a research agreement in June 2012 and estimated lease exit charges related to the Company's former facility at 325 Vassar Street in Cambridge, Massachusetts. Minimum lease payments under this lease are \$0.9 million in 2013 and \$0.9 million in

Table of Contents

2014. The Company's obligation related to its termination of a research agreement was accelerated as a result of the closing of the Company's IPO, and, as a result, this termination obligation was paid in full in June 2013. Refer to Note 9, *Collaborations*, for additional information regarding the research agreement.

During 2012, the Company accrued \$3.0 million related to these contract termination obligations, with the associated costs allocated between research and development expenses and general and administrative expenses on the statement of operations and comprehensive (loss) income. No cash payments related to these obligations were made during 2012, resulting in a total estimated recorded liability of \$3.0 million related to these obligations as of December 31, 2012. During the nine months ended September 30, 2013, the Company recorded a net non-cash liability reduction of \$0.1 million and made cash payments of \$2.3 million, resulting in total remaining contract termination obligations of \$0.6 million as of September 30, 2013. The non-current portion of contract termination obligations is included in other long-term liabilities.

5. Income Taxes

The Company's losses before income taxes consist solely of domestic losses. Income tax expense for the year ended December 31, 2012 consisted solely of current state expense as the Company was able to utilize federal net operating loss carryforwards to fully offset federal taxable income for the year. The Company had no current or deferred income tax expense for the year ended December 31, 2011 due to its net operating loss position. The Company did not record a federal or state income tax provision or benefit for the nine months ended September 30, 2012 and 2013 due to the losses incurred and expected to be incurred in the corresponding annual periods as well as the Company's continued maintenance of a full valuation allowance against its net deferred tax assets.

A reconciliation of the federal statutory income tax rate and the Company's effective income tax rate is as follows:

	Year Ended December 31,	
	2011	2012
Federal statutory income tax rate	34.0%	34.0%
State income taxes	5.5	5.1
Research and development tax credits	3.3	68.6
Permanent items	(0.8)	(41.7)
Change in valuation allowance	(41.7)	(60.9)
Return-to-provision adjustments		3.6
Change in deferred taxes		(9.0)
Other	(0.3)	0.2
Effective income tax rate	(0.0)%	(0.1)%

Table of Contents**Deferred Tax Assets (Liabilities)**

The Company's deferred tax assets (liabilities) consist of the following:

	December 31,	
	2011	2012
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	\$ 15,703	\$ 5,478
Research and development credit carryforwards	1,511	1,890
Capitalized start-up costs	2,921	2,720
Capitalized research and development costs	671	568
Deferred revenue		8,925
Accruals and allowances	616	1,961
Other	346	420
Gross deferred tax assets	21,768	21,962
Deferred tax asset valuation allowance	(21,544)	(21,881)
Total deferred tax assets	224	81
Deferred tax liabilities:		
Depreciation and other	(224)	(81)
Total deferred tax liabilities	(224)	(81)
Net deferred tax asset (liability)	\$	\$

The Company evaluated the expected recoverability of its net deferred tax assets as of December 31, 2011 and 2012 and determined that there was insufficient positive evidence to support the recoverability of these net deferred tax assets, concluding it is more likely than not that its net deferred tax assets would not be realized in the future; therefore the Company has provided a full valuation allowance against its net deferred tax asset balance as of December 31, 2011 and 2012. The valuation allowance increased by \$0.3 million in 2012 compared to 2011.

As of December 31, 2012, the Company had operating loss carryforwards of approximately \$14.1 million and \$13.0 million available to offset future taxable income for United States federal and state income tax purposes, respectively. The United States federal tax operating loss carryforwards expire commencing in 2027. The state tax operating loss carryforwards expire commencing in 2031. Additionally, as of December 31, 2012 the Company had research and development tax credit carryforwards of approximately \$1.2 million and \$1.0 million available to be used as a reduction of federal income taxes and state income taxes, respectively. The balance of federal research and development tax credit carryforwards does not include a federal research and development tax credit related to 2012 research and development activity due to the expiration of the federal research and development tax credit at the end of 2011. In 2013, the federal research and development tax credit was extended with retroactive application to January 1, 2012. The Company expects to record a federal research and development tax credit of \$0.8 million for the year ending December 31, 2013 related to research and development expenses incurred in 2012.

The Company's ability to use its operating loss carryforwards and tax credits to offset future taxable income is subject to restrictions under Section 382 of the United States Internal Revenue Code (the "Internal Revenue Code"). These restrictions may limit the future use of the operating loss carryforwards and tax credits if certain ownership changes described in the Internal Revenue Code occur. Future changes in stock

Edgar Filing: Epizyme, Inc. - Form 424B4

ownership may occur that would create further limitations on the Company's use of the operating loss carryforwards and tax credits. In such a situation, the Company may be required to pay income taxes, even though significant operating loss carryforwards and tax credits exist.

F-16

Table of Contents***Uncertain Tax Positions***

As of December 31, 2011 and 2012, the Company had no recorded unrecognized tax benefits. The Company has not yet conducted a study of its research and development credit carryforwards. This study may result in an increase or decrease in the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is determined, no amounts are recorded as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the valuation allowance with no resulting impact on overall income tax expense or the consolidated statement of operations and comprehensive (loss) income.

The Company files income tax returns in the U.S. federal tax jurisdiction and Massachusetts state tax jurisdiction. Since the Company is in a loss carryforward position, the Company is generally subject to examination by the U.S. federal, state and local income tax authorities for all tax years in which a loss carryforward is available.

6. Commitments and Contingencies***Commitments***

In June 2012, the Company entered into an agreement to lease office and laboratory space at Technology Square in Cambridge, Massachusetts under an operating lease agreement with a term through November 30, 2017, with an option to extend the term of the lease for an additional five-year period at the then-current market rent, as defined in the lease. With the execution of this lease, the Company was required to provide a \$0.5 million letter of credit as a security deposit. The Company has recorded cash held to secure this letter of credit as restricted cash in restricted cash and other assets on the consolidated balance sheet. The Company recognizes rent expense, inclusive of escalation charges, on a straight-line basis over the initial term of the lease agreement. The Company began recognizing rent expense related to the Technology Square lease in December 2012, when the Company gained access to the leased space.

The Company's contractual commitments under this lease as of December 31, 2012 were as follows:

	(in thousands)
2013	\$ 1,852
2014	1,906
2015	1,965
2016	2,023
2017	1,907
Total commitments	\$ 9,653

In September 2013, the Company entered into an amendment to its Technology Square lease under which the Company leased additional office space for aggregate rent payments of \$2.5 million. These additional rent payments are expected to be paid from the commencement of the lease for this additional space, which is projected to be in the first quarter of 2014, through the end of the existing lease agreement, November 30, 2017.

Rent expense, excluding contract termination costs related to the Vassar Street lease described in Note 4, *Accrued Expenses*, was \$0.9 million and \$1.2 million for the years ended December 31, 2011 and 2012, respectively.

Contingencies

In January 2008, the Company entered into a license agreement with a university to obtain an exclusive license to certain patents and patent applications related to the Company's technology (the License

Table of Contents

Agreement). In connection with the License Agreement, the Company is required to pay up to \$1.9 million upon the achievement of specified research, development and regulatory milestones. The milestone payments are due within 60 days following the occurrence of each milestone event. The Company has paid milestones of \$0.1 million under the License Agreement as of December 31, 2012. The next potential milestone payment that the Company might be obligated to pay is \$0.2 million that would be payable upon the initiation of a Phase 2 clinical trial for any product developed under the License Agreement.

7. Redeemable Convertible Preferred Stock

Prior to the completion of its IPO, the Company had outstanding Series A, Series B and Series C redeemable convertible preferred stock (collectively, the Preferred Stock). The Company classified the Preferred Stock outside of stockholders' (deficit) equity because the shares contained redemption features that were not solely within the Company's control. In connection with the closing of the Company's IPO, all of the Company's outstanding Preferred Stock automatically converted into common stock at a one-for-three ratio as of June 5, 2013. No Preferred Stock was outstanding as of September 30, 2013.

In April 2012, in connection with the execution of a collaboration agreement with Celgene Corporation and Celgene International Sàrl, collectively referred to as Celgene, the Company issued and sold 9,803,922 shares of its Series C Preferred Stock, \$0.0001 par value per share (the Series C Preferred Stock), at a price of \$2.55 per share (the Series C Original Issue Price), for gross proceeds of \$25.0 million. The Company determined that the price paid by Celgene of \$2.55 per share included a premium of \$0.31 over the fair value per share of the Company's Series C Preferred Stock based on the results of a contemporaneous valuation. Accordingly, the Company considered the \$3.0 million premium as additional arrangement consideration pursuant to the collaboration agreement, resulting in \$22.0 million attributed to the Series C Preferred Stock. Refer to Note 9, *Collaborations*, for additional information regarding the Company's collaboration agreement with Celgene. Refer to Note 12, *Related Party Transactions*, for additional information regarding the Company's relationship with Celgene.

Preferred Stock consisted of the following as of December 31, 2011:

	Preferred Shares Authorized	Issuance Date(s)	Preferred Shares Issued and Outstanding (in thousands except share data)	Redemption Value / Liquidation Preference	Carrying Value	Common Stock Issuable Upon Conversion
Series A	14,000,000	2/28/2008	3,756,248	\$ 3,756	\$ 3,683	1,252,081
		5/16/2008	10,243,752	10,244	10,222	3,414,581
Series B	14,000,000		14,000,000	14,000	13,905	4,666,662
	38,096,000	9/18/2009	14,285,716	15,000	14,911	4,761,902
		12/4/2009	5,714,286	6,000	5,951	1,904,762
		9/30/2011	18,095,241	19,000	18,980	6,031,746
	38,096,000		38,095,243	40,000	39,842	12,698,410
	52,096,000		52,095,243	\$ 54,000	\$ 53,747	17,365,072

Table of Contents

Preferred Stock consisted of the following as of December 31, 2012:

	Preferred Shares Authorized	Issuance Date(s)	Preferred Shares Issued and Outstanding (in thousands except share data)	Redemption Value / Liquidation Preference	Carrying Value	Common Stock Issuable Upon Conversion
Series A	14,000,000	2/28/2008	3,756,248	\$ 3,756	\$ 3,697	1,252,081
		5/16/2008	10,243,752	10,244	10,226	3,414,581
Series B	14,000,000		14,000,000	14,000	13,923	4,666,662
	38,096,000	9/18/2009	14,285,716	15,000	14,928	4,761,902
		12/4/2009	5,714,286	6,000	5,961	1,904,762
		9/30/2011	18,095,241	19,000	18,983	6,031,746
	38,096,000		38,095,243	40,000	39,872	12,698,410
Series C	9,803,922	4/2/2012	9,803,922	25,000	22,361	3,267,974
			61,899,922	61,899,165	\$ 79,000	\$ 76,156

The differences between the respective redemption values and carrying values were being accreted over the period from the date of issuance to the earliest possible redemption date. For the year ended December 31, 2012, the Company recorded \$0.5 million of accretion of redeemable convertible preferred stock to redemption value. The rights, preferences and privileges of the Preferred Stock were as follows:

Conversion Prior to the automatic conversion of the Preferred Stock in connection with the closing of the Company's IPO, each share of Preferred Stock was convertible, without the payment of additional consideration and at the option of the holder, into the number of shares of common stock determined by dividing the respective Original Issue Price for such series of Preferred Stock by the applicable conversion price then in effect for such series of Preferred Stock. As of December 31, 2012, the conversion prices of the Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock were \$3.00, \$3.15 and \$7.65, respectively, resulting in a one-for-three exchange ratio for each series of Preferred Stock. The conversion prices for each series of Preferred Stock were subject to adjustment in the event of certain dilutive issuances of common stock or common stock equivalents in which such issuances are made without consideration or for consideration less than the pre-issuance conversion prices of the Preferred Stock, and, in such a case, the conversion prices were to be adjusted in proportion to the amount by which the consideration received for such dilutive issuance was less than the respective pre-issuance conversion prices. The dilutive issuances which could trigger such an adjustment excluded issuances of common stock or common stock equivalents effected (i) as a dividend, distribution or stock split, (ii) under the Company's equity compensation plans or like arrangements, (iii) as a result of a qualified public offering, as defined, or in an initial public offering in which all shares of Preferred Stock would convert to common stock, as well as (iv) in contemplation of transactions or arrangements approved by the Board of Directors or holders of the Preferred Stock, as applicable.

All shares of Preferred Stock were automatically convertible into common stock upon the earlier of (i) the closing of an underwritten public offering in which the public offering price was at least \$30.60 per share (subject to appropriate adjustment in the event of any stock dividend, stock split, combination or other similar recapitalization with respect to the common stock) and the net proceeds raised equaled or exceeded \$50.0 million or (ii) the election of the holders of at least 50.1% of the outstanding shares of Preferred Stock, voting together as a single class on an as-converted to common stock basis. As described in Note 13, *Subsequent Events*, on May 13, 2013, the Company's one-for-three reverse stock split of its common stock became effective, effectively changing the conversion prices of the Preferred Stock. Additionally, in May 2013, the Company's preferred stockholders approved a change to the definition of qualified public offering, as described in Note 13, *Subsequent Events*. In connection with the closing of the Company's IPO, all of the Company's outstanding Preferred Stock automatically converted to common stock at a one-for-three ratio as of June 5, 2013.

Table of Contents

Voting Rights The holders of Preferred Stock were entitled to vote as a single class with the holders of common stock on all matters and were entitled to the number of votes equal to the number of whole shares of common stock into which the shares of the particular series of Preferred Stock were convertible. The holders of Preferred Stock, voting together as a single class on an as-converted to common stock basis, were entitled to elect five directors to the Company's Board of Directors and the holders of Preferred Stock and the holders of common stock, voting together as a single class on an as-converted to common stock basis, were entitled to elect the remaining directors.

Dividends The holders of Series C Preferred Stock were entitled to receive non-cumulative dividends in preference to any dividends on any other series of Preferred Stock or common stock, and the holders of Series A Preferred Stock and Series B Preferred Stock were entitled to receive non-cumulative dividends in preference to any dividends on common stock, in each case, only when and if declared by the Company's Board of Directors. As of December 31, 2012, no dividends had been declared.

Liquidation Preference In the event of any liquidation, dissolution or winding-up of the Company, including a deemed liquidation event, as defined in the Company's certificate of incorporation to include certain mergers or a disposition of all or substantially all the assets of the Company (a Deemed Liquidation Event), before any distribution of payments could be made to common stockholders or the holders of the Series A Preferred Stock and Series B Preferred Stock, the holders of Series C Preferred Stock were entitled to receive the greater of (i) an amount per share equal to the Series C Original Issue Price, plus any dividends declared but unpaid thereon, or (ii) the amount a holder of such Preferred Stock received if such holder converted such Preferred Stock into common stock immediately prior to the Deemed Liquidation Event (the Series C Liquidation Preference). If the available assets were insufficient to pay the holders of Series C Preferred Stock the full amount to which they were entitled, the holders of Series C Preferred Stock were to share ratably in any distribution of the assets available for distribution in proportion to the respective amounts that would otherwise have been payable if such amounts were paid in full. After satisfaction of the Series C Liquidation Preference and before any distribution of payments was made to common stockholders, the holders of Series A Preferred Stock and Series B Preferred Stock, on a pari passu basis, were entitled to receive from any assets legally available for distribution, the Series A Original Issue Price for each share of Series A Preferred Stock held by such holder and the Series B Original Issue Price for each share of Series B Preferred Stock held by such holder, plus, in each case, any dividends declared but unpaid thereon (the Series A and B Liquidation Preferences). If the available assets were insufficient to pay the holders of Series A and Series B Preferred Stock the full amount to which they are entitled, the holders of Series A and Series B Preferred Stock were to share ratably in any distribution of the assets available for distribution in proportion to the respective amounts that would otherwise have been payable if such amounts were paid in full.

After satisfaction of the Series C Liquidation Preference and the Series A and B Liquidation Preferences, any remaining assets legally available for distribution were to be distributed among the holders of Series A Preferred Stock, Series B Preferred Stock and common stock pro rata based on the number of shares of common stock held by each, assuming full conversion of all outstanding shares of Series A Preferred Stock and Series B Preferred Stock. However, the holders of Series A Preferred Stock and Series B Preferred Stock were limited to the receipt of an aggregate amount (including through payment of the Series A and B Liquidation Preferences described above) equal to the greater of (i) \$3.00 per share of Series A Preferred Stock held by such holder and \$3.15 per share of Series B Preferred Stock held by such holder, or (ii) the amount the holder of such series of Preferred Stock would have received if such holder converted such series of Preferred Stock into common stock immediately prior to the Deemed Liquidation Event.

Redemption At any time on or after April 2, 2017 and at the request of the holders of at least 50.1% of the then-outstanding shares of Preferred Stock, the Company would have been required to redeem all of the then-outstanding shares of Preferred Stock at an amount, on a per share basis, equal to the applicable original issue price of such series of Preferred Stock, plus all declared but unpaid dividends.

Table of Contents

For the periods during which the Preferred Stock remained outstanding, the Company had evaluated each of its series of Preferred Stock and determined that they should be considered an equity host and not a debt host as defined by ASC 815, *Derivatives and Hedging*. This evaluation was necessary in order to determine if any embedded features required bifurcation and, therefore, separate accounting as a derivative liability. The Company's analysis followed the whole instrument approach, which compares an individual feature against the entire preferred stock instrument which includes that feature. The Company's analysis was based on a consideration of the Preferred Stock's economic characteristics and risks and more specifically evaluated all the stated and implied substantive terms and features including (i) whether the Preferred Stock included redemption features, (ii) whether the preferred stockholders were entitled to dividends, (iii) the voting rights of the Preferred Stock and (iv) the existence and nature of any conversion rights. As a result of the Company's determination that the Preferred Stock was an equity host, the embedded conversion feature was not considered a derivative liability.

8. Stockholders (Deficit) Equity

Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. Common stockholders are entitled to dividends when and if declared by the Board of Directors.

As of December 31, 2012, a total of 24,495,720 shares of common stock were reserved for issuance upon (i) the conversion of outstanding Preferred Stock, (ii) the exercise of outstanding stock options, and (iii) the issuance of stock awards under the Company's 2008 Stock Incentive Plan.

As described in Note 2, *Summary of Significant Accounting Policies*, prior to the Company's IPO, the Company prepared valuations to support the fair value of its common stock at key points in time. In conducting the valuations, the Company considered all objective and subjective factors that it believed to be relevant for each valuation conducted, including its best estimate of its business condition, prospects and operating performance at each valuation date.

9. Collaborations***Celgene***

Overview. In April 2012, the Company 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 the DOT1L HMT, including the Company's product candidate EPZ-5676, and any other HMT targets from the Company's platform for patients with genetically defined cancers, excluding targets covered by the Company's two other existing therapeutic collaborations (the available targets).

Under the terms of the agreement, the Company received a \$65.0 million upfront payment and \$25.0 million from the sale of Series C Preferred Stock to an affiliate of Celgene, of which \$3.0 million was considered a premium and included as collaboration arrangement consideration for a total upfront payment of \$68.0 million. In addition, the Company is eligible to earn up to \$60.0 million in substantive clinical development milestone payments and up to \$100.0 million in substantive regulatory milestone payments related to DOT1L. The Company is also eligible to earn up to \$65.0 million in payments, including a combination of substantive clinical development milestone payments and an option exercise fee for each selected target, and up to \$100.0 million in substantive regulatory milestone payments for each available target as to which Celgene exercises its option during an initial option period ending in July 2015. Celgene has the right to extend the option period until July 2016 by

Edgar Filing: Epizyme, Inc. - Form 424B4

making a significant option extension payment. As to DOTIL and each available target as to which Celgene exercises its option, the Company retains all product rights in the United States and is eligible to receive royalties for each target at defined percentages ranging from the mid-single digits to the mid-teens on net product sales outside of the United States subject to reduction in specified circumstances. Due to the uncertainty of pharmaceutical development and

F-21

Table of Contents

the high historical failure rates generally associated with drug development, the Company may not receive any milestone or royalty payments from Celgene. The first potential milestone payment that the Company might be entitled to receive under this agreement is a \$25.0 million substantive milestone for achieving proof-of-concept, as defined in the agreement, for its DOT1L inhibitor. This milestone payment would be recognized as collaboration revenue upon achievement.

Through December 31, 2012 and September 30, 2013, in addition to amounts allocated to Celgene's purchase of shares of the Company's Series C Preferred Stock, the Company had received a total of \$68.0 million in upfront payments under the Celgene agreement, including the \$3.0 million implied premium on Celgene's purchase of shares of the Company's Series C Preferred Stock described in Note 7, *Redeemable Convertible Preferred Stock*. The Company recognized \$23.9 million of collaboration revenue in the consolidated statement of operations and comprehensive (loss) income related to this agreement during the year ended December 31, 2012 and \$20.3 million and \$10.8 million of collaboration revenue during the nine months ended September 30, 2012 and 2013, respectively. As of December 31, 2012 and September 30, 2013, the Company had deferred revenue of \$44.1 million and \$33.3 million, respectively, related to this agreement.

Agreement Structure and Accounting Analysis. The Company granted Celgene an exclusive license, for all countries other than the United States, to HMT inhibitors directed to DOT1L and an option, on a target-by-target basis, to exclusively license, for all countries of the world other than the United States, rights to HMT inhibitors directed to other available targets during an initial three year period, which period may be extended by Celgene for one year upon an additional payment (the option period). During the option period, Celgene has the right to exercise its option to non-U.S. rights to available targets until the effectiveness of an investigational new drug application (IND) for an HMT inhibitor directed to such available target. Once a target is selected, Celgene does not have the right to replace it with another target. If Celgene does not exercise its option with respect to an available target prior to the end of the option period, the Company would retain worldwide rights to HMT inhibitors directed to that target.

For the DOT1L target, the Company is obligated to conduct and solely fund research and development costs of the Phase 1 clinical trials for EPZ-5676, after which point Celgene and the Company will equally co-fund global development and each party will solely fund territory-specific development costs for its territory. These future co-development activities were determined to be a contingent deliverable at the inception of the agreement due to the substantial clinical uncertainty that existed at agreement inception as to the success of the product candidate in planned Phase 1 clinical trials and, as a result, are being accounted for separately from the deliverables identified at the inception of the arrangement. In the third quarter of 2013, the Company recorded accounts receivable of \$0.7 million related to non-Phase 1 global development costs incurred by the Company and subject to the co-funding provisions of the agreement. Co-funded amounts receivable from Celgene are recorded as a reduction to research and development expense.

For the available targets, the Company must conduct and fully fund research and development activities through the option period. For any available target licensed to Celgene, the Company is obligated to conduct and solely fund research and development activities through the effectiveness of the first IND for an HMT inhibitor directed to such target, after which point Celgene and the Company will equally co-fund global development and each party will solely fund territory-specific development costs for its territory for such target. These future co-development activities were determined to be a contingent deliverable at the inception of the agreement due to the substantial clinical uncertainty that existed at agreement inception as to a product candidate achieving IND effectiveness and, as a result, will be accounted for separately when the activities occur. During the option period, the Company is required to use commercially reasonable efforts to conduct platform discovery activities necessary to characterize and identify available targets and HMT inhibitors directed to available targets and targets licensed to Celgene.

The significant deliverables of this multiple-element revenue arrangement were determined to be the DOT1L license, the licenses to available targets and the research services for DOT1L and the available targets.

Table of Contents

The license for DOT1L is a deliverable as the Company was obligated at contract inception to provide Celgene with the rights to develop, manufacture and commercialize products directed at the target. The Company concluded that the options to license available targets were not substantive as the Company was not at risk with regard to Celgene exercising its options due to the size of the upfront payment. While Celgene is not contractually required to exercise its options to acquire any licenses to available targets, the overall purpose of the agreement was for Celgene to license available targets and develop and commercialize compounds for those targets outside of the United States. Without exercising its options to license available targets, Celgene could not obtain the economic benefit needed in order to recover its significant upfront payment. Since the options are not considered substantive, the licenses for available targets were considered to be deliverables at the inception of the arrangement.

The Company concluded that, prior to IND effectiveness, the DOT1L license did not have standalone value apart from the related research services due to the limited economic benefit that Celgene would derive from the DOT1L license if it did not obtain the research services. In particular, the Company concluded that prior to IND effectiveness, the license could not be used for its intended purpose without the highly specialized skills and know-how relating to HMT inhibitors that are only available from the Company. After IND effectiveness, the Company concluded that the DOT1L license would have standalone value apart from any remaining undelivered development services because Celgene, or other market participants, would have the ability to execute human clinical trials on the identified compound. Accordingly, the DOT1L license and related research services were accounted for as a combined unit of accounting prior to IND effectiveness. After IND effectiveness, the research services have been accounted for as separate units of accounting which have standalone value upon delivery.

With respect to the licenses to the available targets, the Company concluded that, prior to IND effectiveness, the licenses do not have standalone value apart from the related research services due to the limited economic benefit that Celgene would derive if it did not obtain the research services. In particular, the Company concluded that prior to IND effectiveness, a license could not be used for its intended purpose without the highly specialized skills and know-how relating to HMT inhibitors that are only available from the Company. Accordingly, the licenses to the available targets and related research services have been accounted for as a combined unit of accounting prior to IND effectiveness. The Company has also concluded that the individual licenses would have standalone value from one another; accordingly, the licenses to available targets and research services will be combined into units of accounting on a license-by-license basis prior to IND effectiveness. This conclusion was based on the determination that Celgene could derive benefit from any license and research services, prior to IND effectiveness, without regard to or receipt of any other license and accompanying research services prior to IND effectiveness.

The number and timing of the licenses for the available targets depends upon the Company's research progress and Celgene's option election. Because the options to available targets are not considered substantive, any option exercise payments would be considered to be part of the total consideration for purposes of allocating the arrangement consideration. Accordingly, the Company has identified the allocable arrangement consideration as the \$65.0 million upfront payment, the \$3.0 million premium on Celgene's purchase of Series C Preferred Stock and an amount for option exercise fees for Celgene's expected selection of available targets that is based on a fixed option exercise fee for each target selected. Although there is no contractual limit to the number of licenses to available targets that could be delivered during the option period and the number of selected targets is not known, the Company has estimated the number of available targets that it believes are reasonably likely to be selected by Celgene during the option period, based on information available to management at the time the agreement was executed, including the stage of development of the Company's available targets, for the purpose of determining the allocable arrangement consideration. The Company concluded that Celgene would select three targets based on the status of research on prioritized targets within the Company's product platform at the inception of the agreement and the likelihood of three candidates reaching IND effectiveness within the selection period ending in July 2015. The allocable arrangement consideration has been allocated to the identified deliverables using the relative selling price method. The Company estimated the selling price of the DOT1L license deliverable and each available target license deliverable using management's best estimate of selling

Table of Contents

price after considering market data regarding the pricing of development and commercialization licenses for development candidates at similar stages of development after considering the territories covered by the licenses, as well as entity-specific factors such as the pricing terms of the Company's previous collaboration arrangements, recent research and development results related to the Company's product platform and preclinical product candidates, the market potential for each target and the Company's pricing practices and pricing objectives. The Company estimated the selling price of the research services to be provided in connection with the DOT1L license deliverable and each available target license deliverable using management's best estimate of selling price based on the Company's cost of providing the services plus an applicable profit margin of 10%, which is commensurate with observable market data for similar services. Under this method, the relative selling price of each deliverable was estimated based on the Company's analysis of (i) the stage of development of DOT1L and the available targets at both the inception of the arrangement and the potential option exercise dates; (ii) the market potential for each target; (iii) the level of effort required to advance DOT1L through the completion of Phase 1 clinical trials and each available target to IND effectiveness and (iv) the research funding structure for each program.

The Company expects to recognize the allocated arrangement consideration as follows:

DOT1L and related research services

The Company has allocated \$15.7 million to the DOT1L license and related research services prior to IND effectiveness based on the factors previously described and recognized this revenue ratably over the period from contract inception through the date of IND effectiveness in July 2012, as the related research services were provided.

The remaining DOT1L research services have been determined to represent two separate units of accounting. Accordingly, based on the factors previously described, \$12.1 million has been allocated to the post-IND research services to be provided in connection with the lead product candidate for DOT1L, EPZ-5676, and \$18.8 million has been allocated to the research services to be provided in connection with other potential DOT1L product candidates. The Company is recognizing revenue ratably for each unit of accounting over the period that the corresponding research services are to be provided, which for the post-IND research services for EPZ-5676 is from the date of IND effectiveness in July 2012 through the estimated date of completion of the Phase 1 clinical trial as defined in the agreement, which was initially estimated to be 17 months, and for the other potential DOT1L product candidates has been estimated to be 37 months, from contract inception through the estimated date of IND effectiveness for a licensed compound from the other potential DOT1L product candidates. Revenue recognized in the nine months ended September 30, 2013 reflects the Company's current plan to complete the ongoing Phase 1 trial of EPZ-5676 in 2014. As a result, the remaining deferred revenue of approximately \$2.1 million attributed to this deliverable as of September 30, 2013 will be recognized ratably through December 31, 2014.

The Company's estimates of these revenue recognition periods are subject to the risks inherent in drug discovery. The Company will continue to re-assess the periods over which such services will be provided to consider any revisions to the estimated date of completion of the Phase 1 clinical trial for EPZ-5676 or IND effectiveness for any other DOT1L product candidate.

Available target licenses and related research services

The Company has allocated \$81.4 million to the available target licenses and related research services. Because the targets which Celgene could select would be at a similar stage of development, the Company expects to recognize, on a selected target-by-selected target basis, an equal amount of the allocated arrangement consideration over the period beginning when each available target is selected through the estimated date of IND effectiveness for each selected target. No available targets had been selected as of December 31, 2012 or September 30, 2013.

Edgar Filing: Epizyme, Inc. - Form 424B4

If Celgene exercises its option to extend the initial three year option period for one additional year, then the Company would be entitled to a significant option term extension payment. To the extent that Celgene extends

F-24

Table of Contents

the option period for an additional year, the Company would, at the time of any exercise of the extension option, allocate such payment based on its expectation as to the number of available targets that might be selected during the additional one year period and defer any option term extension payment until such time as a license to an available target was delivered.

Milestone payments under this arrangement consist of up to \$160.0 million in clinical development and regulatory milestones for DOT1L and up to \$165.0 million in option exercise fees and clinical development and regulatory milestones for each available target. The Company evaluated the milestones under this arrangement and believes that the milestones are substantive given the significant uncertainty as to the outcome of the substantial research efforts to be performed by the Company in order to achieve the milestones. Therefore, the milestones will be recognized as collaboration revenue upon achievement.

On a licensed target-by-licensed target basis, the Company has the right, in its sole discretion, to opt-out of further participation in and co-funding of development, other than specified costs necessary to complete development activities in process at the time the Company exercises its opt-out right. The Company can exercise its opt-out right at specified times before the scheduled initiation of the first pivotal clinical trial or before the estimated date of filing of the first new drug application for an HMT inhibitor directed to the licensed target or any time after regulatory approval of an HMT inhibitor directed to the licensed target. Following an opt-out, the Company is no longer required to co-fund global development for the applicable program, and it is obligated to grant Celgene an exclusive license to HMT inhibitors directed to the applicable target in the United States. Following its opt-out, if any, the Company will be eligible to receive specified milestone payments and royalties based on net product sales in the United States of HMT inhibitors directed to the licensed target. The Company would recognize revenue related to the milestones and royalties on any transferred target when earned, as the Company would have no performance obligations after exercising its opt-out. Based on the terms of the opt-out, the Company may not exercise its opt-out rights prior to completing its performance obligations under any of the deliverables identified at the inception of the agreement. None of the upfront cash payments, option exercise payments or option extension payment are subject to refund as a result of the opt-out provisions.

Agreement Termination Rights. The Company's agreement with Celgene will expire on a product-by-product and country-by-country basis on the date of the expiration of the applicable royalty term with respect to each licensed product in each country and in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries. The royalty term for each licensed product in each country is the period commencing with first commercial sale of the applicable licensed product in the applicable country and ending on the latest of expiration of specified patent coverage, specified regulatory exclusivity or a specified period of years.

Celgene has the right to terminate the agreement with respect to one or more licensed targets or in its entirety, upon 60 or 120 days' notice depending on the timing of such termination. The agreement may also be terminated in its entirety during the option period, and on a licensed target-by-licensed target basis after the option term, by either Celgene or the Company in the event of a material breach by the other party, in the event the other party, or an affiliate or sublicensee of the other party, participates or actively assists in a legal challenge to specified patent(s) of the terminating party or in the event the other party becomes subject to specified bankruptcy, insolvency or similar circumstances. There are no cancellation, termination or refund provisions in this arrangement that contain material financial consequences to the Company.

Eisai

Overview. In April 2011, the Company entered into a collaboration and license agreement with Eisai Co. Ltd. (Eisai) under which the Company granted Eisai an exclusive worldwide license to its small molecule HMT inhibitors directed to the EZH2 HMT, including the Company's product candidate 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. Additionally, as part of the research collaboration the Company agreed to provide research and

Table of Contents

development services related to the licensed compounds through December 31, 2014 (the research period). Eisai solely funds all research, development and commercialization costs for licensed compounds, except for the cost obligations that the Company will undertake if it exercises its opt-in right to co-develop, co-commercialize and share profits with Eisai as to licensed products in the United States.

Under the terms of the agreement, the Company had recorded a total of \$21.3 million in cash and accounts receivable as of December 31, 2012, including a \$3.0 million upfront payment, \$7.0 million in preclinical research and development milestone payments and \$11.3 million for research and development services. Through September 30, 2013, the Company had recorded a total of \$32.5 million in cash and accounts receivable under the terms of the agreement, including a \$6.0 million clinical development milestone achieved in June 2013 and an additional \$5.2 million for research and development services during the nine months ended September 30, 2013. The Company is eligible to earn up to \$25.0 million in additional clinical development milestone payments, including substantive milestone payments of up to \$10.0 million, up to \$55.0 million in regulatory milestone payments and up to \$115.0 million in sales-based milestone payments. The Company is also eligible to receive royalties at a percentage in the mid-single digits on any net product sales outside of the United States and at a percentage from the mid-single digits to low double-digits on any product sales in the United States, subject to reduction in specified circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty or profit share payments from Eisai. The next potential milestone payment that the Company might be entitled to receive under this agreement is a \$10.0 million substantive milestone for the initiation of the Phase 2 portion of the Phase 1/2 clinical trial. This milestone payment would be recognized as collaboration revenue upon achievement.

Through December 31, 2012 and September 30, 2013, the Company had recorded a total of \$21.3 million and \$32.5 million, respectively, in cash and accounts receivable. During the years ended December 31, 2011 and 2012, the Company recognized \$6.6 million and \$11.5 million of collaboration revenue, respectively, and during the nine months ended September 30, 2012 and 2013, the Company recognized \$9.3 million and \$12.4 million of collaboration revenue, respectively, related to this agreement. As of December 31, 2012 and September 30, 2013, the Company had deferred revenue of \$3.2 million and \$2.0 million, respectively, related to this agreement.

Agreement Structure and Accounting Analysis. The significant deliverables of this multiple-element revenue arrangement were determined to be the worldwide license rights to EZH2 compounds and the research and development services. At the inception of the arrangement, the Company concluded that the license cannot be used for its intended purpose without the highly specialized skills and know-how relating to HMT inhibitors that is only available from the Company. The Company has therefore concluded that the delivered exclusive license lacked standalone value apart from the research and development services due to the limited economic benefit that Eisai would derive from the license if it did not obtain the Company's research and development services. Consequently, the Company is accounting for these deliverables as a combined unit of accounting and is recognizing the \$3.0 million upfront payment received from Eisai related to this agreement ratably over the research period. Funding for research and development services is being recognized as collaboration revenue in the period in which the related research and development costs are incurred.

Upon the execution of this agreement, in addition to the \$3.0 million upfront payment, the Company received another \$3.0 million payment for a preclinical research and development milestone that was deemed to have already been achieved. Because this initial \$3.0 million milestone was certain at the execution of the agreement and did not require substantive effort by the Company, it has been combined with the upfront payment and is being recognized as collaboration revenue ratably over the research period. The Company has evaluated the remaining milestones under this agreement and determined that the milestones through human proof-of-concept are substantive, given the significant uncertainty as to the outcome of the substantial research efforts to be performed by the Company in order to achieve the milestones. Therefore, payments for the achievement of any milestones through human proof-of-concept are being recognized as revenue upon achievement, assuming all other revenue recognition criteria are met. In the first quarter of 2012, the Company commenced a trial for the

Table of Contents

lead product candidate, EPZ-6438, representing the first substantive research milestone under this arrangement. Accordingly, the \$4.0 million milestone payment received from Eisai upon the achievement of this preclinical research and development milestone was recognized as revenue upon achievement. In the second quarter of 2013, the first patient was enrolled in the Phase 1/2 clinical trial of EPZ-6438, representing the first substantive clinical development milestone under this arrangement. Accordingly, the \$6.0 million milestone payment due from Eisai upon the achievement of this milestone was recognized as revenue upon achievement. Evaluation of milestones after human proof-of-concept will be dependent upon the Company's decision to participate or not participate in the profit share and co-commercialization arrangement with Eisai.

The Company's opt-in right to co-commercialize and share profits may be exercised on a licensed compound-by-licensed compound basis prior to the end of a specified period following Eisai's provision to the Company of specified information following the licensed compound's achievement of clinical proof-of-concept. If the Company exercises its opt-in right as to a licensed compound, the licensed compound becomes a shared product as to which: (i) Eisai's obligation to pay royalties to the Company as to such shared product in the United States will terminate; (ii) Eisai and the Company will share in net profits or losses with respect to such shared product in the United States; (iii) 25.0% of specified past development costs will become creditable by Eisai against future milestone payments or royalties due to the Company, subject to certain limitations specified in the agreement; (iv) all subsequent milestones that become payable by Eisai after the Company exercises its opt-in right will be decreased by 50.0% in certain circumstances; and (v) Eisai and the Company will share equally in subsequent development costs allocated to the United States. All previous milestones earned by the Company are not subject to reimbursement.

If the Company elects to exercise its opt-in right, (i) future research and development costs for the shared product would be recorded on a collaboration basis, in which case the Company's 50.0% share of the costs would be recorded as research and development expense and (ii) the recognition of future milestones may be re-evaluated. If the Company does not exercise its opt-in right, the remaining milestones will not be considered substantive, as Eisai would then control the development leading to the achievement of such milestones, which would generally be achieved after the Company's performance obligations are complete.

Agreement Termination Rights. The Company's agreement with Eisai will remain in effect until the later of expiration of all royalty obligations under the agreement with respect to all licensed products or, if the Company exercises its option, until the shared product is no longer being developed or commercialized by the parties in or for the United States or the parties' agreement with respect to co-commercialization and profit sharing otherwise terminates. The royalty term for each licensed product in each country, other than shared products in the United States, is the period commencing with first commercial sale of the applicable licensed product in the applicable country and ending on the latest of expiration of specified patent coverage, specified regulatory exclusivity or a specified period of years.

Eisai may terminate the agreement for its convenience in its entirety or as to one or more major market countries, as defined in the agreement, upon 90 days' prior written notice to the Company. Eisai also has the right to terminate the agreement in its entirety immediately if, in good faith, it believes that it is not advisable for it to continue to develop or commercialize the licensed products from a scientific, regulatory or ethical perspective as a result of a bona fide serious safety issue regarding the use of any licensed product. The agreement may also be terminated by either party in the event of a material breach by the other party or by the Company in the event Eisai, or an affiliate or sublicensee, participates or actively assists in an action or proceeding challenging or denying the validity of one of the Company's patents. There are no cancellation, termination or refund provisions in this arrangement that contain material financial consequences to the Company.

GlaxoSmithKline

Overview. In January 2011, the Company entered into a collaboration and license agreement with Glaxo Group Limited (an affiliate of GlaxoSmithKline) (GSK) to discover, develop and commercialize novel small molecule HMT inhibitors directed to available targets from the Company's platform. Under the terms of the

Table of Contents

agreement, the Company granted GSK the option to obtain exclusive worldwide license rights to HMT inhibitors directed to up to three targets. GSK selected and licensed three targets and the term during which it was entitled to select targets expired in July 2012.

Under the agreement, the Company received an upfront payment of \$20.0 million. Through December 31, 2012 and September 30, 2013, the Company had also received \$3.7 million and \$6.0 million, respectively, of fixed research funding and \$8.0 million of preclinical research and development milestone payments through each such date. The Company is eligible to receive up to \$21.0 million in additional substantive preclinical research and development milestone payments, up to \$99.0 million in clinical development milestone payments, up to \$240.0 million in regulatory milestone payments and up to \$270.0 million in sales-based milestone payments. In addition, GSK is required to pay the Company royalties at percentages between the mid-single digits to the low double-digits, on a licensed product-by-licensed product basis, on worldwide net product sales, subject to reduction in certain specified circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or royalty payments from GSK. The next potential milestone payment that the Company might be entitled to receive under this agreement is a substantive research milestone; however, due to the varying stages of development of each licensed target, the Company is not able to determine the next milestone that might be achieved, if any.

Through December 31, 2012 and September 30, 2013, the Company had received a total of \$31.7 million and \$34.0 million, respectively, in payments under the GSK agreement. During the year ended December 31, 2012 the Company recognized \$9.7 million of collaboration revenue, and during the nine months ended September 30, 2012 and 2013, the Company recognized \$6.7 million and \$9.0 million, respectively, of collaboration revenue related to this agreement. The Company did not recognize any collaboration revenue in the year ended December 31, 2011 related to this agreement as none of the delivered elements of the arrangement had standalone value at that time apart from the undelivered elements of the arrangement. As of December 31, 2012 and September 30, 2013, the Company had deferred revenue of \$22.0 million and \$15.3 million, respectively, related to this agreement.

Agreement Structure and Accounting Analysis. For each selected target in the collaboration, the Company is primarily responsible for research until the selection of the development candidate, and GSK will be solely responsible for subsequent development and commercialization. The Company is responsible for providing research and development services with respect to the selected targets pursuant to agreed-upon research plans during a research term that ends in January 2015. GSK provided a fixed amount of research funding during the second and third years of the research term. If the Company conducts activities in the fourth year of the research term, GSK is obligated to provide research funding equal to 100.0% of research and development costs, subject to specified limitations.

The significant deliverables of this multiple-element revenue arrangement were determined to be exclusive licenses to three targets and corresponding research services for each target. At the inception of the arrangement, the Company concluded that the licenses cannot be used for their intended purpose without the highly specialized skills and know-how relating to HMT inhibitors that is only available from the Company. The Company has therefore concluded that the target licenses lacked standalone value apart from the related research services due to the limited economic benefit that GSK would derive from the licenses if it did not obtain the Company's research services and due to the lack of transferability of the exclusive licenses. The Company is therefore accounting for these deliverables, on a license-by-license basis, as a combined unit of accounting. The Company concluded that the option to secure licenses for three targets was not substantive, as the Company was not at risk with regard to GSK exercising its option due to the size of the upfront payment and the research funding commitment. Since the option was not considered substantive, the Company considered the licenses to be deliverables at the inception of the agreement. While the Company concluded that there were three units of accounting, each consisting of a license to a target and the research and development services related to that target, because the targets were at similar stages of development at the inception of the agreement, had equal

Table of Contents

probabilities of success and the research services in each unit of accounting would be performed concurrently on a ratable basis over the research term, the Company allocated the arrangement consideration equally across the three targets. Accordingly, the \$30.0 million of allocable arrangement consideration, consisting of the \$20.0 million upfront payment, \$4.0 million in milestone payments achieved during the selection term and the \$6.0 million fixed research funding, is being recognized as collaboration revenue ratably on a license-by-license basis from the conclusion of the selection term, in July 2012, through the end of the research term, or earlier if a target reaches development candidate selection, at which point GSK is solely responsible for development and commercialization.

During the selection term, the Company received \$4.0 million upon the achievement of preclinical research and development milestones which required effort in the form of research activities by the Company and was not certain to be achieved at the execution of the agreement. However, because GSK had the right to drop a target and select a replacement target at any point during the selection term, the Company, in such a case, would have been obligated to perform the validation work for a replacement target. Consequently, this \$4.0 million in preclinical research and development milestones has been combined with the upfront payment and fixed research funding and is being recognized as collaboration revenue ratably over the research term. The Company has evaluated the remaining milestones under this agreement and determined that the milestones through development candidate selection are substantive given the significant uncertainty as to the outcome of the substantial research efforts to be performed by the Company in order to achieve the milestones and will be recognized as revenue upon achievement, assuming all other revenue recognition criteria are met. The milestones after development candidate selection are not considered substantive because the Company does not contribute effort to the achievement of such milestones, which would generally be achieved after the research term. In the third quarter of 2012, the Company achieved two additional preclinical research and development milestones and received payments totaling \$4.0 million. The preclinical research and development milestones achieved in 2012 required effort in the form of research activities by the Company and were not certain to be achieved at the execution of the agreement. Additionally, at the time of the achievement of these preclinical research and development milestones, the selection term had expired and, as such, these milestones were determined to be substantive, and the milestone was recognized as revenue upon achievement.

Under the agreement, the Company also granted GSK the option to acquire up to 10.0% of the securities issued in its next qualified venture capital financing, if any, which meets conditions set forth in the agreement. The Company is not obligated to undertake any such financing and one has not occurred since the Company granted GSK this right.

Agreement Termination Rights. The agreement will expire on a product-by-product and country-by-country basis on the date of the expiration of the applicable royalty term with respect to each licensed product in each country and in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries. The royalty term for each licensed product in each country is the period commencing with the first commercial sale of the applicable licensed product in the applicable country and ending on the later of expiration of specified patent coverage or a specified period of years.

GSK has the right to terminate the agreement at any time with respect to one or more selected targets or in its entirety, upon 90 days prior written notice to the Company. The agreement may also be terminated with respect to one or more selected targets or in its entirety by either GSK or the Company in the event of a material breach by the other party. The agreement may be terminated with respect to selected targets by the Company in the event GSK, or an affiliate or sublicensee of GSK, participates or actively assists in a legal challenge to one of the patents exclusively licensed to GSK under the agreement with respect to the applicable target.

The Leukemia & Lymphoma Society

In June 2011, The Leukemia & Lymphoma Society (LLS) and the Company entered into an arrangement to support preclinical and Phase 1 development of the Company's DOT1L-targeted HMT inhibitors for mixed

Table of Contents

lineage leukemia. Under this arrangement, LLS committed to provide up to \$7.5 million in development milestone-based payments to the Company to support the program through Phase 1 clinical trials in exchange for defined future royalties and transfer payments.

The Company received \$2.6 million in funding from LLS through May 2012, including upfront payments of \$1.1 million and a milestone payment of \$1.5 million received in March 2012 for a clinical candidate declaration. The Company paid LLS \$0.4 million as a transfer payment relating to the Company's entry into its collaboration agreement with Celgene.

In June 2012, the Company exercised its option to terminate this arrangement and repaid LLS \$0.8 million, representing the portion of the upfront payment that had not yet been spent on research. Upon the Company's exercise of its termination option, LLS elected to receive a termination fee equal to the aggregate amount of funding provided by LLS through the termination date, less any amounts previously repaid. Accordingly, the Company did not recognize any revenue in 2012 related to either the LLS upfront payment or the milestone achieved. Except for certain acceleration provisions described in the agreement, the termination fee was payable in three equal annual installments plus 10.0% interest. Accordingly, the Company had accrued \$2.0 million as of December 31, 2012, representing the present value of its obligation to LLS in connection with the termination of this agreement. Upon the closing of the Company's IPO, the Company's obligation to LLS was accelerated, and, as a result, this termination obligation was paid in full in June 2013. Refer to *Celgene* for additional information regarding the collaboration agreement with Celgene.

Multiple Myeloma Research Foundation

In June 2011, the Company entered into a research agreement with the Multiple Myeloma Research Foundation, Inc. (MMRF). Under the agreement, MMRF has agreed to provide the Company with up to \$1.0 million to assist the research and development of the Company's HMT inhibitors targeting WHSC1 for myeloma in the form of research and development milestone-based funding. The Company is not obligated to repay any of the funds provided. MMRF is entitled to receive up to an aggregate of four times the funding actually paid by MMRF to the Company through a 3.0% royalty on net product sales by the Company and its affiliates of HMT inhibitor products targeting WHSC1. If the Company licenses specified rights to its HMT inhibitor products targeting WHSC1 to a third party or undergoes a specified change of control event, MMRF is entitled to receive a specified portion of the proceeds of the transaction that, when aggregated with royalties paid to MMRF, does not exceed four times the funding actually paid by MMRF to the Company.

Through December 31, 2012 and September 30, 2013, the Company has received a total of \$0.3 million from MMRF, consisting of an upfront payment of \$0.2 million and research milestone payments of \$0.1 million. The agreement required substantive research activities by the Company and the success of such research was uncertain at the time of the execution of the agreement. Accordingly, the research milestone payment was considered substantive and was recognized as revenue upon achievement.

The Company is recognizing the \$0.2 million upfront payment over the term of the agreement as the related research activities are performed. During 2012, the Company recognized approximately \$0.1 million of the \$0.2 million upfront payment as collaboration revenue. As of December 31, 2012 and September 30, 2013, the Company had deferred revenue of approximately \$0.1 million related to the MMRF agreement.

The next potential milestone payment that the Company might be eligible to receive is \$0.2 million that would be paid at the successful conclusion of certain hit finding activities.

Roche

In December 2012, Eisai and the Company entered into an agreement with Roche Molecular Systems, Inc. (Roche) under which Eisai and the Company are funding Roche s development of a companion diagnostic to

F-30

Table of Contents

identify patients who possess certain point mutations in EZH2. The development costs under the agreement with Roche will be the responsibility of Eisai until such time, if any, as the Company exercises its opt-in right under its collaboration agreement with Eisai. Under the terms of the agreement, Eisai agreed to pay Roche defined milestone payments of up to \$21.0 million to develop and to make commercially available the companion diagnostic. As a result, the cost of the companion diagnostics agreement prior to the Company's potential future exercise of its opt-in right under the Eisai collaboration will not be reflected in the Company's consolidated statements of operations and comprehensive (loss) income. If the Company exercises its opt-in right to co-develop, co-commercialize and share profits in the United States as to EPZ-6438, Eisai will be entitled to offset up to 25.0% of the funding amount it has previously paid to Roche against future milestone payments and royalties that Eisai may be obligated to pay to the Company under the Eisai collaboration and license agreement, and the Company will become obligated to fund up to half of the defined milestones that remain payable to Roche as of the time the Company opts-in.

The Company's agreement with Roche will expire when Eisai or the Company are no longer developing or commercializing the Company's product directed to EZH2. Eisai and the Company may terminate the agreement by giving Roche 90 days' written notice if the Company and Eisai discontinue development and commercialization of the Company's product directed to EZH2 or determine, in conjunction with Roche, that the diagnostic is not needed for use with the Company's product directed to EZH2. Either Eisai and the Company or Roche may also terminate the agreement in the event of a material breach by the other party, in the event of material changes in circumstances that are contrary to key assumptions specified in the agreement or in the event of specified bankruptcy or similar circumstances. Under specified termination circumstances, Roche may become entitled to specified termination fees, which Eisai and the Company would be obligated to bear in the same manner that they bear the funding amounts payable to Roche.

Abbott

In February 2013, the Company entered into an agreement with Abbott Molecular Inc. (Abbott) under which the Company agreed to fund Abbott's development of a companion diagnostic to identify patients with the mixed lineage leukemia (MLL-r) genetic alteration targeted by the Company's EPZ-5676 product candidate. Under the terms of the agreement, the Company paid Abbott an upfront payment of \$0.9 million upon the execution of the agreement, is obligated to make aggregate milestone-based development payments of up to \$6.0 million and is obligated to reimburse Abbott for specified costs expected to be incurred in connection with Abbott conducting clinical trials to obtain the necessary regulatory approvals for the companion diagnostic (the reimbursable costs). The reimbursable costs are not to exceed \$0.9 million unless any excess costs are agreed to in advance by both the Company and Abbott. In addition to the upfront payment, the Company expects to pay an aggregate of approximately \$1.5 million in milestone-based development payments under this agreement during 2013.

Under the agreement with Abbott, Abbott is obligated to use commercially reasonable efforts to develop and make commercially available the companion diagnostic. Abbott has exclusive rights to commercialize and retain all proceeds from its commercialization of the companion diagnostic.

The agreement with Abbott will expire when the Company is no longer commercializing EPZ-5676. The Company may terminate the agreement for convenience by giving Abbott 60 days' written notice, and the Company will be obligated to pay Abbott a termination fee if it exercises such right to terminate the agreement for convenience after the date 18 months following the execution of the agreement but prior to the completion of the development program for the companion diagnostic. Either Abbott or the Company may also terminate the agreement in the event of a material breach by the other party, in the event of specified injunctions that may issue in the future based on infringement of third party patents or in the event of specified bankruptcy or similar circumstances.

Table of Contents**10. Employee Benefit Plans***Stock Incentive Plan*

In 2008, the Company's Board of Directors adopted and the Company's stockholders approved the 2008 Stock Incentive Plan (the 2008 Plan), which provided for the granting of certain defined stock incentive awards to employees, members of the Company's Board of Directors and non-employee consultants, advisors or other service providers. As of December 31, 2012, the Company had reserved 4,407,306 shares of common stock under the 2008 Plan for issuance, and there were 369,980 shares available for future grant. In April 2013, the Company's Board of Directors adopted and the Company's stockholders approved the 2013 Stock Incentive Plan (the 2013 Plan), which provides for the granting of certain defined stock incentive awards to employees, members of the Company's Board of Directors and non-employee consultants, advisors or other service providers. Upon the closing of the IPO, the Company ceased granting stock incentive awards under the 2008 Plan, and any shares of common stock subject to awards under the 2008 Plan that expire, terminate, or are otherwise surrendered, canceled, forfeited or repurchased without having been fully exercised or resulting in any common stock being issued will become available for issuance under the 2013 Plan. Additionally, in May 2013, the Company's Board of Directors adopted and the Company's stockholders approved the 2013 Employee Stock Purchase Plan (the 2013 ESPP), which provides participating employees the option to purchase shares of the Company's common stock at defined purchase prices over six month offering periods.

Stock incentive awards granted under the 2013 Plan may be incentive stock options, non-qualified stock options, restricted stock awards, restricted stock units, stock appreciation rights and other stock-based awards under the applicable provisions of the Internal Revenue Code. Incentive stock options are granted only to employees of the Company. Non-qualified stock options and restricted stock may be granted to officers, employees, consultants, advisors and other service providers. Incentive and non-qualified stock options and restricted stock granted to employees generally vest over four years, with 25.0% vesting upon the one-year anniversary of the grant and the remaining 75.0% vesting monthly over the following three years. Non-qualified stock options granted to consultants and other non-employees generally vest over the period of service to the Company. Incentive and non-qualified stock options expire ten years from the date of grant. Non-qualified stock options granted to members of the Company's Board of Directors generally vest over the recipient's term of Board service.

Stock-Based Compensation

Total stock-based compensation related to stock options, restricted stock and the employee stock purchase plan was \$0.3 million and \$0.7 million in the years ended December 31, 2011 and 2012, respectively, and \$0.2 million and \$1.8 million in the nine months ended September 30, 2012 and 2013, respectively.

Stock-based compensation expense is classified in the consolidated statements of operations and comprehensive (loss) income as follows:

	Year Ended December 31, 2011	2012	Nine Months Ended September 30, 2012	2013
	(in thousands)			
	(unaudited)			
Research and development	\$ 160	\$ 448	\$ 104	\$ 695
General and administrative	145	241	106	1,124
Total	\$ 305	\$ 689	\$ 210	\$ 1,819

Table of Contents**Stock Options**

The Company uses the Black-Scholes option-pricing model to measure the fair value of stock option awards. Key assumptions used in this pricing model on the date of grant for options granted to employees are as follows:

	Year Ended December 31,		Nine Months Ended	
	2011	2012	September 30, 2012	2013 (unaudited)
Risk-free interest rate	2.0%	0.7%	0.7%	0.9%
Expected life of options	6.0 years	6.0 years	6.0 years	6.0 years
Expected volatility of underlying stock	100.0%	98.9%	98.8%	94.7%
Expected dividend yield	0.0%	0.0%	0.0%	0.0%

There were no stock option awards granted to non-employees in 2012 or the nine months ended September 30, 2013.

The risk-free interest rate is based upon the U.S. Treasury yield curve in effect at the time of grant, with a term that approximates the expected life of the option. The Company calculates the expected life of options granted to employees using the simplified method as the Company has insufficient historical information to provide a basis for estimate. The Company determines the expected volatility based on the historical volatility of a peer group of comparable publicly traded companies with product candidates in similar stages of development to the Company's product candidates. The Company has applied an expected dividend yield of 0.0% as the Company has not historically declared a dividend and does not anticipate declaring a dividend during the expected life of the options.

The following is a summary of stock option activity for the year ended December 31, 2012 and the nine months ended September 30, 2013:

	Number of Options	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Term (In Years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2011	2,795,402	\$ 0.51		
Granted	766,297	2.34		
Exercised	(15,800)	0.48		
Forfeited or expired	(53,205)	0.57		
Outstanding at December 31, 2012	3,492,694	\$ 0.90	7.4	\$ 9,211
Exercisable at December 31, 2012	2,236,152	\$ 0.66	6.8	\$ 6,457
Granted (unaudited)	1,483,328	7.51		
Exercised (unaudited)	(177,212)	0.97		
Forfeited or expired (unaudited)	(25,780)	2.74		

Edgar Filing: Epizyme, Inc. - Form 424B4

Outstanding at September 30, 2013 (unaudited)	4,773,030	\$ 2.94	7.7	\$ 176,875
Exercisable at September 30, 2013 (unaudited)	2,557,179	\$ 0.70	6.7	\$ 100,489

During the years ended December 31, 2011 and 2012, the Company granted stock options to purchase an aggregate of 547,557 shares of its common stock and 766,297 shares of its common stock, respectively, with a

F-33

Table of Contents

weighted average grant date fair value per option share of \$0.48 and \$1.83, respectively. During the nine months ended September 30, 2013, the Company granted stock options to purchase an aggregate of 1,483,328 shares of its common stock with a weighted average grant date fair value per option share of \$7.57. The total grant date fair value of options that vested during the years ended December 31, 2011 and 2012 was \$0.3 million and \$0.6 million, respectively. The aggregate intrinsic value of stock options exercised was insignificant during 2011 and 2012.

As of December 31, 2012, there was \$1.2 million of unrecognized stock-based compensation related to stock options that are expected to vest. These costs were expected to be recognized over a weighted average remaining vesting period of 2.4 years. As of September 30, 2013, there was \$10.4 million of unrecognized stock-based compensation related to stock options that are expected to vest. These costs are expected to be recognized over a weighted average remaining vesting period of 2.8 years.

Restricted Stock

The fair value of restricted stock is based on the estimated fair value of the Company's common stock.

The following is a summary of restricted stock activity for the year ended December 31, 2012 and the nine months ended September 30, 2013:

	Number of Shares	Weighted Average Grant Date Fair Value per Share
Outstanding as of December 31, 2011	31,638	\$ 0.27
Granted	33,333	0.60
Vested	(42,748)	0.36
Outstanding as of December 31, 2012	22,223	\$ 0.60
Vested (unaudited)	(12,501)	0.60
Outstanding as of September 30, 2013 (unaudited)	9,722	\$ 0.60

During the year ended December 31, 2012 the Company granted 33,333 shares of restricted stock with a weighted-average grant date fair value per share of \$0.60. The Company did not grant any restricted stock during the year ended December 31, 2011 or during the nine months ended September 30, 2013. The intrinsic value of restricted stock that vested during each of the years ended December 31, 2011 and 2012 was \$0.1 million.

As of December 31, 2012 and September 30, 2013, there was an insignificant amount of unrecognized stock-based compensation related to restricted stock that is expected to vest.

401(k) Savings Plan

The Company has a defined contribution 401(k) savings plan (the 401(k) Plan). The 401(k) Plan covers substantially all employees, and allows participants to defer a portion of their annual compensation on a pretax basis. Company contributions to the 401(k) Plan may be made at the discretion of the Board of Directors. As of December 31, 2012, the Company had made no contributions to the 401(k) Plan.

11. (Loss) Earnings per Share

As described in Note 2, *Summary of Significant Accounting Policies*, the Company computes basic and diluted earnings (loss) per share using a methodology that gives effect to the impact of outstanding participating securities (the two-class method).

Table of Contents

Basic and diluted (loss) earnings per share allocable to common stockholders are computed as follows:

	Year Ended December 31,		Nine Months Ended	
	2011	2012	2012	September 30, 2013
	(in thousands except per share data)			
Net (loss) income	\$ (20,957)	\$ (702)	\$ 3,836	\$ (19,413)
Less: accretion of redeemable convertible preferred stock to redemption value	45	486	326	264
Less: income allocable to participating securities			3,239	
(Loss) income allocable to common stockholders	\$ (21,002)	\$ (1,188)	\$ 271	\$ (19,677)
Weighted average shares outstanding	1,434	1,645	1,637	13,212
Basic (loss) earnings per share allocable to common stockholders	\$ (14.65)	\$ (0.72)	\$ 0.17	\$ (1.49)

	Year Ended December 31,		Nine Months Ended	
	2011	2012	2012	September 30, 2013
	(in thousands except per share data)			
Net (loss) income	\$ (20,957)	\$ (702)	\$ 3,836	\$ (19,413)
Less: accretion of redeemable convertible preferred stock to redemption value	45	486	326	264
Less: income allocable to participating securities			3,092	
(Loss) income allocable to common stockholders	\$ (21,002)	\$ (1,188)	\$ 418	\$ (19,677)
Weighted average shares outstanding	1,434	1,645	1,637	13,212
Effect of dilutive securities			1,004	
Diluted weighted average shares outstanding	1,434	1,645	2,641	13,212
Diluted (loss) earnings per share allocable to common stockholders	\$ (14.65)	\$ (0.72)	\$ 0.16	\$ (1.49)

In June 2013, the Company issued an additional 5,913,300 shares of common stock in connection with its IPO and 20,633,046 shares of common stock in connection with the automatic conversion of its Preferred Stock upon the closing of the IPO. The issuance of these shares resulted in a significant increase in the Company's shares outstanding, to 28,408,698 shares as of September 30, 2013, and weighted average shares outstanding for the nine months ended September 30, 2013 when compared to the comparable prior year period and is expected to continue to impact the year-over-year comparability of the Company's (loss) earnings per share calculations through 2014.

The following common stock equivalents were excluded from the calculation of diluted loss per share allocable to common stockholders because their inclusion would have been antidilutive. The redeemable convertible preferred stock numbers shown in the table are on a common stock equivalent basis as a result of the reverse stock split described in Note 13, *Subsequent Events*:

	Year Ended December 31,		Nine Months Ended	
	2011	2012	2012	September 30, 2013
	(in thousands)			

Edgar Filing: Epizyme, Inc. - Form 424B4

Redeemable convertible preferred stock	17,365	20,633	
Stock options	2,795	3,493	4,773
Unvested restricted stock	32	22	10
Shares issuable under employee stock purchase plan			2
	20,192	24,148	4,785

F-35

Table of Contents

12. Related Party Transactions

In connection with its entry into the collaboration agreement with Celgene, on April 2, 2012, the Company sold Celgene 9,803,922 shares of its Series C Preferred Stock. As a result of this transaction, Celgene owned 12.5% of the Company's fully diluted equity as of December 31, 2012. Refer to Note 9, *Collaborations*, for additional information regarding this collaboration agreement. In the second quarter of 2013, in connection with the IPO, Celgene made an additional investment in the Company, acquiring an additional 66,666 shares of the Company's common stock. Additionally, as a result of the IPO, Celgene's shares of Series C Preferred Stock automatically converted to common stock of the Company at a one-for-three ratio, collectively resulting in Celgene owning 3,334,640 shares of the Company's common stock as of September 30, 2013, representing 10.0% of the Company's fully diluted equity and 11.7% of the voting interests of the Company as of September 30, 2013.

During the year ended December 31, 2012, the Company recognized \$23.9 million in collaboration revenue under the Celgene collaboration arrangement and, as of December 31, 2012, had recorded \$44.1 million of deferred revenue related to the Celgene collaboration arrangement. During the nine months ended September 30, 2012 and 2013, the Company recognized \$20.3 million and \$10.8 million in collaboration revenue, respectively, under the Celgene collaboration arrangement and, as of September 30, 2013, had recorded \$33.3 million of deferred revenue related to the Celgene collaboration arrangement. Additionally, in the nine months ended September 30, 2013, the Company recorded \$0.7 million in global development co-funding from Celgene as a reduction to research and development expense. Accordingly, as of September 30, 2013, the Company had accounts receivable of \$0.7 million related to this collaboration arrangement.

13. Subsequent Events

In connection with preparing for its initial public offering, the Company's Board of Directors and stockholders approved a one-for-three reverse stock split of the Company's common stock. The reverse stock split became effective on May 13, 2013. All share and per share amounts in the consolidated financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common stock to additional paid-in capital. In addition, in May 2013, the Company's Board of Directors and stockholders approved an amendment of the Company's certificate of incorporation to, among other things, change the definition of a qualified public offering to remove the per share price requirement and to set the threshold at gross proceeds to the Company of at least \$50.0 million.

Table of Contents

4,492,679 Shares

Epizyme, Inc.

Common Stock

PROSPECTUS

February 4, 2014

Citigroup

Cowen and Company

Leerink Partners

JMP Securities

Wedbush PacGrow Life Sciences

BTIG