Epizyme, Inc.
Form 424B5
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Registration No. 333-203847

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and they are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED JANUARY 5, 2016

Preliminary Prospectus Supplement

(To Prospectus Dated May 29, 2015)

$120,000,000

Epizyme, Inc.

Common Stock

$ Per Share

We are offering $120,000,000 of shares of our common stock. Our common stock is listed on The NASDAQ Global Market under the symbol EPZM. The last reported sale price of our common stock on The NASDAQ Global Market on January 4, 2016 was $15.28 per share.

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

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

Emerging Growth Company.

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

	Per Share	Total
Public offering price	$	$
Underwriting discount(1)	$	$
Proceeds, before expenses, to Epizyme, Inc.	$	$

(1) We refer you to Underwriting beginning on page S-53 of this prospectus supplement for additional information regarding total underwriter compensation.

We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to an additional $18,000,000 of shares of our common stock. See Underwriting for more information.

The underwriters expect to deliver the shares to purchasers on or about , 2016 through the book-entry facilities of The Depository Trust Company.

Joint Bookrunners

Citigroup **Leerink Partners** **RBC Capital Markets**

Co-Lead Managers

JMP Securities **Wedbush PacGrow**

Co-Manager

Mizuho Securities

Prospectus Supplement dated , 2016

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PROSPECTUS

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ABOUT THIS PROSPECTUS SUPPLEMENT

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

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

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

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

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

consolidated subsidiary.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

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

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

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

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

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under Risk Factors beginning on page S-12 of this prospectus supplement, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision.

Company Overview

Epizyme is a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize novel epigenetic therapies for cancer patients. We are leaders in discovering and developing small molecule inhibitors of a class of enzymes known as histone methyltransferases, or HMTs. We are also expanding our development efforts beyond HMTs and are developing small molecule inhibitors of other chromatin modifying proteins, or CMPs. CMPs mediate selective and reversible modifications to chromatin, a complex of chromsomal DNA and histone proteins that controls gene expression. This chromatin remodeling and its resultant control of gene expression are part of a larger regulatory system, commonly referred to as epigenetics. Genetic alterations within CMPs or that indirectly affect CMPs can result in changes to their activity and drive multiple types of cancer, including hematological cancers and solid tumors. We believe that inhibiting altered CMPs presents the opportunity to create, develop and commercialize multiple targeted therapeutics.

Our goal is to become a fully integrated oncology company developing novel epigenetic therapies for cancer patients. Our lead product candidate, tazemetostat, is a potent and selective inhibitor of the EZH2 HMT, an enzyme that plays an important role in various cancers. In our ongoing phase 1 clinical trial of tazemetostat in patients with relapsed or refractory non-Hodgkin lymphoma, or NHL, or advanced solid tumors, tazemetostat has shown meaningful clinical activity as a monotherapy, with an acceptable safety profile. We are currently evaluating tazemetostat in two phase 2 studies in adults and one phase 1 study in children. In addition, in the first half of 2016, we plan to initiate clinical trials of tazemetostat in combination with other therapies being used or investigated for the treatment of NHL. These trials include one study in front line elderly patients with diffuse large B-cell lymphoma, or DLBCL, an aggressive form of NHL. We also are exploring in preclinical testing other tumor types that may be sensitive to tazemetostat. We own the global development and commercialization rights to tazemetostat outside of Japan. Eisai Co. Ltd, or Eisai, holds the rights to develop and commercialize tazemetostat in Japan, and holds a limited right of first negotiation for the rest of Asia. Tazemetostat is protected by U.S. composition of matter patents, which are expected to expire in 2032.

We have several additional programs in development, including a clinical program of pinometostat, an inhibitor of the DOT1L HMT, for the treatment of children with MLL-r, an acute leukemia with genetic alterations of the MLL gene. Under our collaboration with Celgene Corporation and Celgene RIVOT Ltd., an affiliate of Celgene Corporation, which we collectively refer to as Celgene, we own commercialization rights to pinometostat in the United States and Celgene owns commercialization rights to pinometostat outside the United States. Along with Celgene, we are also investigating in preclinical studies combinations of pinometostat with other targeted therapies for the treatment of adults with MLL-r.

Beyond these two clinical stage programs, we have also identified five novel epigenetic targets for which we are developing small molecule inhibitors in preclinical drug discovery. We own all development and commercialization rights to these programs.

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We have additional small molecule HMT inhibitors that are being developed under our collaborations with Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK, and Celgene. Under our collaboration with GSK, GSK is developing small molecule inhibitors against three novel HMT targets. We discovered these HMT inhibitors using our proprietary drug discovery platform and successfully delivered them to GSK under the collaboration. GSK has worldwide rights to the inhibitors of these three HMT targets. Under our collaboration with Celgene, we are developing small molecule inhibitors directed to three other HMT targets in addition to pinometostat. Under the collaboration, we are responsible for all preclinical discovery work as well as phase 1 clinical development for all three targets. Celgene has the option to acquire worldwide rights to inhibitors directed at two of the three targets, and the option to acquire ex-U.S. rights to inhibitors directed to the third target. We retain rights to develop and commercialize the third target in the United States.

All of our novel targets have been identified internally using our proprietary drug discovery platform, and all of our small molecule inhibitors have been discovered internally.

Tazemetostat Development Program

We are developing tazemetostat for the treatment of NHL and genetically defined solid tumors. We are currently conducting a comprehensive development program for tazemetostat that includes an ongoing five-arm phase 2 study in adult patients with NHL, as well as a phase 2 study in adults with INI1-negative tumors, certain SMARCA4-negative tumors or synovial sarcoma and a phase 1 study in pediatric patients with the same genetically defined solid tumor types. In our ongoing phase 1 study in patients with relapsed or refractory NHL or advanced solid tumors, tazemetostat has shown meaningful clinical activity, with objective responses in both settings. We believe the activity and tolerability profile observed to date, as well as the significant need for new therapies in both NHL and genetically defined solid tumors, support the rationale for further development of tazemetostat.

Our phase 1 study in relapsed or refractory NHL or advanced solid tumors is being conducted in France, the United Kingdom and Australia. As of November 7, 2015, 58 patients were enrolled in the study. The phase 1 study is comprised of a dose escalation study, a dose expansion study, and two clinical pharmacology studies: a food effect study and a drug-drug interaction study. Enrollment in the dose escalation, dose expansion and food effect studies are complete, and enrollment in the drug-drug interaction study is ongoing. Interim results from the phase 1 study, including efficacy results for the solid tumor patients, were reported at the European Cancer Congress 2015, or ECC, in Vienna, Austria, on September 26, 2015, and interim results from the phase 1 study, including efficacy results for the NHL patients, were reported at the 57th American Society of Hematology Annual Meeting, or ASH, in Orlando, Florida, on December 7, 2015.

Our five-arm phase 2 NHL study is currently being conducted in the United Kingdom, France and Australia. The U.S. Food and Drug Administration, or FDA, recently accepted our Investigational New Drug, or IND, application for tazemetostat for DLBCL, which will allow us to expand the treatment of DLBCL patients in the study to sites in the United States. We also plan to expand the study to include sites in Belgium, Canada, Germany, Italy and Poland. Our phase 2 study in adults and phase 1 study in children with genetically defined solid tumors are now enrolling patients in the United States, and we expect to expand enrollment in both studies internationally in 2016.

We own global development and commercialization rights to tazemetostat outside Japan. Eisai holds the rights to develop and commercialize tazemetostat in Japan, and holds a limited right of first negotiation for the rest of Asia. We discovered tazemetostat using our proprietary drug discovery platform.

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Tazemetostat Non-Hodgkin Lymphoma Program

At ASH, we presented updated data from our ongoing phase 1 study of tazemetostat in NHL or advanced solid tumors, including efficacy data with respect to patients with NHL. All NHL patients were either refractory to or relapsed from prior therapy, which included autologous stem cell transplant in eight of the 21 patients with NHL that were dosed in the study. Of these 21 patients, 18 patients, or 85%, had been treated previously with three or more systemic anti-cancer therapies. As of the November 7, 2015 cutoff date, the following clinical data were reported:

- Twenty-one patients with relapsed or refractory NHL were enrolled into the phase 1 study; 16 of the 21 patients were response-evaluable as defined by the study protocol.
- Tazemetostat showed activity across different subtypes of NHL, including germinal-center and non-germinal center DLBCL and follicular lymphoma, in patients with wild-type EZH2 and mutant EZH2.
- Nine of 16 (56%) response-evaluable NHL patients achieved an objective response.
- On an intent-to-treat basis, seven of 12 (58%) response-evaluable NHL patients treated at or above the recommended phase 2 dose of 800 mg twice daily (BID) achieved an objective response.
- Four patients remained on study at data cutoff with ongoing objective responses, including three patients who had been on drug for at least 17 months.
- The 800 mg BID dose showed superior tolerability, equivalent anti-tumor activity and equivalent pharmacodynamic activity as compared to the 1600 mg BID dose.
- Tazemetostat was well-tolerated. The majority of adverse events were grade 1 or grade 2 within the 55 patients with NHL and solid tumors who were evaluable for safety. The most common adverse events, regardless of attribution, were asthenia, anorexia, thrombocytopenia, nausea, constipation, diarrhea, and vomiting. Four grade 3 or greater treatment-related adverse events have been observed including one each of: grade 3 hypertension, grade 3 liver function test elevation, grade 4 thrombocytopenia, and grade 4 neutropenia.

We are conducting a registration-supporting international 150-patient, five-arm phase 2 clinical trial of tazemetostat for the treatment of NHL.

Patients in the phase 2 NHL study are stratified into one of five arms:

- Germinal center DLBCL, wild-type EZH2,

Germinal center DLBCL, mutant EZH2,

Non-germinal center DLBCL,

Follicular lymphoma, wild-type EZH2, and

Follicular lymphoma, mutant EZH2.

Overall, enrollment in the five-arm phase 2 NHL study is proceeding as expected. Each of these arms will enroll 30 patients subject to an interim futility analysis for each arm. To date, based on preliminary response data, we believe we have surpassed futility in two of the five arms, and we have not yet achieved the necessary events to determine futility or non-futility in the other three arms. Definitive futility analyses will be determined at a later date by an independent data safety monitoring board. We plan to present interim data from the phase 2 five-arm NHL study at a medical conference in mid-2016. The primary endpoint of the study is overall response rate. Secondary endpoints include duration of response, progression free survival, overall survival, safety and population pharmacokinetics.

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We have entered into an agreement with Roche Molecular Systems, Inc. for the development of a companion diagnostic for use with tazemetostat for NHL patients with EZH2 point mutations, and are using this diagnostic for the screening of patients in the ongoing phase 2 five-arm NHL study. We have made significant progress in elucidating the mechanism of action of tazemetostat in both mutant and wild-type EZH2 NHL. In preclinical studies, EZH2 gain-of-function mutations have led to oncogenic repression of gene transcription by accelerating trimethylation of the EZH2 substrate H3K27. Our preclinical studies with wild-type EZH2 lymphoma cells suggest that EZH2 acts as a gatekeeper for B-cells that influences whether these cells differentiate into activated B-cells or remain within the germinal center state. This hypothesis is supported by cumulative pre-clinical data with EZH2 inhibitors, including pre-clinical models showing synergy with B-cell signaling inhibitors and antagonism by natural B-cell signaling agonists that drive B-cells into a more differentiated state.

We believe the annual incidence rate of mutant and wild-type EZH2 germinal and non-germinal center B-cell lymphomas is approximately 155,000 patients in the United States and major overseas pharmaceutical markets, with non-germinal center B-cell lymphomas constituting a slight majority of these incidences of B-cell lymphomas. We believe the prevalence of these B-cell lymphomas in major pharmaceutical markets is significantly higher than the annual incidence as many of these patients survive beyond the year in which they are diagnosed.

Common treatments for both DLBCL and follicular lymphoma are multi-agent chemotherapy, usually combined with rituximab (Rituxan), including R-CHOP, a standard front line treatment, R-ICE and R-DHAP, along with other rituximab containing chemotherapy regimens, which are more often used as salvage regimens following the failure of front line treatment. R-CHOP and R-DHAP are combinations of the cancer agent rituximab, chemotherapy drugs and a steroid; R-ICE is a combination of rituximab and three chemotherapy drugs. Certain patients with DLBCL may also be treated with an allogeneic stem cell transplant.

According to published data from GBI Research, the value of the NHL market in the major developed markets is expected to increase to more than $9 billion by 2020. While current therapies successfully treat more than 50% of DLBCL patients in the front line setting, there remains an unmet medical need in patients who have relapsed or are not responding to treatment. Follicular lymphoma is generally considered to be incurable with existing therapies. According to a review article published in the 2011 American Society of Hematology Education Book, after standard treatment, approximately one-third of DLBCL patients in a population based registry had refractory disease or had suffered a relapse within a median of four years.

Tazemetostat Solid Tumor Program

At the ECC, we presented data from our ongoing phase 1 study of tazemetostat in patients with NHL or advanced solid tumors, including efficacy data with respect to patients with solid tumors. As of the data cutoff of August 31, 2015, we had enrolled 30 patients with solid tumors into this ongoing phase 1 study, including eight patients in a food effect sub-study. Of these 30 patients, eight had INI1-negative tumors, comprised of five with malignant rhabdoid tumors, or MRT, and three with epithelioid sarcomas. Additionally, three patients had SMARCA4-negative tumors including two patients with malignant rhabdoid tumor of ovary, or MRTO, which is also referred to as small cell carcinoma of the ovary hypercalcemic type, and one patient with thoracic sarcoma. Nineteen patients had other solid tumors that were not characterized by INI1 or SMARCA4 loss, including three patients with synovial sarcomas. More than half of the solid tumor patients were relapsed or refractory and had been treated previously with three or more systemic anti-cancer therapies. As of the August 31, 2015 cutoff date, the following clinical data were reported:

A total of 11 patients with INI1-negative or SMARCA4-negative tumors have been treated. The tumor histology of these patients includes MRT, MRTO, epithelioid sarcoma and thoracic sarcoma. Nine of these 11 patients have been treated at or above the recommended phase 2 dose of 800 mg BID.

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Six of the 11 patients experienced a reduction in tumor size as best response, with four patients experiencing tumor reduction of over 30%.

Of the five patients with an INI1-negative malignant rhabdoid tumor, one patient achieved a complete response at week eight and had remained on study and in complete response through week 65.

Of three patients with SMARCA4-negative tumors, two patients have MRTO. One MRTO patient achieved a partial response at week 8 and had remained on study through week 25. A second MRTO patient achieved stable disease and had remained on study through week 26.

Of three patients with an INI1-negative epithelioid sarcoma, one patient achieved a partial response of short duration and had remained on study with stable disease through week 25. A second patient had remained on study with stable disease through week 24.

Clinical activity was not observed in the 19 patients with other tumors, including the three patients with synovial sarcomas.

Inhibition of EZH2, as measured by post-treatment H3K27 trimethylation compared to baseline, was observed in tumor tissue of INI1-negative patients as assessed by immunohistochemistry.

We believe stable disease is a clinically meaningful outcome in this patient population, where in a clinical study of children with rhabdoid tumors, the median survival was less than one year, and in a clinical study of patients with MRTO, the two-year survival rate was less than 35 percent. At the ECC, Dr. Viktor Grünwald, professor at the Medical School of Hanover, Germany, reported data from a cooperative study with The European Organisation for Research and Treatment of Cancer, in which the population of patients with soft tissue sarcoma in the study, stable disease was as good a predictor of overall survival as was a composite of partial and complete responses.

The adult phase 2 multicenter study in adults with genetically defined solid tumors will enroll up to 90 patients in three cohorts.

The first cohort will be comprised of patients with MRT, rhabdoid tumor of the kidney and atypical teratoid rhabdoid tumor, all of which are characterized by INI1- or SMARCA4-negativity.

The second cohort will be comprised of patients with non-rhabdoid INI1-negative tumors including epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumor, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma and renal medullary carcinoma.

The third cohort will be comprised of patients with synovial sarcoma.

Patients will be dosed at 800 mg BID with tablets taken orally. The primary endpoint is overall response rate for patients in the first two cohorts and progression-free survival, or PFS, for patients in the synovial sarcoma cohort.

Secondary endpoints include duration of response, overall survival, PFS for patients with INI1-negative tumors, safety and pharmacokinetics. We plan to present interim data from the phase 2 study of tazemetostat in adults with genetically defined solid tumors at a medical conference in late 2016.

The pediatric phase 1 multicenter study in patients with genetically defined solid tumors will enroll approximately 40 patients in a dose escalation design, followed by dose expansion, with an oral suspension of tazemetostat. The study will enroll patients with the same INI1-negative tumors, SMARCA4-negative tumors or synovial sarcoma as in the phase 2 adult study. The primary endpoint of the study is safety, with the objective of establishing the recommended phase 2 dose in pediatric patients. Secondary endpoints include pharmacokinetics, objective response rate, duration of response, PFS and overall survival.

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INI1 and SMARCA4 are subunits of SWI/SNF, a chromatin modifying protein complex, which opposes the activity of PRC2, the complex within which EZH2 resides. Loss of INI1 or SMARCA4, in specific cell backgrounds, is believed to cause dysregulation in the balance between SWI/SNF and PRC2 and thus cause tumors to become sensitive to EZH2 inhibition. This effect was observed in a preclinical study of tazemetostat in a xenograft model of MRT in which tazemetostat caused a dose dependent regression in INI1-negative tumors. INI1-negative tumors can appear in many different tissue types, and can appear as malignant rhabdoid tumor, epithelioid sarcoma, extraskeletal myxoid chondrosarcoma and peripheral nerve sheath tumor, among several others. SMARCA4-negative tumors can also appear as different tumor types, including MRTO. Synovial sarcoma is characterized by a reciprocal translocation between chromosome 18 and the X chromosome which leads to INI1 dysregulation.

INI1-negative or certain SMARCA4-negative tumors are typically aggressive cancers with few to no treatments approved for these tumors. For example, current treatment of malignant rhabdoid tumors consists of surgery, chemotherapy and radiation therapy, which are associated with limited efficacy and significant treatment-related morbidity. INI1-negative tumors are most commonly seen in infants and toddlers, while SMARCA4-negative tumors and synovial sarcoma are most commonly seen in teenagers and young adults. We believe approximately 3,200 new patients with INI1-negative tumors, certain SMARCA4-negative tumors or synovial sarcoma are diagnosed annually in the United States and other major pharmaceutical markets; however, we believe that the actual number may be higher as these types of genetically defined cancers are significantly under-reported today.

Combination Studies and Other Development Plans

In the first half of 2016, we plan to initiate two trials of tazemetostat in combination with other NHL therapies. The first of these trials will be in front line elderly patients with DLBCL and will combine tazemetostat with R-CHOP. In preclinical models of NHL, tazemetostat showed synergy with R-CHOP, and in particular the prednisone component. Our second planned combination study in NHL will combine tazemetostat with either a B-cell signaling agent or an immuno-oncology agent. In preclinical studies, tazemetostat showed synergy with a number of different B-cell signaling agents, including inhibitors of the kinases BTK and PI3K, as well as inhibitors of BCL-2, a regulator of apoptosis, or programmed cell death. Reports from various investigators have suggested that EZH2 inhibition also sensitizes tumors to checkpoint inhibition, through enhanced exposure of tumor antigens to the immune system and enhanced chemokine signaling to improve trafficking and infiltration of helper T-cells to the tumor microenvironment.

Beyond EZH2 mutations, we believe there may be other genetic defects that affect the sensitivity of B-cells to tazemetostat. We are working to validate such defects through genetic sequencing of tumors of patients treated in our ongoing five-arm phase 2 NHL study and in our ongoing adult and pediatric solid tumor studies.

In addition to our studies in NHL and genetically defined solid tumors, in the third quarter of 2016, we plan to initiate a phase 2 study of tazemetostat in relapsed or refractory patients with mesothelioma characterized by mutations in an enzyme called BAP1, which is involved in regulating EZH2 expression. In preclinical studies of mesothelioma, loss-of-function mutations in BAP1 led to increased expression and activity of EZH2, and this increased activity was a key oncogenic event. In addition, in animal models of mesothelioma, inhibition of EZH2 by a small molecule inhibited growth of tumor cells in BAP1-mutated mesothelioma. Relapsed or refractory mesothelioma remains an unmet medical need. First line treatment typically includes the chemotherapy drugs cisplatin and pemetrexed (Alimta). Median overall survival after standard of care treatment is approximately 13 months. BAP1 loss-of-function mutations are associated with approximately 46% of mesothelioma. We estimate total annual incidence of mesothelioma is approximately 12,000 patients in the major pharmaceutical markets.

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Other Pipeline Programs

We are conducting a phase 1 clinical study of pinometostat in pediatric MLL-r patients. This phase 1 study is designed to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of pinometostat in patients between the ages of three months and 18 years and is also expected to enable a preliminary assessment of activity. We plan to present preliminary results from this study at a medical conference in the second half of 2016.

We and Celgene are also exploring in preclinical studies combinations of pinometostat with other anti-cancer agents to enhance pinometostat s efficacy in the adult MLL-r population. Under our collaboration with Celgene, we hold rights to commercialize pinometostat in the United States, and Celgene holds worldwide rights to commercialize pinometostat outside the United States.

In addition to our clinical programs, we also have a pipeline of small molecule inhibitors in preclinical development that target our other prioritized CMPs. These programs are directed to specific cancers, including both hematological and solid tumors. Under our collaboration with GSK, GSK is developing our compounds for three CMPs, including the HMT enzyme PRMT5. Under our collaboration with GSK, we have the potential to earn up to $18.0 million in additional preclinical research and development milestone payments, up to $109.0 million in clinical development milestone payments, up to $275.0 million in regulatory milestone payments, up to $218.0 million in sales-based milestone payments and royalties at percentages up to the low double digits on worldwide net product sales of these three programs. Through September 30, 2015, GSK has paid us $53.0 million under our collaboration.

In July 2015, we amended our collaboration agreement with Celgene to focus on small molecule HMT inhibitors against three predefined targets in addition to pinometostat. Celgene holds an option to license global rights for the HMT inhibitors against two of these additional targets at the time of the IND filing, and must make another payment at the end of phase 1 clinical development for each target to retain its license. We are responsible for these two programs through the end of phase 1 clinical trials, and, if it exercises its option with respect to these programs, Celgene will solely fund all development costs on a worldwide basis after the completion of phase 1 development. For the HMT inhibitors targeting the third target, Celgene holds an option to license ex-U.S. rights at the time of the IND filing, and must make another payment at end of phase 1 clinical development to retain its license, and we retain U.S. development and commercialization rights. We are responsible for the third program through the end of phase 1 clinical trials. After the completion of phase 1 development, if Celgene has exercised its option, we and Celgene will equally co-fund global development and each party will solely fund territory-specific development costs for its respective territory. For these three option targets, we are eligible to receive a total of up to $75.0 million in development milestone and license payments, $365.0 million in regulatory milestone payments, $170.0 million in sales-based milestone payments, and royalties on each of the targets. Through September 30, 2015, Celgene has paid us $109.8 million under our collaboration.

Proprietary Drug Discovery Platform

We have built a proprietary drug discovery platform that we use to create small molecule inhibitors of HMTs and other CMPs that control gene expression. Our platform includes target identification and validation tools, such as chemical genomics techniques and CRISPR gene editing technology, which we use to genetically knock out targets of interest and test for anti-proliferative effects. We have a biased library of over 32,000 small molecule CMP inhibitors. We conduct broad cross-screening activities to identify novel uses of these compounds as starting points for drug discovery. We then utilize an integrated combination of biochemistry, biology, structural biology and medicinal chemistry to optimize these compounds and generate development candidates that may be advanced to preclinical development and potentially clinical development. To date, we have

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generated chemical matter directed to eight novel CMPs, including tazemetostat and pinometostat, compounds directed to three targets that are in preclinical evaluation at GSK, and compounds directed to three other targets that are in preclinical development under our collaboration with Celgene. In addition, we have ongoing drug discovery programs directed to five other prioritized, novel CMP targets. We own all development and commercialization rights to these five programs.

Corporate Strategy

Our goal is to become a fully integrated development and commercial oncology company developing novel epigenetic therapies for cancer patients. We have a robust proprietary drug discovery platform and the demonstrated ability to move candidates into clinical development. As we prepare to commercially launch tazemetostat, if approved, we plan to build out the infrastructure necessary to support the successful launch and marketing of this asset. The key elements of our strategy to achieve this goal are to:

Rapidly Advance the Clinical Development of Tazemetostat. We are executing a comprehensive clinical development program of tazemetostat for NHL and certain genetically defined solid tumors. If we see compelling early evidence of a therapeutic effect in any of these trials, we plan to meet with regulatory authorities to discuss the possibility of an expedited clinical development and regulatory pathway for the applicable program. If safe and sufficiently active in the target patient populations, we believe that tazemetostat may be able to rely on an expedited regulatory approval process.

Seek to Expand the Range of Potential Indications for Tazemetostat. The R-CHOP combination study we are pursuing is designed to investigate the utility of tazemetostat in front line DLBCL, which would expand the potential commercial opportunity for tazemetostat. We also have over two dozen academic collaborations which are investigating the role of tazemetostat in other cancer types in preclinical models. If we see strong preclinical evidence of sensitivity of specific tumors to EZH2 inhibition, and if a medical need exists, we will consider initiating proof of concept in human clinical trials. For example, on the basis of preclinical findings under a collaboration with Memorial Sloan Kettering Cancer Center, we plan to initiate in the third quarter of 2016, a phase 2 study of tazemetostat in relapsed or refractory patients with BAP1-mutated mesothelioma.

Establish Commercialization and Marketing Capabilities in the United States. We have retained commercialization rights in the United States for all of our programs, other than the three programs that are the subject of our GSK collaboration and two of the programs that are the subject of our collaboration with Celgene. We plan to retain commercialization rights in the United States and possibly selected foreign jurisdictions in connection with any future oncology collaborations. We intend to build a focused specialty sales force and marketing capabilities to commercialize any of our oncology drugs that receive regulatory approval in the United States, and the capability of leading global commercial strategy.

Use Our Drug Discovery Platform to Build a Pipeline of Proprietary CMP Inhibitors. Using our proprietary drug discovery platform, we are developing additional novel, small molecule inhibitors of CMPs involved in cancer. We currently hold U.S. development and commercialization rights to one of our three preclinical programs subject to Celgene s option under our collaboration. We are devoting a substantial

portion of our research efforts at identifying and optimizing chemical matter against this novel HMT target. In addition, we have identified five novel CMP targets against which we are developing small molecule inhibitors in preclinical drug discovery, for which we own all development and commercialization rights.

Leverage Collaborations. Our therapeutic collaborations with Celgene, GSK and Eisai provide us with access to the considerable scientific, development, regulatory and commercial capabilities of our collaborators. Our collaborations with Celgene and GSK potentially provide us with significant funding

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for both our specific development programs and our product platform. We believe that collaborations like these can contribute to our ability to rapidly advance our product candidates, build our product platform and concurrently progress a wide range of discovery and development programs, and may seek to enter into additional therapeutic collaborations in the future.

Develop Companion Diagnostics for Use with Our Therapeutic Product Candidates. We plan to seek to develop companion diagnostics for use in connection with our therapeutic product candidates where necessary. 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 are more likely to benefit from the therapy. We intend to develop diagnostics based on currently available diagnostic technologies to the extent possible in order to minimize development and regulatory risk of our diagnostic programs. We are working with Roche to develop a companion diagnostic, based on currently available technology, for use with tazemetostat for NHL patients with EZH2 point mutations and are relying on existing laboratory tests for use with pinometostat to identify MLL-r patients. We also plan to develop a companion diagnostic to identify the relevant mutations in patients in BAP1 for our mesothelioma program.

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 supplement immediately following this prospectus supplement summary. These risks include the following:

We have incurred significant losses since our inception. Our accumulated deficit was $221.2 million as of September 30, 2015, 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 research and development is focused on the creation of novel epigenetic therapies for cancer patients, 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 clinical trials of inhibitors of HMTs.

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 our ongoing phase 1 clinical trial of tazemetostat in NHL or solid tumors were achieved in a limited number of patients, were observed in an open-label setting, are not statistically significant and might not be achieved by any other patient treated with tazemetostat in any of our clinical trials.

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.

We cannot predict whether or when any of our product candidates will prove effective or safe in clinical trials, if they will receive regulatory approval or if we will be able to participate in any expedited review and approval programs for such 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.

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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.

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.

Company 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 supplement. We have included our website address in this prospectus supplement 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 supplement are the property of their respective owners.

Implications of Being an Emerging Growth Company

As a company with less than $1 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 certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

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 will remain an emerging growth company until the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues of $1 billion or more; (ii) December 31, 2018; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission based on the market value of our common stock held by non-affiliates. If the market value of our common stock that is held by non-affiliates exceeds

$700 million as of June 30, 2016, we would cease to be an emerging growth company as of the end of 2016.

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 allows an emerging growth company to 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 exemption from new or revised accounting standards and, therefore, are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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The Offering

Common Stock offered by Epizyme	$120,000,000 of shares.
Common Stock to be outstanding after this offering	49,583,677 shares, which is based on an aggregate offering of $120,000,000 of our common stock at an assumed public offering price of $15.28 per share (the last reported sale price of our common stock on The NASDAQ Global Market on January 4, 2016).
Option to purchase additional shares	The underwriters have an option to purchase up to an additional $18,000,000 of shares of our common stock from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus supplement.
Use of Proceeds	We estimate that the net proceeds to us from this offering, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, will be approximately $112.7 million, or approximately $129.7 million if the underwriters exercise their option to purchase additional shares from us in full, in each case, based on an assumed public offering price of $15.28 per share (the last reported sale price of our common stock on The NASDAQ Global Market on January 4, 2016). We plan to use the net proceeds from this offering, together with our existing cash and cash equivalents, to fund our ongoing and planned clinical trials of tazemetostat, to fund market development activities for tazemetostat, to fund research and development to advance our pipeline of preclinical product candidates and expand our product platform, and for working capital and other general corporate purposes. See Use of Proceeds.
Risk Factors	You should read the Risk Factors section of this prospectus supplement beginning on page S-12 for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
NASDAQ Global Market symbol	EPZM

The number of shares of our common stock to be outstanding after this offering is based on the 41,730,274 shares of our common stock outstanding as of November 30, 2015 and excludes:

- 3,169,422 shares of common stock issuable upon the exercise of stock options outstanding as of November 30, 2015, at a weighted average exercise price of $15.04 per share;

37,313 shares of common stock subject to restricted stock units outstanding as of November 30, 2015; and

2,610,227 shares of common stock that have been reserved for issuance in connection with future grants under our equity compensation plans as of November 30, 2015.

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

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RISK FACTORS

Investing in our common stock involves a high degree of risk. Before you decide to invest in our common stock, you should carefully consider the risks and uncertainties described below together with all other information contained in this prospectus supplement, the accompanying prospectus and in our filings with the SEC that we have incorporated by reference in this prospectus supplement and the accompanying prospectus. If any of the following risks actually occurs, 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 the Discovery and Development of Our Product Candidates

Our research and development is focused on the creation of novel epigenetic therapies for cancer patients, 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 novel epigenetic therapies for cancer patients 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, few drugs premised on epigenetics have been discovered. Moreover, those drugs based on an epigenetic mechanism that have received marketing approval are in different target classes than HMTs, where our research and development is principally focused. Although preclinical studies suggest that genetic alterations can result in changes to the activity of HMTs, making them oncogenic, 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 cancer patients 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 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 our efforts and financial resources in the identification and preclinical and clinical development of inhibitors of HMTs and other CMPs. Our ability to generate product revenues, which we do not expect will occur for several 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;

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;

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 proprietary drug discovery platform to build a pipeline of product candidates.

A key element of our strategy is to use and expand our proprietary drug discovery platform to build a pipeline of small molecule inhibitors of HMT and other CMP 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 to specific HMT and other CMP targets, we may not be able to develop product candidates that are safe and effective CMP 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 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.

Product candidates are subject to continued preclinical safety studies, which may be conducted concurrent with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical studies. For example, in the course of our preclinical safety studies of tazemetostat, we observed the development of lymphoma in Sprague Dawley rats. We informed the relevant international regulatory authorities, the FDA and the clinical investigators of this finding in rats, and discussed the results with the regulatory authorities. In August 2015, the FDA accepted our IND for tazemetostat in patients with INI1-negative tumors or synovial sarcoma, and in December 2015, the FDA accepted our IND for tazemetostat in patients with DLBCL. Expansion of our development of tazemetostat outside of these indications in the United States, including BAP1-mutated mesothelioma, will require that we submit an IND or that we submit supplemental materials to the FDA and that we address this matter to the satisfaction of the FDA within the context of patient risk-benefit and in view of the safety and efficacy data from our ongoing and completed clinical trials of tazemetostat. If we are unable to adequately address this matter, we may be unable to conduct clinical trials of tazemetostat in patients with other cancers in the United States, our trials may be

limited to certain patient populations or our ability to conduct other trials in the United States may be delayed.

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, the complete responses that were observed in two patients with MLL-r in the fourth dose cohort of the dose escalation portion of our phase 1 clinical trial of pinometostat were achieved in an open-label setting are not statistically significant and might not be achieved by any other patient treated with pinometostat. We voluntarily ceased patient enrollment into the phase 1 study in adult patients with MLL-r due to insufficient evidence of efficacy of pinometostat as a monotherapy in the third quarter of 2015. We are continuing to conduct a phase 1 dose escalation trial of pinometostat in pediatric patients with MLL-r. Moreover, preclinical and cli