Epizyme, Inc.
Form 10-K
March 13, 2017
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2016

or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission File Number 001-35945

EPIZYME, INC.

(Exact name of registrant as specified in its charter)

Delaware	**26-1349956**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
400 Technology Square, Cambridge, Massachusetts	**02139**
(Address of principal executive offices)	**(Zip code)**

617-229-5872

(Registrant s telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Common stock, $0.0001 par value	**NASDAQ Global Market**
(Title of each class)	**(Name of exchange on which registered)**

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of accelerated filer, large accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act.

Large accelerated filer		Accelerated filer
Non-accelerated filer	(Do not check if a smaller reporting company)	Smaller reporting company

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No

The aggregate market value of the registrant s common stock, par value $0.0001 per share, held by non-affiliates of the registrant on June 30, 2016, the last business day of the registrant s most recently completed second fiscal quarter, was approximately $449.4 million based on the closing price of the registrant s common stock on the NASDAQ Global Market on that date.

The number of outstanding shares of the registrant s common stock, par value $0.0001 per share, as of March 1, 2017 was 58,248,726.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive proxy statement that the registrant intends to file with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant s 2017 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

Table of Contents

Epizyme, Inc.

Annual Report on Form 10-K for the Fiscal Year Ended December 31, 2016

Table of Contents

Table of Contents

Forward-looking Information

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. These statements may be identified by such forward-looking terminology as anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, s statements or variations of such terms. Our forward-looking statements are based on a series of expectations, assumptions, estimates and projections about our company, are not guarantees of future results or performance and involve substantial risks and uncertainty. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements. Our business and our forward-looking statements involve substantial known and unknown risks and uncertainties, including the risks and uncertainties inherent in our statements regarding:

- our plans to develop and commercialize novel epigenetic therapies for patients with cancer and other diseases;
- our ongoing and planned clinical trials, including the timing of initiation and enrollment in the trials, the timing of availability of data from the trials and the anticipated results of the trials;
- our ability to achieve anticipated milestones under our collaborations;
- the timing of and our ability to apply for, 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; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

All of our forward-looking statements are made as of the date of this Annual Report on Form 10-K only. In each case, actual results may differ materially from such forward-looking information. We can give no assurance that such expectations or forward-looking statements will prove to be correct. An occurrence of or any material adverse change in one or more of the risk factors or risks and uncertainties referred to in this Annual Report on Form 10-K or included in our other public disclosures or our other periodic reports or other documents or filings filed with or furnished to the Securities and Exchange Commission, or the SEC, could materially and adversely affect our business, prospects, financial condition and results of operations. Except as required by law, we do not undertake or plan to update or revise any such forward-looking statements to reflect actual results, changes in plans, assumptions, estimates or

projections or other circumstances affecting such forward-looking statements occurring after the date of this Annual Report on Form 10-K, even if such results, changes or circumstances make it clear that any forward-looking information will not be realized. Any public statements or disclosures by us following this Annual Report on Form 10-K which modify or impact any of the forward-looking statements contained in this Annual Report on Form 10-K will be deemed to modify or supersede such statements in this Annual Report on Form 10-K.

Table of Contents

PART I

Item 1. Business

Overview

Epizyme is a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize novel epigenetic therapies for patients with cancer and other diseases. We are leaders in discovering and developing small molecule inhibitors of a class of enzymes known as histone methyltransferases, or HMTs, as well as other chromatin modifying proteins, or CMPs. CMPs mediate selective and reversible modifications to chromatin, a complex of chromosomal 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, as well as other diseases. We believe that inhibiting altered CMPs presents the opportunity to create, develop and commercialize multiple targeted therapeutics.

Our lead product candidate, tazemetostat, is an oral, first-in-class potent and selective inhibitor of the EZH2 HMT, an enzyme that is implicated in a wide range of cancers. In our clinical trials of tazemetostat in patients with relapsed or refractory non-Hodgkin lymphoma, or NHL, and in patients with certain molecularly defined solid tumors, tazemetostat showed meaningful clinical activity as a monotherapy, and was generally well tolerated. We are conducting a broad clinical development program for tazemetostat as both a monotherapy and combination treatment, in relapsed/refractory and front-line disease, across a number of subtypes of NHL and in patients with and without EZH2 activating mutations. We are also testing tazemetostat in several different types of molecularly defined solid tumors, including INI1- and SMARCA4-negative tumors, which we collectively refer to as INI1-negative tumors, in adults and children and in adults with mesothelioma characterized by BAP1 loss-of-function.

In the second quarter of 2017, we expect to present data from all arms of our five-arm Phase 2 clinical trial of tazemetostat as a monotherapy in molecularly defined solid tumors that have reached the pre-specified futility analysis, including the epithelioid sarcoma and synovial sarcoma arms, and from all five arms of our Phase 2 clinical trial of tazemetostat as a monotherapy in NHL. We also plan to meet with regulators, starting with the U.S. Food and Drug Administration, or FDA, by mid-2017, to discuss our solid tumor data, and in the second half of 2017 to discuss our NHL data, to seek to define the paths to registration for tazemetostat as a monotherapy for such indications.

We are actively studying tazemetostat in combination with other anti-cancer agents as part of our broad development plan for tazemetostat. We have entered into collaborations to evaluate tazemetostat in combination with other therapies approved for, or being investigated for, the treatment of diffuse large B-cell lymphoma, or DLBCL, an aggressive form of NHL. We have initiated an immuno-oncology Phase 1b study in collaboration with Genentech, a member of the Roche Group, to investigate the combination of tazemetostat and Genentech s approved anti-PD-L1 cancer immunotherapy, Tecentriq (atezolizumab). The study is evaluating this combination regimen for the treatment of patients with relapsed or refractory DLBCL. We have initiated a Phase 1b/2 clinical trial in collaboration with the Lymphoma Study Association, or LYSA, a premier cooperative French lymphoma group, to evaluate tazemetostat in combination with R-CHOP in a front line setting in newly diagnosed, elderly, high-risk patients with DLBCL. R-CHOP is the standard of care front-line combination treatment for patients with DLBCL. In March 2017, we opened an additional arm of our ongoing Phase 2 NHL study to investigate tazemetostat in combination with prednisolone for patients with relapsed or refractory DLBCL and to begin a combination study of tazemetostat in follicular lymphoma, or FL.

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. Tazemetostat has been granted Fast Track designation by the FDA in patients with

Table of Contents

DLBCL with EZH2 activating mutations and orphan drug designation by the FDA for the treatment of malignant rhabdoid tumors, or MRT. The orphan drug designation applies to INI1-negative MRT as well as SMARCA4-negative malignant rhabdoid tumor of ovary, or MRTO.

We have collaboration agreements with Celgene Corporation and Celgene RIVOT Ltd., an affiliate of Celgene Corporation, which we collectively refer to as Celgene, Glaxo Group Limited (an affiliate of GlaxoSmithKline), or GSK, and Eisai. We have also partnered with Roche Molecular Systems, Inc., or Roche Molecular, to develop a companion diagnostic, for use with tazemetostat to identify NHL patients with EZH2 activating mutations. These collaborations provide us with access to considerable scientific, development, regulatory and commercial capabilities. As of December 31, 2016, we had received $207.8 million in non-equity funding under these collaborations.

Since our inception, we have pioneered the discovery and development of novel epigenetic medicines. We have discovered and developed three first-in-class experimental medicines that are in clinical trials, including tazemetostat. In addition to tazemetostat, we plan to evaluate pinometostat, an inhibitor of the DOT1L HMT that is the subject of our collaboration with Celgene, under a cooperative research and development agreement, or CRADA, with the Cancer Therapy Evaluation Program, or CTEP, of the National Cancer Institute, or NCI, as a combination therapy for patients with acute leukemias. Under our collaboration with GSK, GSK is evaluating GSK3326595, a protein arginine methyltransferase 5, or PRMT5, inhibitor invented by us and licensed to GSK under the collaboration, in a Phase 1 clinical trial in patients with solid tumors and NHL. We have additional small molecule HMT inhibitors that are being developed under our collaborations with Celgene and GSK. We have also identified multiple novel epigenetic targets for which we are developing small molecule inhibitors in preclinical drug discovery. We own the global development and commercialization rights to these programs. 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.

Corporate Strategy

Our goal is to become a fully integrated development and commercial biopharmaceutical company developing novel epigenetic therapies for patients with cancer and other diseases. We have a robust proprietary drug discovery platform and the demonstrated ability to move candidates into clinical development. We plan to build out the infrastructure necessary to support the successful launch and marketing of tazemetostat or any other product candidate that receives marketing approval. The key elements of our strategy to achieve this goal are to:

Rapidly Advance the Clinical Development of Tazemetostat. We are executing a broad clinical development program of tazemetostat for molecularly defined solid tumors, NHL and mesothelioma. We plan on presenting data from our Phase 2 trials in certain molecularly defined solid tumors and NHL in the second quarter of 2017 and interacting with regulatory agencies, beginning with the FDA, by mid-2017 with the goal of defining our registration pathways. Due to a lack of treatment options and the severity of disease associated with INI1-negative tumors, we believe that this molecularly defined patient population may represent the fastest potential path to new drug application, or NDA, submission and commercial launch for tazemetostat.

Seek to Expand the Range of Potential Indications for Tazemetostat. We are conducting a broad development program for tazemetostat as a monotherapy and in combination with other therapies. These efforts include our two ongoing combination trials in DLBCL evaluating tazemetostat with Tecentriq and tazemetostat with R-CHOP, as well as our combination arm with prednisolone in DLBCL and our planned

combination study in FL. 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 human clinical trials.

Table of Contents

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 collaborations. We intend to build a focused field presence and marketing capabilities to commercialize any of our product candidates that receive regulatory approval in the United States, as well as 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. We currently hold U.S. development and commercialization rights to one of our three preclinical programs subject to Celgene s option under our collaboration. In addition, we have identified multiple novel CMP targets against which we are developing small molecule inhibitors in preclinical drug discovery, for which we own global development and commercialization rights. We expect to declare our next development candidate in 2017 with the goal of commencing clinical trials of three new product candidates by 2020.

Leverage Collaborations. Our strategic collaborations with Celgene, GSK, Eisai, Genentech, LYSA, Roche Molecular Systems, Inc., or Roche Molecular, NCI and numerous external academic researchers provide us with access to the scientific, development, regulatory and commercial capabilities of our collaborators. 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. We may seek to enter into additional strategic 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 appropriate. 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 Molecular to develop a companion diagnostic, based on currently available technology, for use with tazemetostat to identify NHL patients with EZH2 activating mutations. We also plan to develop a companion diagnostic to identify patients with BAP1 loss-of-function for our mesothelioma program.

Table of Contents

Our Epigenetic Pipeline

Overview. The following table summarizes our current pipeline:

[1] Eisai holds rights to tazemetostat in Japan
[2] Additional arm of existing five-arm NHL Phase 2 Study
[3] Study not yet initiated
[4] Celgene holds ex-US rights to pinometostat
[5] GSK holds global development and commercialization rights
[6] Celgene holds option to license ex-US rights for one target and global rights for the other two targets

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 2017 there will be approximately 1.7 million new cases of cancer and approximately 600,000 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.

Table of Contents

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. 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.

Targeted Therapies. Another 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 Herceptin and Tarceva, affect cellular signaling pathways that are critical for the growth of cancer. 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.

Anti-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 inhibitors of CMPs as novel precision therapeutics for patients with cancer and other diseases with significant unmet medical needs. Our focus is on the discovery, development and eventual commercialization of small molecule inhibitors of CMPs for applications in diseases that are uniquely dependent on the enzyme activity of a specific CMP. Among the CMP target classes, we have had a particular emphasis on the HMTs, which have been shown to play pathogenic roles in a number of human diseases. Today, we have programs in multiple CMP classes including HMTs. Beyond cancer, however, HMTs and other CMPs have been implicated as pathogenic drivers of a number of diseases with significant unmet medical need.

Background of Epigenetics and Chromatin Remodeling. Epigenetics refers to a broad regulatory system that controls gene expression without altering the makeup of the genes themselves. Genes are composed of DNA, and in nature, this DNA is wrapped around a core of proteins known as histones. Together, the DNA and histone proteins form a complex known as chromatin that is the basic structural component of chromosomes. The structure of chromatin at specific gene locations can exist either in an open state that permits gene expression or in a more closed state that silences gene expression. The shifting of gene-specific chromatin structure is referred to as chromatin remodeling. Chromatin remodeling is affected by the reversible placement of small chemical groups acetyl groups, methyl groups and others onto specific sites on the DNA and the histone proteins, in concert with enzyme-catalyzed topographical changes to the contacts between DNA and histones. Some CMPs place these chemical groups onto specific sites on histones or DNA, some remove these marks in site-specific ways, others recognize the uniquely marked sites on histones and bind to these marked sites, and still other CMPs drive topographical changes to histone-DNA interactions within chromatin. Where, when and how such chromatin remodeling reactions occur, determines which genes in a cell are turned on or off at any particular time. When the function of these CMPs is altered, the program of gene expression is changed in ways that often leads to disease.

Background on Cancers Characterized by Dysregulation of EZH2. EZH2 is an HMT that can become an oncogenic driver for NHL and a variety of other solid tumors, such as MRT, epithelioid sarcoma and MRTO. As a result, EZH2 has become an important target of oncological drug research.

Table of Contents

Molecularly Defined Solid Tumors

Background on INI1-Negative Solid Tumors. 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 present as epithelioid sarcoma, MRT, extraskeletal myxoid chondrosarcoma, peripheral nerve sheath tumor, myoepithelial carcinoma and renal medullary carcinoma, among several others. SMARCA4-negative tumors can also appear as different tumor types, including MRTO.

INI1-negative or certain SMARCA4-negative tumors are typically aggressive cancers with few to no approved treatments. For example, current treatment of MRT consists of surgery, chemotherapy and radiation therapy, which are associated with limited efficacy and significant treatment-related morbidity in this population. INI1-negative tumors are most commonly seen in infants through young adults, while SMARCA4-negative tumors are most commonly seen in teenagers and young adults. We believe that approximately 2,000 new patients with INI1-negative tumors and certain SMARCA4-negative tumors 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 molecularly defined cancers are significantly under-reported today. MRTO accounts for less than 1% of all ovarian cancer diagnoses, with an average age of 24 years at diagnosis. MRTO is characterized by an aggressive clinical course with a two-year survival rate of less than 35%.

Preclinical Studies Solid Tumors. In addition to genetic alterations in EZH2 itself, alterations in distal genes can also lead to an oncogenic dependency on EZH2 activity. Members of the SWI/SNF chromatin remodeling complex are frequently mutated in various tumor types, and loss of the INI1 or SMARCA2/A4 subunits can inhibit SWI/SNF activity, thereby causing enhanced EZH2 activity at select tumor suppressor genes due to the opposing activity of SWI/SNF and PRC2. Consistent with this mechanism, tazemetostat has demonstrated activity in preclinical *in vitro* and *in vivo* studies against select INI1-negative and SMARCA2/A4-deficient tumors including MRT and MRTO.

Tazemetostat Clinical Program in Molecularly Defined Solid Tumors

Our clinical investigation of tazemetostat began with a first-in-human mega-study that included Phase 1 dose escalation cohorts in solid tumors and NHL, dose expansion cohorts in solid tumors and NHL, a food effect sub-study and a drug-drug interaction sub-study. Our Phase 1 study in patients with relapsed or refractory NHL or in patients with advanced solid tumors was conducted globally. We completed enrollment in the study with 64 patients. Interim results from the Phase 1 study, with a focus on efficacy results for the solid tumor patients and safety results on the entire study population, which at that time totaled 51 patients, were reported at the European Cancer Congress, or ECC, in Vienna, Austria, on September 26, 2015.

The primary objective of the Phase 1 study was to evaluate the safety and tolerability of tazemetostat and to determine the recommended dose for Phase 2 trials. In the Phase 1 trial, tazemetostat was administered orally as a monotherapy, twice daily in continuous 28-day cycles. In the dose escalation portion of the study, patients were enrolled in one of five dose cohorts at dose levels of 100, 200, 400, 800, or 1600 mg twice daily. In the dose expansion portion of the study, patients received either 800 or 1600 mg twice daily. In the food effect portion of the study, patients received a single 200 mg dose, with or without food, on the eighth day prior to the start of continuous dosing, a single 200 mg dose, with or without food, one day prior to the start of continuous dosing, and 400 mg twice daily, from the start of the continuous dosing phase. In the drug-drug interaction portion of the study, patients received midazolam dosed

with tazemetostat to evaluate the effect on cytochrome P450 3A-mediated drug metabolism. Cytochrome P450 3A is one member within a family of enzymes involved in the metabolism of many medicines, and dosing tazemetostat with midazolam in a clinical study is a common way of evaluating potential interactions with other drugs that are metabolized by this pathway.

Table of Contents

As of the data cutoff of August 31, 2015, we had enrolled 30 patients with solid tumors into this Phase 1 study. Of these 30 patients, eight had INI1-negative tumors, comprised of five with MRT and three with epithelioid sarcomas. Additionally, three patients had SMARCA4-negative tumors including two patients with MRTO, which is also referred to as small cell carcinoma of the ovary hypercalcemic type, or SCCOHT. Nineteen patients had other solid tumors that were not characterized by INI1 or SMARCA4 loss. 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 had been treated.
- Five of the 11 patients with INI1- or SMARCA4-negative tumors experienced clinical benefit consisting of a complete response, or CR, partial response, or PR, or prolonged stable disease, or SD.
- Of the five patients with an INI1-negative malignant rhabdoid tumor, one patient achieved a CR at week eight and had remained on study and in CR through week 65.
- Of three patients with SMARCA4-negative tumors, two patients presented with MRTO. One MRTO patient achieved a PR at week 8 and had remained on study through week 25. A second MRTO patient achieved SD and had remained on study through week 26.
- Of three patients with an INI1-negative epithelioid sarcoma, two patients had remained on study with SD through at least 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. At the 2015 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, demonstrating that for 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 PRs and CRs.

At the 57th American Society of Hematology Annual Meeting, or the 2015 ASH Annual Meeting, in Orlando, Florida on December 7, 2015, we presented updated safety data on the overall patient population, which included 55 patients with molecularly defined solid tumors as well as NHL, showing tazemetostat continued to be generally well tolerated.

Based on the Phase 1 study results, we are conducting a registration-supporting, global Phase 2 study in patients with INI1-negative solid tumors and synovial sarcoma. This study is enrolling up to 180 patients. The patients in the trials

are stratified into one of five cohorts:

Epithelioid sarcoma. Epithelioid sarcoma is a soft tissue sarcoma characterized by loss of INI1. There are currently no approved systemic therapies for the treatment of patients with epithelioid sarcoma, and outcomes are extremely poor. Following review by the Independent Data Monitoring Committee for this study, we expanded the targeted enrollment in this cohort from 30 to 60 patients based on encouraging early activity, including confirmed objective responses. This study represents the largest trial conducted to date in patients with this rare tumor type.

Rhabdoid tumors. Rhabdoid tumors are aggressive cancers with few to no approved treatments today. Current treatment of malignant rhabdoid tumors consists of surgery, chemotherapy and radiation therapy, which are associated with limited efficacy and significant treatment-related morbidity. They

Table of Contents

can be characterized by loss of INI1, as in the case of MRT, rhabdoid tumor of kidney and AT/RT, or by the loss of SMARCA4, as in the case of MRTO. Target enrollment in this cohort is up to 30 patients.

Other INI1-negative tumors. This arm of the study includes multiple different INI1-negative tumors that are not defined by the other four arms, including chordoma, other INI1 sarcomas, malignant peripheral nerve sheath tumor and myoepithelial carcinoma. Target enrollment in this cohort is up to 30 patients.

Renal medullary carcinoma. Renal medullary carcinoma is a rare and highly aggressive INI1-negative tumor of the kidney predominantly found in patients with sickle cell trait. Target enrollment in this cohort is up to 30 patients.

Synovial sarcoma. Unlike the cancers in the other four arms of the study, synovial sarcoma is characterized by a functional dysregulation of INI1, rather than by a complete loss of INI1. The synovial sarcoma arm of the Phase 2 trial has been fully enrolled at approximately 30 patients. Although this arm of the study surpassed its interim futility hurdle, and as of March 1, 2017 some patients remain on treatment, we concluded that the activity of tazemetostat in this cohort was insufficient to continue further investigation of tazemetostat in this population as a monotherapy.

Patients in the five-arm Phase 2 study in molecularly defined solid tumors are dosed at 800 mg twice daily with tablets taken orally. The primary endpoint for the epithelioid sarcoma arm is a composite endpoint including overall response rate and disease control rate. The primary endpoint for the synovial sarcoma arm is disease control, defined as a CR, PR or SD, at 16 weeks. The primary endpoint for the other cohorts is overall response rate. Secondary endpoints include duration of response, overall survival, progression-free survival, or PFS, overall survival and safety and pharmacokinetics. Pending abstract acceptance, we plan to present interim data from the ongoing Phase 2 study in molecularly defined solid tumors at the American Society of Clinical Oncology Annual Meeting, or ASCO, in Chicago, Illinois in June 2017.

In parallel to the Phase 2 adult study, we are conducting a global Phase 1 dose-escalation and expansion study of tazemetostat in approximately 110 children with INI1-negative solid tumors. In this trial, we are using an oral suspension formula of tazemetostat. As of March 1, 2017, we were progressing with the dose escalation portion of the trial. 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. In June 2016, we were invited to speak at the FDA Pediatric Subcommittee of the Oncologic Drugs Advisory Committee meeting to review our ongoing Phase 1 pediatric study. We received valuable feedback from Committee members on developing tazemetostat to treat rare and extremely aggressive cancers in pediatric patients.

Tazemetostat has been granted orphan drug designation by the FDA for the treatment of MRT. The orphan drug designation applies to INI1-negative MRT as well as SMARCA4-negative MRTO.

Mesothelioma with BAP1 loss-of-function

Background on Mesothelioma. Mesothelioma is a rare form of cancer that typically occurs in the lining surrounding the lungs but can also occur in the lining surrounding other organs. Relapsed or refractory mesothelioma remains an unmet medical need. First line treatment typically includes the chemotherapy drugs cisplatin and pemetrexed (Alimta). Mesothelioma is a very difficult to treat disease, as fewer than 10% of patients live five years following

diagnosis. Median overall survival after standard of care treatment is approximately 13 months. We estimate the total annual incidence of mesothelioma is approximately 12,000 patients in the major pharmaceutical markets. Current literature estimates BAP1 loss-of-function to be associated with approximately 46% to 66% of mesothelioma cases.

Table of Contents

Preclinical Studies Mesothelioma. In preclinical studies of mesothelioma, BAP1 loss-of-function led to increased expression and activity of EZH2. In addition, in animal models, inhibition of EZH2 by tazemetostat inhibited growth of tumor cells in mesothelioma characterized by BAP1 loss-of-function.

Tazemetostat Mesothelioma Clinical Program

We are conducting a global Phase 2 monotherapy trial of tazemetostat in relapsed or refractory patients with mesothelioma characterized by BAP1 loss-of-function. This trial will enroll up to 67 patients with relapsed or refractory mesothelioma. The first part of the trial will evaluate safety and pharmacokinetics in 12 patients, regardless of BAP1 status. The second phase of the trial will evaluate disease control rate in 55 patients with mesothelioma characterized by BAP1 loss-of-function. The first patient in the study was dosed in August 2016 and enrollment is ongoing. Patients are dosed at 800 mg twice daily with tablets taken orally. The primary endpoint of the trial is disease control rate, defined as CR, PR, or SD, at 12 weeks.

Other Solid Tumor Types

In October 2016, we announced a CRADA with the NCI to evaluate tazemetostat in clinical trials in a variety of hematologic malignancies and solid tumors. The initial NCI-sponsored study under the CRADA will evaluate tazemetostat in a Phase 2 clinical trial in adult patients with ovarian cancer and in a Phase 2 study in pediatric patients with solid tumors and lymphoma. As part of the agreement, additional clinical trials will be considered. NCI will predominantly fund the studies and manage study operations. In preclinical studies conducted by us and third parties, inhibition of EZH2 reduced ovarian tumor cell growth.

Non-Hodgkin Lymphoma

Background on NHL. Two types of NHL, DLBCL of germinal-center origin and FL, are associated with oncogenic EZH2 mutations. In our preclinical studies, we observed that NHL cells were sensitive to EZH2 inhibitors such as tazemetostat and that NHL cells bearing EZH2 mutations were particularly responsive to such treatment. EZH2 plays a critical role at various stages in normal B-cell maturation, and a particularly important role during the stage of B-cell development known as the germinal center reaction. Recent research has demonstrated that EZH2 acts as a key gatekeeper for B-cell maturation and differentiation. Our own ongoing research suggests that it is a combination of stem or progenitor cell of origin together with specific genetic lesions that confer sensitivity of cancer cells to EZH2 inhibition. An analysis of patient samples with germinal center derived NHL has revealed a number of genetic alterations that impact EZH2 function in ways that may confer sensitivity to EZH2 inhibition. While DLBCL and FL remain the initial NHL target patient populations for tazemetostat, our clinical and preclinical data suggest patients with other forms of B-cell NHL may also benefit from tazemetostat.

The population of patients with NHL is large and growing. We estimate the annual incidence rate of NHL in the major pharmaceutical markets to be over 150,000 patients. We estimate that the number of front line and relapsed/refractory DLBCL patients in the United States and the five largest EU countries as measured by population, or EU5, that receive treatment in any year are approximately 50,000 and 21,000, respectively. DLBCL can be further subdivided into lymphoma originating from the germinal center of the lymph node, known as GCB DLBCL, and lymphoma originating from B-Cells of a more mature lineage, known as non-GCB DLBCL. We estimate that approximately 60% of DLBCL tumors are non-GCB and approximately 40% are GCB. We estimate that approximately 20% of GCB DLBCL tumors carry an EZH2 activating mutation, representing an annual drug-treated relapsed or refractory population of approximately 1,700 patients in the United States and EU5.

We estimate that the number of FL patients in the United States and EU5 that receive treatment in any year is approximately 25,000 front line patients and 18,000 relapsed/refractory patients. We estimate that approximately 20% of FL tumors carry an EZH2 activating mutation, representing an annual drug-treated relapsed or refractory

Table of Contents

population of approximately 3,600 patients in the United States and EU5. Common treatments for both DLBCL and FL include multi-agent chemotherapy, usually combined with rituximab (Rituxan), including R-CHOP, 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. 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. FL is generally considered to be incurable with existing therapies.

Preclinical Studies NHL. In preclinical development, tazemetostat demonstrated *in vitro* and *in vivo* activity in both mutant and wild-type EZH2 NHL. EZH2 is the catalytic subunit of the PRC2 chromatin remodeling complex, and activating mutations led to increased trimethylation of H3K27, a PRC2 substrate, and subsequent oncogenic repression of gene transcription. Consistent with this mechanism, *in vivo* mouse studies demonstrated drug efficacy and durability of response in EZH2-mutant NHL models treated with tazemetostat. Our preclinical studies with wild-type EZH2 lymphoma cells suggest that EZH2 acts as a key regulator of B-cell maturation, and therefore germinal center lymphomas are also likely to depend on EZH2 activity. We believe this hypothesis is supported by cumulative preclinical data with EZH2 inhibitors, and preclinical models demonstrating synergy of tazemetostat with B-cell signaling inhibitors, indicating that tazemetostat induces a cell fate decision.

Tazemetostat NHL Clinical Program

We are executing a broad clinical development program for tazemetostat as both a monotherapy and combination treatment in relapsed/refractory and front-line NHL, as summarized below.

Tazemetostat Monotherapy Clinical Trials for NHL

Interim results from our Phase 1 study in patients with relapsed or refractory NHL or advanced solid tumors, including efficacy results for 21 NHL patients and safety results from the entire study population of 45 patients, including patients with advanced solid tumors, were reported at the 2015 ASH Annual Meeting.

Table of Contents

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 who 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 FL, and in DLBCL, in patients with wild-type EZH2 and mutant EZH2. All patients with FL in the Phase 1 study had wild-type EZH2.

- Eight of 16 response-evaluable NHL patients achieved an objective response.

- The 800 mg twice daily dose showed superior tolerability, equivalent anti-tumor activity and equivalent pharmacodynamic activity as compared to the 1600 mg twice daily 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.

In addition, at the American Society of Hematology Meeting on Lymphoma Biology, or ASH Lymphoma, in June 2016, we presented an update on the patients with relapsed or refractory NHL in our Phase 1 study of tazemetostat. As of the data cutoff date of May 27, 2016, three patients with NHL remained on study, all with CRs, including one patient whose response evolved from PR to CR at 22 months.

Based on the Phase 1 results, we are evaluating tazemetostat in a global five-arm Phase 2 study in up to 270 patients with relapsed or refractory NHL across five cohorts. Patients are dosed at 800 mg twice daily with tablets taken orally. The three arms enrolling patients with DLBCL are enrolling 60 patients each, and the two arms enrolling patients with FL are enrolling 45 patients each. The study cohorts are as follows:

- DLBCL with Germinal Center B-cell, or GCB, subtype and EZH2 mutations;

- DLBCL with GCB subtype and wild-type EZH2;

- DLBCL with non-GCB subtype;

FL with EZH2 mutations; and

FL with wild-type EZHZ2.

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.

In June 2016, also at ASH Lymphoma, we presented interim data from this ongoing, global, registration supporting five-arm Phase 2 study of tazemetostat in patients with relapsed or refractory NHL. The presentation represented an early evaluation of the data, as the study was less than one-third enrolled as of the data cutoff date of May 27, 2016, with many patients still on treatment. Tazemetostat was generally well tolerated and demonstrated clinical activity consisting of objective responses in a heavily pre-treated patient population.

As of the data cutoff date of May 27, 2016, 82 patients across all five study arms were evaluable for safety. Efficacy was assessed on 47 evaluable patients from the four cohorts that had surpassed their pre-specified futility hurdles as of the data cutoff date. The non-evaluable patients included 16 patients in the arms that had surpassed futility but were too early for efficacy evaluation or for whom data were not yet entered and 19 patients from the FL with wild-type EZH2 cohort, which surpassed its pre-specified futility hurdle later in 2016.

Table of Contents

Tazemetostat was generally well tolerated in the overall patient population, consistent with the experience observed in the Phase 1 trial. The majority of adverse events were grade 1 or grade 2 within the 82 safety-evaluable patients. The most common treatment-related adverse events (greater than or equal to 5%) were nausea, asthenia, thrombocytopenia, neutropenia and fatigue, of which seven were grade 3 or higher. All adverse events resulted in low rates of both dose reductions (4%) and dose discontinuations (6%).

Among the 47 efficacy-evaluable patients, objective responses, which consist of either a CR or a PR were observed. In addition, SD was also observed in a significant percentage of patients. In the Phase 1 experience, Epizyme observed responses that evolved over time from SD, to a PR, and ultimately to a CR. As of the data cutoff, best responses across the four cohorts were as follows:

DLBCL with GCB subtype and EZH2 mutations (n=5): one PR and two SD;

DLBCL with GCB subtype and wild-type EZH2 (n=19): two CRs, one PR and six SD;

DLBCL with non-GCB subtype (n=20): two CRs, four PRs and five SD; and,

FL with EZH2 mutations (n=3): three PRs.

All of the patients who had achieved a CR and the majority of patients who had achieved a PR or SD as best response were still on tazemetostat treatment as of the data cutoff date.

Patients in the Phase 2 trial design are assigned to each cohort based on their cell of origin and EZH2 mutational status. Per the protocol, the cell of origin classification was originally conducted according to a test known as the Hans algorithm. Subsequently, we evaluated cell of origin in the patients in the Phase 2 study using the newer and more accurate cell of origin classifier, Nanostring s Lymph2Cx test, or Nanostring. Using Nanostring, we reclassified two patients from the non-GCB DLBCL arm with PRs to the GCB DLBCL arm with EZH2 mutation. Utilizing the same data set presented at ASH Lymphoma and the cell of origin determination by Nanostring, the efficacy evaluation by cohort changes as follows:

DLBCL with EZH2 mutations (n=7): three PR and two SD, or 43% overall response rate;

DLBCL with wild-type EZH2 (n=35): four CRs, three PR and ten SD, or 20% overall response rate;

FL with EZH2 mutations (n=3): three PRs, or 100% overall response rate.

The revised efficacy evaluation under Nanostring does not include two patients, one with SD and one with progressive disease as best response, previously reported as DLBCL with wild-type EZH2, who will be reassessed based on circulating tumor DNA. As of March 1, 2017, we had completed enrollment in the three arms of the study with wild-type DLBCL and FL. We are continuing to enroll the two remaining arms for GCB DLBCL and FL patients with EZH2 mutations. Pending abstract submission and acceptance, we plan to present interim data from the ongoing

five-arm Phase 2 NHL study at the International Conference on Malignant Lymphoma, or ICML, in Lugano, Switzerland in June 2017.

In November 2016, we received Fast Track designation from the FDA for DLBCL patients with EZH2 mutations. Within the NHL market, we believe DLBCL and FL patients whose tumors contain activating EZH2 mutations may represent the fastest path to NDA submission and commercial launch for tazemetostat.

Tazemetostat Combination Clinical Trials for NHL

In addition to evaluating tazemetostat as a monotherapy, we are investigating the combination of tazemetostat with other cancer agents in both the relapsed/refractory and front-line settings.

Tecentriq. Based on preclinical evidence showing that EZH2 inhibition may enhance the activity of checkpoint inhibitors, we entered into a collaboration agreement with Genentech to conduct a global Phase 1b study combining tazemetostat with Tecentriq, the first FDA approved PD-L1 inhibitor. The

Table of Contents

global study was initiated in the fourth quarter of 2016 and is being conducted by Genentech. The study will enroll approximately 45 patients with relapsed or refractory DLBCL. Primary endpoints in the trial include safety and combination tolerability with the objective of establishing a recommended Phase 2 dose. Secondary and exploratory endpoints include overall response, objective response, duration of response, pharmacokinetics and preliminary biomarker assessment.

R-CHOP. We are studying tazemetostat in combination with R-CHOP, the current standard of care for newly-diagnosed patients with DLBCL, in collaboration with LYSA. We have generated preclinical data showing synergy between tazemetostat and the chemotherapy and steroid components of R-CHOP. This multi-center Phase 1b/2 study in front-line, elderly high-risk patients with DLBCL will enroll up to 133 patients. Primary endpoints in the trial include CR rate as well as safety and tolerability of the combination. Secondary endpoints include overall response rate and progression free survival. The trial was initiated in the fourth quarter of 2016.

Prednisolone. In March 2017, we opened an additional arm of our ongoing Phase 2 NHL study to investigate tazemetostat in combination with prednisolone for patients with relapsed or refractory DLBCL. We determined to conduct this combination trial based on substantial preclinical synergy data with prednisolone, a standard agent in a variety of NHL treatment regimens, including R-CHOP. The objective of this new arm of the ongoing Phase 2 NHL study is to evaluate the clinical synergy of the agents and to explore the potential of prednisolone to slow progression in patients with aggressive disease.

FL combination. We have seen extensive preclinical synergy of tazemetostat with a number of targeted agents and chemotherapies used for, or in development for the treatment of, FL. We plan to initiate a combination study of tazemetostat with one or more of these agents in 2017.

DOT1L Cancers

Background on DOT1L Cancers. DOT1L is an HMT that can become oncogenic and cause certain subtypes of acute leukemia, such as 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%. 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 histone 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 leukemia. 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.

Pinometostat DOT1L Inhibitor

We are developing pinometostat as an intravenously administered small molecule inhibitor of DOT1L for the treatment of acute leukemias with alterations in the mixed lineage leukemia, or MLL, gene, specifically rearrangements of MLL as a consequence of chromosomal translocation, referred to as MLL-r, which includes partial tandem duplications of the MLL gene, referred to as MLL-PTD. We invented pinometostat using our proprietary product platform.

Table of Contents

Under the CRADA that we entered with the NCI in October 2016 for pinometostat, the NCI has agreed to evaluate the safety and efficacy of pinometostat in patients with acute leukemias. Initial studies will evaluate the combination of pinometostat with standard-of-care therapies or targeted agents in acute myeloid leukemia, acute lymphoid leukemia, or MLL-r. As part of the agreement, additional clinical trials will be considered. NCI will predominantly fund the studies and manage study operations.

We and Celgene are exploring in preclinical studies combinations of pinometostat with other anti-cancer agents to enhance pinometostat s efficacy in the adult MLL-r population. We retain all U.S. rights to pinometostat and have granted Celgene an exclusive license to pinometostat outside of the United States. Pinometostat has been granted orphan drug designation by the FDA and the European Commission for the treatment of acute myeloid leukemia, or AML, and acute lymphoblastic leukemia, or ALL.

Previously, we conducted a Phase 1 study in 51 adults with MLL-r and a Phase 1 study in 18 children with MLL-r. Although two patients in the adult study experienced CRs, we did not see sufficient activity to justify continuing development of pinometostat as a monotherapy in this indication.

Other Pipeline Programs

In addition to tazemetostat and pinometostat, 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 malignancies and solid tumors.

Under our collaboration with GSK, GSK is developing small molecule inhibitors against three novel HMT targets, which were discovered by us using our proprietary drug discovery platform. In September 2016, GSK advanced the first of these three programs into clinical testing. This drug candidate, GSK3326595, a PRMT5 inhibitor, is being tested in a Phase 1 clinical trial in patients with solid tumors and NHL. GSK has worldwide rights to the inhibitors of the three HMT targets that we delivered to them under the collaboration.

Under our collaboration with Celgene, we are developing small molecule inhibitors directed to three 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 inhibitors directed at the third target in the United States.

In addition to tazemetostat, pinometostat and our partnered programs, we have ongoing drug discovery programs directed to multiple other novel CMP targets. We own all development and commercialization rights to these programs.

The Epizyme Discovery Platform

Targeting oncogenic CMPs affords us multiple opportunities to create, develop and commercialize novel, precision therapeutics. To realize the full breadth of this opportunity, we created and continue to expand and enhance our proprietary discovery platform. Our platform aims to optimize the effectiveness of drug discovery and development by creatively addressing four key components of the process:

Judicious Target Selection. Selection of an appropriate target is a critical and challenging aspect of drug discovery. We are meeting the challenges of target selection with a unique combination of novel, optimized approaches to CRISPR technology, proprietary chemical biology methods and cellular and organismal biology

16

approaches that allow us to rigorously and rapidly test targeting hypotheses. Our selection of a target CMP for drug discovery generally requires five critical elements to be satisfied. The target must:

- Be a causal driver of pathogenicity and/or represent a unique vulnerability to therapeutic intervention, thus creating a basis for a wide therapeutic index;
- Offer a strategy for patient stratification;
- Be amenable to inhibition by a small molecule by virtue of the target s molecular structure, and small molecule inhibition of the target must be disease modifying;
- Address a significant unmet medical need for patients; and
- Represent a meaningful commercial opportunity.

With respect to the first two of these elements, a common approach in drug discovery is to develop a small molecule drug candidate against a target which itself contains a genetic lesion that causes disease. This is exemplified among the CMPs by gain-of-function mutations within the HMT target EZH2 in subsets of germinal center lymphoma patients. However, through our combined functional genomics and chemical biology approaches, we have also revealed previously unrecognized synthetic lethal relationships affecting CMPs, wherein a genetic lesion that occurs at an unrelated gene product (protein) creates a unique dependency of a disease cell on the enzymatic activity of the CMP. This provides a novel approach to developing small molecule drugs that impact genetic lesions that were generally considered not amenable to drug development. For example, we have observed several cases in which pathogenic loss-of-function genetic lesions at one protein creates a unique reliance of a disease state on the enzymatic activity of a seemingly unrelated CMP, which can then be targeted for small molecule drug therapy. One example of this is the way in which INI deletions render certain cells sensitive to EZH2 inhibition.

Deep Understanding of Target Biochemistry and Biology in the Context of Pathophysiology. Once a target is selected, we invest heavily in understanding the biochemistry and biology of that target in the context of cellular pathophysiology. Knowing how a CMP functions in the cell(s) of interest, details of its catalytic mechanism, which ancillary proteins bind to the target within the cell and impact activity, and its pattern of substrate utilization, all contribute importantly to our ability to create relevant biochemical and cellular assays for compound screening and evaluation.

Comprehensive Molecular Discovery. We take a broad approach to drug discovery that includes an early emphasis on optimization of compounds by evaluating them against multiple criteria. Rather than focusing exclusively on target potency, we evaluate our chemical leads for a spectrum of pharmacological properties at an early point in the drug discovery process. Compounds are simultaneously optimized for target and cellular potency, drug-target residence time, drug metabolism and pharmacokinetics, or DMPK properties, and oral bioavailability. To accomplish this, we integrate a number of molecular science skill bases, together with biological sciences, to form comprehensive matrix discovery teams. These include: medicinal chemistry, enzymology, structural biology, biochemistry and biophysics and preclinical DMPK. We have also applied of comprehensive molecular discovery approach not only to individual targets, but also to target classes, such as the HMTs, through our cross-screening paradigm. As a result, we have

created a proprietary library of CMP-targeted compounds that today numbers over 35,000 compounds. We have also facilitated drug discovery by solving the co-crystal structures of over 800 CMPs in complex with our small molecule inhibitors. This has allowed us to develop a deep understanding of target class medicinal chemistry and has resulted in the creation of novel chemical starting points for targeted discovery programs.

Early Integration of Preclinical and Clinical Development. We involve our preclinical and clinical teams early in the drug discovery process. We engage our clinicians and translational medicine experts during the target selection process to ensure that informed decisions are being made with respect to our five key elements of target selection. These researchers continue to participate in the program matrix teams to ensure early development of cogent approaches to clinical translation and development. For example, a clear understanding of patient

Table of Contents

population and their needs with respect to route of administration, dosing form, and dosing schedule, informs team decisions with respect to multi-parametric pharmacological optimization of lead compounds. Likewise, expertise in chemistry, manufacturing and controls, or CMC, and safety assessment are engaged early in the discovery process to ensure successful transition of compounds from discovery through clinical evaluation.

We believe that our discovery platform provides us with an important competitive advantage in identifying pathogenic CMPs and creating novel precision therapeutics to treat the diseases caused by these CMPs.

Collaborations

We have entered into several key strategic collaborations. These therapeutic collaborations have provided us with $207.8 million in non-equity funding through December 31, 2016. Our Celgene and GSK collaborations provide us with the potential for significant research, development, regulatory and sales-based milestone payments as well as royalties or profit sharing on net product sales. Our Celgene collaboration also provides us with development co-funding. In addition, we have entered into a collaboration to develop a companion diagnostic with Roche Molecular. Key terms of these collaborations are summarized below.

Celgene

Overview. In July 2015, we entered into an amendment and restatement of our collaboration and license agreement dated April 2012 with Celgene. Under the original agreement, we granted Celgene an exclusive license, for all countries other than the United States, to small molecule HMT inhibitors targeting DOT1L, including pinometostat, and an option, on a target-by-target basis, to exclusively license, for all countries other than the United States, rights to small molecule HMT inhibitors targeting any other HMT targets, excluding EZH2 and targets covered by our collaboration and license agreement dated January 8, 2011 with GSK. Under the original agreement, Celgene s option was exercisable during an option period that would have expired in July 2015. Under the amended and restated collaboration and license agreement:

Celgene retains its exclusive license to small molecule HMT inhibitors targeting DOT1L, including pinometostat,

Celgene s option rights have been narrowed to HMT inhibitors targeting three predefined targets (the Option Targets),

The exclusive licenses to HMT inhibitors targeting two of the Option Targets that Celgene may acquire have been expanded to include the United States, with the exclusive license to the third Option Target continuing to be for all countries other than the United States,

Celgene s option period has been extended for each of the Option Targets and is exercisable at the time of our investigational new drug, or IND, filing for an HMT inhibitor targeting the applicable Option Target, upon the payment by Celgene at such time of a pre-specified development milestone-based license payment,

Celgene s license may be maintained beyond the end of Phase 1 clinical development for each of the Option Targets, upon payment by Celgene at such time of a pre-specified development milestone-based license payment, and

Our research and development obligations with respect to each Option Target under the amended agreement have been extended for at least an additional three years, subject to Celgene exercising its option with respect to such Option Target at IND filing. Subject to our Opt-Out rights described below, our research and development obligations have been expanded to include the completion of a Phase 1 clinical trial as to each Option Target following Celgene s exercise of its option at IND filing.

To date, we have received $75.0 million of upfront payments (including $10.0 million as part of the amended and restated agreement) and $25.0 million from the sale of our series C preferred stock to an affiliate of Celgene, of

Table of Contents

which $3.0 million was considered a premium and included as collaboration arrangement consideration for a total upfront payment of $78.0 million. In addition, we have received a $25.0 million clinical development milestone payment in 2014 and $7.0 million of global development co-funding through December 31, 2016. We are eligible to earn up to $75.0 million in development milestones and license payments, up to $365.0 million in regulatory milestone payments and up to $170.0 million in sales milestone payments related to the Option Targets. We remain eligible to earn $35.0 million in an additional clinical development milestone payment and up to $100.0 million in regulatory milestone payments related to DOT1L.

We are also eligible to receive royalties as follows:

- As to DOT1L, we retain all product rights in the United States and are eligible to receive royalties at defined percentages ranging from the mid-single digits to the mid-teens on annual net product sales outside of the United States, subject to reductions in specified circumstances;

- As to the Option Target for which Celgene s option rights do not include the United States, if Celgene exercises its option as to such Option Target, we will retain all product rights in the United States and will be eligible to receive royalties, once an initial threshold of net product sales (for which we will not receive royalties) is exceeded, at defined percentages ranging from the mid-single digits to the low-double digits on net product sales outside of the United States, subject to reductions in specified circumstances; and

- As to the other two Option Targets, if Celgene exercises its option as to those Option Targets, we will be eligible to receive royalties, once an initial threshold of net product sales (for which we will not receive royalties) is exceeded, for each such Option Target at defined percentages ranging from the mid-single digits to the low-double digits on net product sales on a worldwide basis, subject to reductions in specified circumstances.

For DOT1L and, after Celgene s payment of the specified IND filing license payment for each Option Target, for each such Option Target, we are responsible for the conduct and funding of Phase 1 clinical trials, subject to our right to opt-out of such responsibilities as described below. Celgene may obtain a license to small molecule HMT inhibitors targeting each Option Target at the time of our IND filing for an HMT inhibitor for such target by exercising its option and paying us a specified license payment. Celgene may maintain its license with respect to an Option Target at the conclusion of the Phase 1 clinical trial of the Option Target by paying us a specified additional license payment. If Celgene does not elect to obtain a license during the option exercise period applicable to an Option Target, or to pay the specified IND license payment or end of Phase 1 license payment, we will retain worldwide rights to HMT inhibitors directed to the Option Target, other than HMT inhibitors that may be provided by Celgene if we were to agree to their introduction into the collaboration.

Research Obligations. We are primarily responsible for the research strategy under the collaboration. During each applicable option period we are required to use commercially reasonable efforts to carry out an agreed research plan for each Option Target, subject to our Opt-Out right described below. For the DOT1L target and each of the Option Targets, we are required to conduct and solely fund development costs of the Phase 1 clinical trials for HMT inhibitors directed to such targets, including for pinometostat. After completion of Phase 1 development, as to DOT1L and the Option Target for which we retain U.S. rights, we and Celgene will equally co-fund global development and each party will solely fund territory-specific development costs for its territory; and, as to the other two Option Targets, after completion of Phase 1 development, Celgene will solely fund all development costs on a worldwide

basis.

Governance. Our collaboration with Celgene is guided by (a) a joint research committee, with authority over all activities performed under the research plan with respect to the two Option Targets as to which we granted worldwide rights; (b) a joint development committee, with authority over shared development activities with respect to DOT1L and the Option Target for which we retain U.S. rights; and (c) a joint commercialization committee, with authority over the commercialization of products developed under shared development

Table of Contents

programs with respect to DOT1L and the Option Target for which we retain U.S. rights. Subject to limitations specified in the amended and restated 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 (a) prior to Celgene s exercise of its option, we generally have final decision-making authority over research and development matters with respect to the Option Targets; (b) with respect to DOT1L and any Option Targets for which Celgene has exercised its option, 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, and except that with respect to the Option Target for which we retain U.S. rights, the parties have mutual decision-making authority even after Celgene exercises its option as long as Celgene engages in a competitive development program with respect to such Option Target. Each party has final decision-making authority over commercialization matters in its respective territory.

Opt-Out Right. On an Option Target-by-Option Target basis, we have the right, in our sole discretion, to opt-out of further participation in any research and/or development activities after completion of the initial research plan and prior to the filing of an IND for an HMT inhibitor directed to the applicable Option Target, or the Pre-IND Opt-Out. Following exercise of a Pre-IND Opt-Out, if Celgene exercises its option as to the Option Target, Celgene will no longer be required, to the extent not already paid, to make the specified IND license payment or end of Phase 1 license payment to us, specified sales milestone payments will no longer be payable and all royalties on net product sales of applicable licensed products that become payable to us will be reduced by a specified percentage. Additionally, if Celgene exercises its option as to such Option Target, we are obligated to grant Celgene an exclusive worldwide license to HMT inhibitors directed to the applicable Option Target, even if we would otherwise retain U.S. rights to HMT inhibitors directed to the applicable Option Target. Additionally, on a licensed program-by-licensed program 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 licensed program opt-out right at specified times: (a) when the clinical trial stopping rules set forth in a clinical trial protocol for DOT1L or the Option Target for which the we retain U.S. rights dictate that such clinical trial be stopped, or the Post-EOP1 Clinical Opt-Out; or (b) for any or no reason, in a licensed program for DOT1L or the Option Target for which we retain U.S. rights, during specified periods before the scheduled initiation of the first pivotal clinical trial or before the estimated date of filing of the first NDA for an HMT inhibitor directed to the licensed target or any time after regulatory approval of an HMT inhibitor directed to the licensed target, or the Late Stage Opt-Out. In the event of a Post-EOP1 Clinical Opt-Out, the royalties that become payable to us on net product sales of licensed products directed to DOT1L or the Option Target for which we retain U.S. rights, as applicable, will be reduced by a specified percentage. Following a Post-EOP1 Clinical Opt-Out or a Late Stage 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 exercise of a Post-EOP1 Clinical Opt-Out or a Late Stage 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.

Exclusivity Restrictions. Subject to exceptions specified in the amended agreement, during the option period, we may not research, develop or commercialize HMT inhibitors directed to DOT1L and the three Option Targets. Subject to exceptions specified in the amended agreement, following each applicable option period, we may not research, develop or commercialize HMT inhibitors directed to DOT1L or any target licensed by Celgene.

Right of First Negotiation. The amended and restated agreement eliminated the right of first negotiation that we had previously granted to Celgene under the original agreement with respect to business combination transactions that we

may desire to pursue with third parties.

Table of Contents

Term and Termination. The amended and restated 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 amended agreement in its entirety, upon 60 or 120 days notice depending on the timing of such termination. The amended 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 amended 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.

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. In March 2014, we and GSK amended certain terms of this agreement for the third target, revising the license terms with respect to candidate compounds and amending the corresponding financial terms, including reallocating milestone payments and increasing royalty rates as to the third target. 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 ended January 8, 2015, or earlier if selection of a development candidate occurred.

Under the agreement, we recorded a $20.0 million upfront payment, a $3.0 million payment upon the execution of the March 2014 agreement amendment, $6.0 million of fixed research funding, $15.0 million of preclinical research and development milestone payments and $9.0 million for research and development services. In addition, in the third quarter of 2016, we recognized a $6.0 million clinical milestone following GSK s initiation of patient dosing in a Phase 1 clinical trial of a PRMT5 inhibitor that we discovered and licensed to GSK. We are eligible to receive up to $18.0 million in additional preclinical research and development milestone payments, up to $103.0 million in clinical development milestone payments, up to $278.0 million in regulatory milestone payments and up to $218.0 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 reduction in specified circumstances.

For each selected target in the collaboration, we were primarily responsible for research until the earlier of selection of a development candidate for the target or January 8, 2015, 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 was 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 conducted in the fourth year of the research term. In December 2013, we and GSK agreed to the selection of a development candidate for an inhibitor of PRMT5, one of the three targets under the agreement, after which point GSK became 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.

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

Table of Contents

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.

Eisai

Overview. In March 2015, we entered into an amended and restated collaboration and license agreement with Eisai, under which we reacquired worldwide rights, excluding Japan, to our EZH2 program, including tazemetostat. Under the amended and restated collaboration and license agreement, we will be responsible for global development, manufacturing and commercialization outside of Japan of tazemetostat and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture tazemetostat and any other EZH2 product candidates in Japan. Under the original collaboration and license agreement, we had granted Eisai an exclusive worldwide license to our small molecule HMT inhibitors directed to EZH2, including tazemetostat, 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 original agreement, we recorded a $3.0 million upfront payment, $7.0 million in preclinical research and development milestone payments, a $6.0 million clinical development milestone and $22.7 million for research and development services through December 31, 2014. We were also eligible to earn up to a total of $195.0 million in clinical development, regulatory and sales-based milestone payments and to receive royalties on product sales. Upon the execution of the amended and restated collaboration agreement in March 2015, we agreed to pay Eisai a $40.0 million upfront payment. We also agreed to pay Eisai up to $20.0 million in clinical development milestone payments, up to $50.0 million in regulatory milestone payments and royalties at a percentage in the mid-teens on worldwide net sales of any EZH2 product, excluding net sales in Japan. We are eligible to receive from Eisai royalties at a percentage in the mid-teens on net sales of any EZH2 product in Japan.

Under the original agreement, Eisai was solely responsible for funding all research, development and commercialization costs for licensed compounds. Under the amended agreement, we are solely responsible for funding global development, manufacturing and commercialization costs for EZH2 compounds outside of Japan, and Eisai is solely responsible for funding Japan-specific development and commercialization costs for EZH2 compounds. In connection with the amendment and restatement of our collaboration and license agreement with Eisai, we and Eisai agreed to the transition to us of ongoing development and manufacturing activities that were being conducted by or on behalf of Eisai. In January 2017, as part of Eisai s obligations under the amended and restated collaboration agreement, Eisai enrolled and dosed the first patient in a Phase 1 study of tazemetostat in patients with relapsed or refractory B-cell NHL in Japan.

In the event that we seek to license rights to a third party to develop or commercialize an EZH2 product in any country in Asia other than Japan, Eisai has a limited right of first negotiation for such rights. In the event that we are awarded a priority review voucher from the FDA with respect to an EZH2 product, Eisai is entitled to specified compensation if we use the voucher on a non-EZH2 program or sell the voucher to a third party.

Governance. Under the amended and restated collaboration and license agreement, development will be guided by a joint steering committee, with Epizyme retaining final decision making authority with respect to global development.

***Exclusivity Restrictions*.** Subject to exceptions specified in the agreement, for an exclusivity period extending until eight years after the first commercial sale of a product covered by the agreement, neither we nor Eisai may 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 expiration of all payment obligations under the agreement with respect to all licensed products. The royalty term for each licensed product in each country commences on the first commercial sale of the applicable licensed product in the applicable country and ends on the latest of expiration of specified patent coverage, expiration of specified regulatory exclusivity or ten years following the first commercial sale. We or Eisai may terminate the agreement for convenience as to our respective territories, upon 90 days prior written notice. The agreement will also terminate as to our territory if we cease all development and commercialization activities for the United States and specified major countries in Europe and as to Eisai s territory if Eisai ceases all development and commercialization activities for Japan. 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. If we terminate the agreement for our convenience, the agreement terminates as a result of our cessation of development and commercialization activities or Eisai terminates the agreement for our uncured material breach, Eisai may elect to have worldwide development and commercialization rights revert to Eisai, and if Eisai so elects, Eisai will be required to pay us specified royalties on net sales of the licensed products and reimburse certain development expenses incurred by us. If Eisai terminates the agreement for its convenience, the agreement terminates as a result of Eisai s cessation of development and commercialization activities or we terminate the agreement for Eisai s uncured material breach or Eisai s, or its affiliate s or sublicensee s, participation in, or assistance with, an action or proceeding challenging or denying the validity of one of our patents, Japanese development and commercialization rights to the licensed products revert to us, and we will be required to pay Eisai specified royalties on net sales of licensed products in Japan.

LYSA

In May 2016, we entered into a collaboration agreement with the Lymphoma Academic Research Organization, or LYSARC, to conduct a combination trial of tazemetostat with R-CHOP. LYSARC is the operational arm of LYSA, a premier cooperative group in France dedicated to clinical and translational research for lymphoma. This multi-center Phase 1b/2 study is evaluating tazemetostat in combination with R-CHOP, as a front-line treatment in elderly, high-risk patients with DLBCL and is being sponsored by LYSARC. LYSA is managing the study operations for the trial, and we are recognizing our share of the related expenses as those costs are incurred over the duration of the trial. The study was initiated in December 2016.

Genentech

In June 2016, we entered into a collaboration agreement with Genentech, a member of the Roche Group, to conduct a Phase 1b clinical trial to investigate the anti-cancer effects of tazemetostat and Genentech s Tecentriq (atezolizumab), when used in combination. The trial will evaluate this combination regimen for the treatment of patients with relapsed or refractory DLBCL. Under the agreement, each company will supply its respective anti-cancer agent to support the trial and share equally in the trial costs. Genentech is managing the study operations for the trial, and we are recognizing our share of the related expenses as those costs are incurred over the duration of the trial. The study was initiated in December 2016.

Companion Diagnostics

Roche Molecular

In December 2012, Eisai and we entered into an agreement with Roche Molecular under which Eisai and we engaged Roche Molecular to develop a companion diagnostic to identify patients who possess certain point mutations of EZH2. In October 2013, this agreement was amended to include additional point mutations in EZH2. The $21.5

million of development costs due under the amended agreement with Roche Molecular were the responsibility of Eisai until the execution of our amended and restated collaboration and license agreement with Eisai in March 2015, at which time we assumed responsibility for the remaining development costs due

Table of Contents

under the agreement. In December of 2015, we entered into the second amendment to the companion diagnostic agreement with Roche Molecular. As of December 31, 2016, we are responsible for the remaining development costs of $12.0 million due under the second amendment as of December 31, 2015. We expect the remaining development costs under the second amendment to be paid and incurred through 2019.

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

Our agreement with Roche Molecular will expire when we are no longer developing or commercializing tazemetostat. We may terminate the agreement by giving Roche Molecular 90 days written notice if we discontinue development and commercialization of tazemetostat or determine, in conjunction with Roche Molecular, that the companion diagnostic is not needed for use with tazemetostat. Either we or Roche Molecular 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 Molecular may become entitled to specified termination fees.

Intellectual Property

We strive to protect the proprietary compounds and 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 technologies, diagnostics and other inventions. Our patent portfolio is currently composed of over 200 issued patents and allowed patent applications and over 400 pending patent applications in the major pharmaceutical markets, that we own as well as license from other parties. 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.

We plan to continue to expand our intellectual property estate by filing patent applications directed to dosage forms, methods of treatment and additional CMP and 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 portfolios for our most advanced programs are summarized below.

EZH2. Our EZH2 patent portfolio includes U.S. Patent No. 8,410,088 covering the composition of matter of tazemetostat. This patent issued on April 2, 2013 and is expected to expire in 2032. Our EZH2 portfolio also includes 19 additional U.S. patents and more than 140 foreign patents, expected to expire between 2031 and 2034, not including extensions. The claims of these patents cover the composition of matter of EZH2 inhibitor compounds and various methods of their making and use. Patent applications in the same families as these patents are pending in a variety of worldwide jurisdictions, including the United States. The EZH2 program portfolio encompasses more than

35 patent families with pending patent applications relating to compositions of matter and methods of making and use of EZH2 inhibitors. The patent families in this portfolio are in various stages of prosecution and include patent applications filed in a variety of worldwide jurisdictions, including the

Table of Contents

United States; Patent Cooperation Treaty (PCT) applications that are eligible for filing in most worldwide jurisdictions, including the United States; and U.S. provisional applications that may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. Our patent applications in the EZH2 portfolio, if issued, would be expected to expire between 2031 and 2036.

DOT1L. Our DOT1L patent portfolio includes U.S. Patent No. 8,580,762 covering the composition of matter of pinometostat. The patent issued on November 12, 2013 and is expected to expire in 2032. Our DOT1L portfolio also includes seven additional U.S. patents and more than 30 foreign patents, expected to expire between 2031 and 2034, not including extensions. The DOT1L program portfolio encompasses more than fifteen patent families relating to compositions of matter of DOT1L inhibitor compounds and methods of their making and use. The patent families in this portfolio are in various stages of prosecution and include patent families with applications filed in a variety of worldwide jurisdictions including the United States; and PCT applications that are eligible for filing in most worldwide jurisdictions, including the United States. These patents and patent applications are wholly owned by us. Our patent applications in the DOT1L portfolio, if issued, would be expected to expire between 2031 and 2036.

Other Targets. We also have patent portfolios directed to targets other than EZH2 and DOT1L, including the HMT targets PRMT1, PRMT3, CARM1 (PRMT4), PRMT5, PRMT6, PRMT8, SMYD2 and SMYD3. These patent portfolios have more than 30 patent families directed to various product candidates with applications filed in the United States, PCT applications that are eligible for filing in most worldwide jurisdictions, including the United States, and U.S. provisional applications that may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. Patents, if issued in these portfolios are expected to expire between 2033 and 2036. For example, we have eight U.S. and a foreign patent that cover PRMT5 inhibitors and methods of their making and use. These patents are expected to expire in 2033, not including extensions.

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 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

Table of Contents

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.

Manufacturing

We do not have any manufacturing facilities and 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. Prior to the execution of the amended and restated collaboration and license agreement with Eisai, Eisai manufactured tazemetostat for preclinical and clinical development. Upon execution of the amended and restated collaboration and license agreement, as part of the transition plan, Eisai agreed to sell us its existing inventories and manufacture additional tazemetostat clinical supplies and the active pharmaceutical ingredient, or API. We took receipt of these API and clinical supplies from Eisai during the year ended December 31, 2015. We have entered into clinical supply agreements with three contract manufacturers, one to produce tazemetostat API and two to produce tazemetostat tablets. We intend to identify and qualify additional manufacturers to provide API, tablets and a pediatric formulation as part of our ongoing manufacturing efforts for tazemetostat. To date, we have obtained materials for pinometostat from multiple third party manufacturers.

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 any companion diagnostics. We are currently collaborating with Roche Molecular for a diagnostic for use with tazemetostat, and we expect to rely on Roche Molecular for the manufacture of the diagnostic it is developing. We may enter into similar agreements for the manufacture of other companion diagnostics.

Commercialization

We have recently begun to establish a commercial infrastructure in preparation for a potential future launch of tazemetostat. 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 other than for the product candidates under our GSK collaboration and two of the three targets under our Celgene collaboration.

Subject to receiving marketing approvals, we expect to commence commercialization activities by building an organization in the United States to sell our products. We believe that such an organization will be able to address the oncologists who are the key specialists in treating the patient populations for which our clinical stage product candidates are being developed. Outside the United States, we may choose to enter into distribution and other marketing arrangements with third parties for any of our product candidates that obtain marketing approval, or may choose to commercialize our products in certain markets, depending upon many factors, including the target market size, availability of reimbursement, and our financial resources at the time.

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 collaboration with Roche Molecular. We expect to coordinate closely with any diagnostic collaborators in connection with the marketing and sale of any 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,

Table of Contents

experience and scientific resources provide us with competitive advantages, we face potential 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. Companies that are developing new epigenetic treatments for cancer that target HMTs include GSK, Novartis AG, Pfizer, Inc., Merck & Co., Inc., Daiichi Sankyo Company Limited, Takeda Pharmaceutical Company Limited, AbbVie Inc., Bayer Schering Pharma AG and Constellation Pharmaceuticals. 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.

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 drugs 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.

Tazemetostat. The most common treatments for DLBCL and FL are chemotherapies, usually combined with the monoclonal antibody Rituxan, or more recently, in the case of FL, Gazyva, which is a next-generation antibody that acts against the same target as Rituxan. While Rituxan and number of other widely used anti-cancer agents are labeled either broadly for NHL or more narrowly for DLBCL or FL, no therapies are approved specifically for the treatment of tumors associated with EZH2 activating mutations. Additionally, no therapies are approved specifically for the treatment of INI1- and SMARCA4-negative tumors. Several tumor histologies are represented in this molecularly defined group, such as epithelioid sarcoma, MRT, and MRTO. Epithelioid sarcoma is treated with surgical resection when it presents as localized disease. When epithelioid sarcoma recurs or metastasizes, it may be treated with systemic chemotherapy or investigational agents since there are no approved systemic therapies specifically indicated for this disease. Although there are no approved therapies for MRT, current treatment for these tumors consists of intensive chemotherapy with or without radiation therapy. MRTO is an aggressive tumor with a poor prognosis that is generally treated with surgery and platinum-based combination chemotherapy at diagnosis. Mesothelioma is typically treated with cisplatin and pemetrexed chemotherapy in the front line setting. There are no established salvage treatments for patients with epithelioid sarcoma, MRT, MRTO, or mesothelioma who relapse or who are refractory to front line treatment.

Pinometostat. There are no approved therapies specifically indicated for MLL-r. There are, however, currently approved therapies for acute lymphoblastic leukemias, or ALL and acute myeloblastic leukemias, or AML, in general. The current standard of care differs according to 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 may receive an allogeneic stem cell transplant.

Research and Development Expenses

For the years ended December 31, 2016, 2015 and 2014, we incurred approximately $91.5 million, $111.2 million, and $75.6 million, respectively, on research and development activities.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries and foreign jurisdictions, including the European Union, 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. 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 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.

28

Table of Contents

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;
- 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;
- 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;
- payment of user fees per published Prescription Drug User Fee Act, or PDUFA, guidelines for that year;
- FDA review and approval of the NDA; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

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 the ClinicalTrials.gov website.

Human clinical trials are typically conducted in four 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

Table of Contents

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. In Phase 4, post-approval studies may be conducted to gain additional experience from the treatment of patients in the intended therapeutic indication.

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, Phase 3 and Phase 4 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.

In general, the FDA accepts foreign safety and efficacy studies that were not conducted under an IND provided that they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. The conduct of these studies must meet at least minimum standards for assuring human subject protection. Therefore, for studies submitted in support of an NDA that were conducted outside the United States and not under an IND, the agency requires demonstration that such studies were conducted in accordance with Good Clinical Practices.

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 is subject to a substantial application user fee. For the federal fiscal year 2017, the application user fee is $2.0 million. The sponsor of an approved NDA is also subject to annual product and establishment user fees, which for fiscal year 2017 are $98,000 per product and $512,000 per establishment. Under 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 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

Table of Contents

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.

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

Table of Contents

provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. For Fast Track products, sponsors may have greater interactions with the FDA regarding drug development and may submit sections of a Fast Track product s NDA before the application is complete.

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.

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 guidance that addresses issues critical to developing *in vitro* companion diagnostics, such as when the FDA will require that the diagnostic and the drug be approved simultaneously. The guidance issued in August 2014 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 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 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.

Table of Contents

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device s safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee, which exceeds $250,000 for most PMAs.

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;
- fines, warning letters or holds on post-approval clinical trials;
- 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.

Table of Contents

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

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.

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 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.

Table of Contents

We may also 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.

In addition, federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, require certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. 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 in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures

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 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 changed the way healthcare is financed by both governmental and private insurers. Among the provisions of the Affordable Care Act of importance to potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government

healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;

Table of Contents

expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer s Medicaid rebate liability;

expanded manufacturers rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of average manufacturer price, or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;

addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;

expanded the types of entities eligible for the 340B drug discount program;

established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers outpatient drugs to be covered under Medicare Part D;

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

the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has been not been clearly defined. PPACA provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and

established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 became law, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations

period for the government to recover overpayments to providers from three to five years. There have been recent public announcements by members of the U.S. Congress and the new presidential administration regarding their plans to repeal and replace the PPACA. However, it remains unclear how a repeal or replacement of current healthcare programs might affect our ability to sell our products and the prices we may obtain for any of our approved products.

Exclusivity and Approval of Competing Products

Patent Term Restoration and Extension. A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of a NDA, plus the time between the submission date of a NDA and the ultimate approval date. Patent term restoration cannot be used to

extend the remaining term of a patent past a total of 14 years from the product s approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

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.

A 505(b)(2) application applies to a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. As with an ANDA, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. 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 ANDAs and 505(b)(2) NDAs for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United 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.

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. We have been granted orphan drug designation in the United States and the European Union for pinometostat, and orphan drug designation in the United States for tazemetostat for the treatment of malignant rhabdoid tumors.

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.

39

Table of Contents

European Union Drug Approval Process

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. 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.

Clinical Trial Approval in the EU. Pursuant to the currently applicable Clinical Trials Directives, an applicant must obtain approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. In April 2014, the EU adopted a new Clinical Trials Regulation, which is set to replace the current Clinical Trials Directive. The new Clinical Trials Regulation will be directly applicable to and binding in all 28 EU Member States without the need for any national implementing legislation, and will become applicable no earlier than 28 May 2016. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial will be required to submit a single application for approval of a clinical trial to a reporting EU Member State (RMS) through an EU Portal. The submission procedure will be the same irrespective of whether the clinical trial is to be conducted in a single EU Member State or in more than one EU Member State. The Clinical Trials Regulation also aims to streamline and simplify the rules on safety reporting for clinical trials.

Marketing Authorization. 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 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 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

Table of Contents

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.

Data and Market Exclusivity. 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. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. 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.

Orphan Drug Exclusivity. 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.

Employees

As of March 1, 2017, we had 112 full-time employees, 76 of whom were primarily engaged in research and development activities and 71 of whom have an M.D. or Ph.D. degree.

Executive Officers of the Company

The following table sets forth the name, age and position of each of our executive officers as of March 1, 2017.

Name	Age	Position
Robert B. Bazemore	49	President, Chief Executive Officer and Director
Andrew E. Singer	46	Executive Vice President of Finance and Administration, Chief Financial Officer and Treasurer
Matthew E. Ros	50	Chief Operating Officer
Susan E. Graf	44	Chief Business Officer
Robert A. Copeland, Ph.D.	60	President of Research and Chief Scientific Officer
Peter T.C. Ho, M.D., Ph.D.	55	Chief Development Officer

Robert B. Bazemore has served as a director and our President and Chief Executive Officer since joining us in September 2015. Prior to joining us, from September 2014 to July 2015, Mr. Bazemore served as the Chief Operating Officer of Synageva BioPharma Corp., a biopharmaceutical company developing therapeutic products for rare disorders. Prior to joining Synageva, Mr. Bazemore served in increasing levels of responsibility at Johnson & Johnson, a healthcare company, including Vice President, Centocor Ortho Biotech Sales & Marketing

from 2008 to 2010, President of Janssen Biotech from March 2010 to October 2013 and Vice President of Global Surgery at Ethicon from October 2013 to September 2014. Prior to Johnson & Johnson, Mr. Bazemore worked at Merck & Co., Inc. for eleven years, where he served in a variety of roles in medical affairs, sales and marketing. Mr. Bazemore is a director of Ardelyx, Inc., a biopharmaceutical company. He received a B.S. in biochemistry from the University of Georgia.

Andrew E. Singer has served as our Executive Vice President of Finance and Administration, Chief Financial Officer and Treasurer since February 2015. Prior to joining us, from 2004 to January 2015, Mr. Singer served in increasing levels of responsibility in the Health Care Investment Banking Group at RBC Capital Markets Corporation, or RBC, an investment bank, serving as a Managing Director from 2007 to 2015. Prior to joining RBC, Mr. Singer worked at Petkevitch & Company, co-founded MVC Capital, and worked at Robertson, Stephens & Co, The Shansby Group and The Blackstone Group. Mr. Singer serves on the board of directors of the J.F. Kapnek Trust. Mr. Singer received a B.A. from Yale University and an M.B.A. from Harvard University Graduate School of Business.

Matthew E. Ros has served as our Chief Operating Officer since May 2016. Prior to joining us, from September 2010 to May 2016, Mr. Ros served in increasing levels of responsibility at Sanofi, a multinational pharmaceutical company, most recently as Chief Operating Officer/Global Head of the Oncology Business unit from December 2014 to May 2016. Prior to that role, Mr. Ros served in the rare disease business of Genzyme, a Sanofi company, where he served as Vice President and Franchise Head of its Pompe disease unit from September 2012 to December 2014. From October 2007 to June 2010, Mr. Ros served at ARIAD Pharmaceuticals, Inc., a global oncology company, most recently as Senior Vice President, Commercial Operations. He started his pharmaceutical career in Bristol-Myers Squibb s Oncology Division, serving in roles with increasing responsibility from 1990-2007. He received a B.S. from the State University of New York, College at Plattsburgh and completed the Executive Education Program in Finance and Accounting for the Non-Financial Manager at Wharton School of the University of Pennsylvania.

Susan E. Graf has served as our Chief Business Officer since April 2016. Prior to joining us, from May 2013 to March 2015, Ms. Graf served as the Vice President, Corporate Development and Strategy for NPS Pharma before it was acquired by Shire in 2015. Prior to joining NPS Pharma, Ms. Graf spent nearly18 years at Roche in a number of leadership and executive positions, including Global Head, Commercial Assessment and Due Diligence for Roche Partnering. Ms. Graf received a Bachelor of Pharmacy degree from Purdue University and an M.B.A. from the Stern School of Business at New York University.

Robert A. Copeland, Ph.D. has served as our President of Research and Chief Scientific Officer since January 2015 and previously served as our Executive Vice President and Chief Scientific Officer from September 2008 to January 2015. Prior to joining us, from January 2003 to September 2008, Dr. Copeland was Vice President, Cancer Biology, Oncology Center of Excellence in Drug Discovery, at GSK. 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.

Peter T.C. Ho, M.D., Ph.D. has served as our Chief Development Officer since September 2014. Prior to joining us, from February 2013 to September 2014, Dr. Ho served as Chief Executive Officer of Metastagen Inc., a pharmaceutical preparation company that he co-founded. Prior to that, Dr. Ho served as President of BeiGene Ltd., a biopharmaceutical company that he co-founded, from October 2010 to December 2012, as Vice President of Oncology Development at Johnson & Johnson from September 2008 to September 2010 and, prior to that, as Senior Vice President of the Oncology Center of Excellence for Drug Development at GSK. Dr. Ho is a board-certified pediatric hematologist/oncologist and was formerly a fellow at the Dana-Farber Cancer Institute, the National Cancer

Center Institute, or NCI, and the FDA. He received a B.A. in biology from the Johns Hopkins University and an M.D. and Ph.D. (pharmacology) from the Yale University School of Medicine.

Table of Contents

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. Our telephone number is (617) 229-5872, and our website is located at www.epizyme.com. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Annual Report on Form 10-K.

Available Information

Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, are available free of charge on our website located at www.epizyme.com as soon as reasonably practicable after they are electronically filed with or furnished to the SEC. These reports are also available at the SEC s Internet website at www.sec.gov. The public may also read and copy any materials filed with the SEC at the SEC s Public Reference Room at 100 F Street, N.E., Washington D.C. 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-SEC-0330.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are posted on our website, www.epizyme.com, under Investor Center and are available in print to any person who requests copies by contacting Epizyme by calling (617) 229-5872 or by writing to Epizyme, Inc., 400 Technology Square, Cambridge, Massachusetts 02139.

Item 1A. Risk Factors

Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K and in other documents that we file with the SEC, in evaluating our company and our business. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing our company. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition and results of operations.

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 patients with cancer and other diseases, 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 patients with cancer and other diseases 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 the CMPs where our research and development is principally focused. Although preclinical studies suggest that genetic alterations can result in changes to the activity of CMPs 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 our first three HMT inhibitors in the clinic are all the first molecules against these targets to enter clinical development. Therefore, we do not know if our approach of inhibiting HMTs or other CMPs to treat patients with cancer and other diseases will be successful.

Table of Contents

Our development efforts are ongoing and we have only two product candidates in clinical trials that we are developing, and one product candidate in clinical trials that has been licensed to GSK. 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.

Our development efforts are ongoing and we have only two product candidates in clinical trials that we are developing, tazemetostat and pinometostat. In addition, GSK has initiated a Phase 1 clinical trial for a PRMT5 inhibitor that it has licensed from us. 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 when anticipated or at all 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 and other diseases. 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.

Table of Contents

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.

Three of our product candidates are in clinical development, and our remaining product candidates are in preclinical development. Two of our product candidates in clinical development are being developed by us and the third product candidate is being developed by GSK. 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. As a result of these findings, coupled with our limited clinical experience in FL at the time of the IND submission in December 2015, we were unable to conduct our Phase 2 trial of tazemetostat in FL patients in the United States until the beginning of 2017. If we are unable to adequately address matters such as this when they arise, we may be unable to conduct clinical trials of our product candidates in the United States or in other countries, our trials may be limited to certain patient populations or our ability to conduct other trials in the United States or in other countries 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 CRs 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 in adults were not achieved by any other patient treated with pinometostat in the Phase 1 clinical trial. 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;
- 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;

preclinical testing may produce results based on which we may decide, or regulators may require us, to conduct additional preclinical studies before we proceed with certain clinical trials, limit the scope of our clinical trials, halt ongoing clinical trials or abandon product development programs;

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;

Table of Contents

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 or a risk evaluation mitigation strategy 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 may 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 certain of our products may be focused on specific patient populations, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. In addition, some of our competitors have ongoing clinical trials for product candidates that may treat the broader patient populations within which our product candidates are being developed for the treatment of a subset of identifiable patients with cancer and other diseases, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors product candidates. For instance, our ongoing clinical trials of tazemetostat in adult and pediatric patients with INI1-negative tumors are targeting rare patient populations. In addition, our Phase 2 clinical trial of tazemetostat in patients with NHL has two arms targeting patients with EZH2 activating mutations in their tumors, one in GCB DLBCL and one in FL. Based on the aggregate scientific literature, we believe that patients with these mutations represent approximately 20% of the total GCB DLBCL and FL population in the United States and other major reimbursable markets. In any clinical study, the actual percentage of patients enrolled with these

Table of Contents

EZH2 mutations may vary from the range suggested by the literature. As a result, these arms of the Phase 2 NHL clinical trial have been, and are likely to continue to be, slower to enroll than the other three arms of the Phase 2 NHL clinical trial.

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;
- the proximity and availability of clinical trial sites for prospective patients; and
- the ability to identify specific patient population for molecularly defined study cohort(s).

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 may cause the value of our company to decline and limit our ability to obtain additional financing.

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 in clinical trials or preclinical testing, 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 when needed, 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 may develop companion diagnostics for our therapeutic product candidates to identify patients for our clinical trials who have the specific cancers that we are seeking to treat as appropriate and when existing, available technology may not be sufficient to identify those patients. 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, we have entered into an agreement with Roche Molecular to develop and commercialize a companion diagnostic for use with tazemetostat for NHL patients with EZH2 activating mutations. 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 any third parties that we engage to assist us are unable to successfully develop companion diagnostics that are needed 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 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 $110.2 million for the year ended December 31, 2016 and $132.4 million for the year ended December 31, 2015. As of December 31, 2016, we had an accumulated deficit of $353.7 million. To date, we have financed our operations primarily through our collaborations, our public offerings, 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 clinical and preclinical studies. We are still in the early to middle stages of development of our product candidates, and we have not completed development of any drug candidates. 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 continue to increase over the next several years as we:

continue our Phase 2 clinical trial of tazemetostat for the treatment of patients with NHL, our Phase 2 clinical trial of tazemetostat for the treatment of adult patients with certain molecularly defined solid tumors and our Phase 1 clinical trial of tazemetostat for the treatment of pediatric patients with certain molecularly-defined solid tumors;

continue our Phase 2 clinical trial of tazemetostat in relapsed or refractory patients with mesothelioma characterized by BAP1 loss-of-function;

continue our clinical trials of tazemetostat in combination with R-CHOP in front line elderly patients with DLBCL and in combination with Genentech s anti-PD-L1 cancer immunotherapy, Tecentriq, in patients with relapsed or refractory DLBCL being conducted by our collaborators;

Table of Contents

- continue our rollover study of tazemetostat in certain patients that have completed prior clinical trial protocols;
- continue the new arm of our ongoing Phase 2 NHL trial of tazemetostat in combination with prednisolone in relapsed or refractory patients with DLBCL;
- design and conduct a new combination trial of tazemetostat in FL;
- pay any milestone payments provided for and achieved under the amended and restated collaboration and license agreement with Eisai;
- conduct research and development for Celgene under our amended and restated collaboration and license agreement;
- 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;
- 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, a product or 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 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 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 our stockholders to lose all or part of their investment in our company.

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 to fund our tazemetostat development program; make any milestone payments provided for and achieved under the amended and restated collaboration and license agreement with Eisai; continue research for Celgene under our amended and restated collaboration and license agreement; and continue research and development and initiate additional

Table of Contents

clinical trials of, and seek regulatory approval for, any future 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 our existing cash, cash equivalents and marketable securities as of December 31, 2016, will be sufficient to fund our planned operating expenses and capital expenditure requirements into at least the third quarter of 2018. 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:

- the progress and results of our ongoing and planned clinical trials;
- the number and development requirements of additional indications for tazemetostat and other product candidates that we may pursue, including the scope, progress, results and costs of discovery research, preclinical development, laboratory testing and clinical trials for such product candidates;
- our ongoing research for Celgene under our amended and restated collaboration and license agreement;
- the costs, timing and outcome of regulatory review of our product candidates;
- milestones, option exercise fees, license fees, and other collaboration-based revenues, if any;
- 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. Commercial revenues, if any, will not be derived until and unless we can achieve sales of commercially available products. 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, 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. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our existing stockholders will be diluted and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or

Table of Contents

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 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 three of the product candidates discovered by us are still in preclinical development. We have not yet demonstrated our ability to 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 about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, 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, the results of any quarterly or annual periods should not be relied upon as indications of future operating performance.

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.

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. 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;

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;

Table of Contents

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 some of our product candidates in the United States, and potentially in global markets, 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 pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of many 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

Table of Contents

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. Companies that are developing new epigenetic treatments for cancer that target HMTs include GSK, Novartis AG, Pfizer, Inc., Merck & Co., Inc., Daiichi Sankyo Company Limited, Takeda Pharmaceutical Company Limited, AbbVie Inc., Bayer Schering Pharma AG and Constellation Pharmaceuticals. 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.

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 many of 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.

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

Table of Contents

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 $20.0 million in product liability insurance coverage in the aggregate, with a per incident limit of $20.0 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.

Our resources for drug development are limited and we 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 and GSK. We also rely on Genentech to manage our combination study of tazemetostat and Tecentriq in relapsed or refractory DLBCL, and on LYSA to manage our combination study of tazemetostat and R-CHOP in newly diagnosed, elderly, high risk patients with DLBCL. With our reacquisition of tazemetostat rights under our amended and restated collaboration and license agreement with Eisai, we no longer have access to such capabilities for tazemetostat except with Eisai in Japan. Our collaborations 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 have the ability or the development capabilities to perform their obligations as expected;
- collaborators may not pursue 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;

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;

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 Annual Report on Form 10-K also apply to the activities of our therapeutic collaborators.

Our existing therapeutic collaborations contain restrictions on our engaging in activities that are the subject of the collaboration with third parties for specified periods of time. For example, under our collaboration agreement with Celgene, subject to specified exceptions, we may not, during the option period, research, develop or commercialize inhibitors directed to DOT1L and the three option targets covered by the agreement outside of the collaboration. 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 CMP targets, we may in the future 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 companion diagnostics when existing, available technology may not be sufficient to identify patients for treatment with our therapeutic product candidates. For example, we are relying on Roche Molecular to develop a companion diagnostic for tazemetostat in NHL to detect activating mutations in EZH2. Our collaborators:

- may not perform their obligations as expected or have difficulty responding to accelerated approval time lines;
- may encounter production difficulties that could constrain the supply of the companion diagnostics;
- may encounter delays or have difficulty obtaining regulatory approval for the companion diagnostic in target markets;
- may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community;
- may not pursue commercialization of any companion diagnostics 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 to conduct our ongoing clinical trials and plan to rely on third party clinical research organizations or third party research collaboratives to conduct our planned clinical trials. We do not plan to independently conduct clinical trials of any future product candidates. We expect to continue to rely on third parties, such as clinical research organizations, 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 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.

Table of Contents

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.

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 and 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.

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.

Table of Contents

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.

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.

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 drug candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those product candidates. We intend to seek patent term extensions for any of our issued patents in any jurisdiction where they are available, however there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted, and even if granted, the

length of such extensions.

Table of Contents

Patent reform legislation such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. 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, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the U.S. Patent and Trademark Office during patent prosecution and additional procedures to attack the validity of a patent at U.S. Patent and Trademark Office administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. In addition, under the Leahy-Smith Act, the United States transitioned to a first inventor to file system in which, assuming that the other statutory requirements are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, 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. For example, we are involved in an opposition proceeding against our European Patent, the claims of which cover a method for determining whether a cancer patient is a candidate for treatment with an EZH2 inhibitor based on their EZH2 mutation status. 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, 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 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.

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 license and research agreements 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 agreements. 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.

Table of Contents

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.

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.

Table of Contents

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

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. 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, export and import 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 submitted an application for or received marketing approval for any of our product candidates in the United States or in any other 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 not responded to an existing therapy or have relapsed.

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 and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

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. We have obtained orphan drug designations for tazemetostat for the treatment of INI1-negative malignant rhabdoid tumors, or MRT as well as MRTO, in the United States and for pinometostat for the treatment of acute lymphoblastic leukemia and acute

myeloid leukemia in the United States and Europe. We may not receive orphan drug designation for these product candidates for other indications, or for any other future clinical candidates we may develop.

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 exclusivity period in Europe 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. In addition, 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, such as the Fast Track designation we received for tazemetostat, may not lead to a faster development or regulatory review or approval process.

We have received Fast Track designation from the FDA for tazemetostat for patients with DLBCL with mutated EZH2 and intend to seek Fast Track designation for tazemetostat for other indications and for our other product candidates as appropriate. 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 eligible for this designation, we cannot assure that the FDA would decide to grant it. Even if we do receive Fast Track designation as we have for tazemetostat, we may not experience a faster development process, review or approval compared to conventional 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.

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

Table of Contents

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 foreign jurisdictions would prevent our product candidates from being marketed in that jurisdiction.

In order to market and sell our products in the European Union and many other foreign 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, a product must be approved for reimbursement before the product can be approved for sale in that country. We or our third party collaborators 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.

If we are required by the FDA to obtain approval of a companion diagnostic in connection with approval of a candidate therapeutic product, and we do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we will not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

According to FDA guidance, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared for that indication. Under the Federal Food, Drug, and Cosmetic Act, companion diagnostics are regulated as medical devices, and the FDA has generally required companion diagnostics intended to select the patients who will respond to cancer treatment to obtain Premarket Approval, or a PMA, for the diagnostic. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device s safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. A PMA is not guaranteed and may take considerable time, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. As a result, if we are required by the FDA to obtain approval of a companion diagnostic for a candidate therapeutic product, and we do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we may not be able to commercialize the product candidate on a timely basis or at all and our ability to generate revenue will be materially impaired.

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 substantial 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 and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose 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 and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions 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 or untitled 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;

damage to relationships with any potential collaborators;

unfavorable press coverage and damage to our reputation;

refusal to permit the import or export of our products;

product seizure;

injunctions or the imposition of civil or criminal penalties; or

litigation involving patients using our products.

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.

Table of Contents

Our relationships with healthcare providers, physicians 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 healthcare providers, physicians and third party payors 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 or arranging 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 through civil whistleblower or *qui tam* actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim;

- 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;

- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, 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

Table of Contents

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. 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.

In March 2010, the U.S. Congress enacted 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 which included changes to the coverage and reimbursement of drug products under government healthcare programs.

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 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;

requirements to report financial arrangements with physicians and teaching hospitals;

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

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

Further, 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

Table of Contents

January 2013, the American Taxpayer Relief Act of 2012 became law, 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 laws may result in additional reductions in Medicare and other healthcare funding. In addition, there have been recent public announcements by members of the U.S. Congress and the new presidential administration regarding their plans to repeal and replace the PPACA. However, it remains unclear how a repeal or replacement of current healthcare programs might affect our ability to sell our products and the prices we may obtain for any of our approved products.

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.

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. 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

Table of Contents

or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines 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.

We are highly dependent on the research and development, clinical and business expertise of our executive officers as well as the other principal members of our management, scientific and clinical teams. Although we have entered into employment letter agreements with our executive officers, each 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.

Table of Contents

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

Our executive officers and directors and their affiliates, if they choose to act together, may have the ability to significantly influence all matters submitted to stockholders for approval.

As of March 1, 2017, our executive officers and directors and their affiliates beneficially own, in the aggregate, shares representing approximately 33% of our common stock. As a result, if these stockholders were to choose to act together, they may be able to 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, could 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;
- 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 stockholders might otherwise receive a premium for their 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;

Table of Contents

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.

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

Although our common stock is listed on The NASDAQ Global Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or sell their 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.

Our stock price has been and may in the future be volatile. 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. From January 1, 2015 until March 1, 2017, the sale price of our common stock as reported on the NASDAQ Global Market ranged from a high of $28.48 to a low of $7.02. 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;

Table of Contents

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 and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents 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.

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:

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 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 the sole source of gain for our stockholders.

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 the sole source of gain for our stockholders 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.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters are located in Cambridge, Massachusetts, where we occupy approximately 42,500 square feet of office and laboratory space. The term of the Cambridge lease expires May 31, 2018. In addition, we occupy approximately 4,000 square feet of office space in Durham, North Carolina. The term of the Durham lease expires on July 31, 2017.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

Table of Contents

PART II

Item 5. Market for the Registrant s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock is traded on the NASDAQ Global Market under the symbol EPZM. Trading of our common stock commenced on May 31, 2013, following the completion of our initial public offering. 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:

	Market Price	
	High	**Low**
Year ended December 31, 2016:		
Fourth quarter	$ 12.35	$ 8.55
Third quarter	$ 10.55	$ 7.12
Second quarter	$ 13.20	$ 8.96
First quarter	$ 15.28	$ 8.79
Year ended December 31, 2015:		
Fourth quarter	$ 18.29	$ 11.26
Third quarter	$ 25.25	$ 12.00
Second quarter	$ 28.48	$ 15.51
First quarter	$ 25.48	$ 16.63

As of March 1, 2017, the number of holders of record of our common stock was 21. This number does not include beneficial owners whose shares are held in street name.

Dividends

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

Stock Performance Graph

The following graph shows a comparison from May 31, 2013, the first date that shares of our common stock were publicly traded, through December 31, 2016 of the cumulative total return on an assumed investment of $100.00 in cash in our common stock, the NASDAQ Composite Index and the NASDAQ Biotechnology Index. Such returns are based on historical results and are not intended to suggest future performance. Data for the NASDAQ Composite Index and NASDAQ Biotechnology Index assume reinvestment of dividends.

The performance graph in this Item 5 is not deemed to be soliciting material or to be filed with the SEC for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or otherwise subject to the liabilities under that Section, and shall not be deemed incorporated by reference into any of our filings under the Securities Act of 1933 or the Securities Exchange Act of 1934, except to the extent we specifically incorporate it by reference into such a filing.

Table of Contents

Item 6. Selected Financial Data

The following selected financial data has been derived from our consolidated financial statements. The information set forth below should be read in conjunction with Item 7. *Management s Discussion and Analysis of Financial Condition and Results of Operations* and with our consolidated financial statements and notes thereto included elsewhere in this document.

	Year Ended December 31,				
	2016	2015	2014	2013	2012
	(In thousands, except per share data)				
Consolidated Statements of Operations Data:					
Collaboration revenue	$ 8,007	$ 2,560	$ 41,411	$ 68,482	$ 45,222
Operating expenses:					
Research and development	91,461	111,209	75,595	57,567	38,482
General and administrative	28,372	23,900	20,866	14,042	7,508
Total operating expenses	119,833	135,109	96,461	71,609	45,990
Operating loss	(111,826)	(132,549)	(55,050)	(3,127)	(768)
Other income (expense), net	1,614	173	154	(7)	67
Income tax expense			109	349	1
Net loss	$ (110,212)	$ (132,376)	$ (55,005)	$ (3,483)	$ (702)
Accretion of redeemable convertible preferred stock to redemption value				264	486
Loss allocable to common stockholders	$ (110,212)	$ (132,376)	$ (55,005)	$ (3,747)	$ (1,188)
Basic and diluted loss per share allocable to common stockholders	$ (1.93)	$ (3.32)	$ (1.67)	$ (0.22)	$ (0.72)
Basic and diluted weighted average shares outstanding	57,126	39,839	33,027	17,049	1,645

	As of December 31,				
	2016	2015	2014	2013	2012
	(In thousands)				
Consolidated Balance Sheets Data:					
Cash and cash equivalents	$ 77,895	$ 208,323	$ 190,095	$ 123,564	$ 97,981
Marketable securities	164,297				
Total assets	252,441	217,903	199,203	162,988	103,511
Deferred revenue	28,809	30,709	23,151	46,872	69,445
Redeemable convertible preferred stock					76,156
Total stockholders equity (deficit)	201,700	169,532	160,282	104,313	(51,126)

77

Table of Contents

Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations

Our management s discussion and analysis of our financial condition and results of operations are based upon our consolidated financial statements included in this Annual Report on Form 10-K, which have been prepared by us in accordance with accounting principles generally accepted in the United States, or GAAP, and with Regulation S-X promulgated under the Securities Exchange Act of 1934, as amended. This discussion and analysis should be read in conjunction with these consolidated financial statements and the notes thereto included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in Part I, Item 1A. *Risk Factors* of this Annual Report on Form 10-K, 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

Epizyme is a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize novel epigenetic therapies for patients with cancer and other diseases. We are leaders in discovering and developing small molecule inhibitors of a class of enzymes known as HMTs as well as other CMPs. CMPs mediate selective and reversible modifications to chromatin, a complex of chromosomal 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, as well as other diseases. We believe that inhibiting altered CMPs presents the opportunity to create, develop and commercialize multiple targeted therapeutics.

Our lead product candidate, tazemetostat, is an oral, first-in-class potent and selective inhibitor of the EZH2 HMT, an enzyme that is implicated in a wide range of cancers. In our clinical trials of tazemetostat in patients with relapsed or refractory NHL and in patients with certain molecularly defined solid tumors, tazemetostat showed meaningful clinical activity as a monotherapy, and was generally well tolerated. We are conducting a broad clinical development program for tazemetostat as both a monotherapy and combination treatment, in relapsed/refractory and front-line disease, across a number of subtypes of NHL and in patients with and without EZH2 activating mutations. We are also testing tazemetostat in several different types of molecularly defined solid tumors, including INI1-negative tumors in adults and children and in adults with mesothelioma characterized by BAP1 loss-of-function.

In 2017, we expect to execute on the following relating to tazemetostat:

- continue dosing patients in our Phase 2 monotherapy trial of tazemetostat in adults with molecularly defined solid tumors and, if accepted, present interim data from this trial at ASCO in Chicago, Illinois in June 2017. We plan on interacting with regulatory agencies, beginning with the FDA, in mid-2017 with the goal of defining our registration pathways for our molecularly defined solid tumor program in adult patients;

- continue dosing patients in our Phase 2 monotherapy study of tazemetostat in adults with relapsed or refractory NHL and submit, and if accepted, present interim data from this trial at ICML in Lugano, Switzerland in June 2017. We plan on interacting with regulatory agencies, beginning with the FDA, in the

second half of 2017 on our NHL program, with the goal of defining our registration pathways in various subtypes of NHL;

continue dosing patients in the dose escalation and expansion phase of our Phase 1 monotherapy study of tazemetostat in children with molecularly defined solid tumors to determine the recommended Phase 2 dose and initiate the dose-expansion stage of the trial;

Table of Contents

advance our combination trial of tazemetostat and Tecentriq in patients with relapsed or refractory DLBCL, determine the recommended Phase 2 dose and advance into the expansion portion of the study;

advance our Phase 1b combination trial of tazemetostat and R-CHOP in front-line patients with DLBCL to determine the recommended Phase 2 dose and advance into the Phase 2 expansion portion of the study;

continue the newly opened additional arm of our ongoing Phase 2 NHL study to investigate tazemetostat in combination with prednisolone for patients with relapsed or refractory DLBCL;

design and initiate a combination trial of tazemetostat in FL; and

complete the first stage of our Phase 2 study of tazemetostat in patients with mesothelioma characterized by a loss-of-function of BAP1 to determine proof of concept and enroll in the second stage of the study.

We own the global development and commercialization rights to tazemetostat outside of 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 have collaboration agreements with Celgene, GSK, and Eisai for research and development activities. We also have a collaboration with Roche Molecular to develop a companion diagnostic to detect EZH2 activating mutations in patients with NHL. These collaborations provide us with access to considerable scientific, development, regulatory and commercial capabilities. We have received $207.8 million in non-equity funding under these collaborations to date.

Since our inception, we have pioneered the discovery and development of novel epigenetic medicines. We have discovered and developed three first-in-class experimental medicines that are in clinical trials. Pinometostat, an inhibitor of the DOT1L HMT that is the subject to our collaboration with Celgene, is currently being evaluated through a CRADA with the CTEP of the NCI, as a combination therapy for patients with acute leukemias. Under our collaboration with GSK, GSK3326595, a PRMT5 inhibitor, is being evaluated by GSK in a Phase 1 clinical trial in patients with solid tumors and NHL. We have additional small molecule HMT inhibitors that are being developed under our collaborations with Celgene and GSK. We have also identified multiple novel epigenetic targets for which we are developing small molecule inhibitors in preclinical drug discovery. We own the global development and commercialization rights to these programs. 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.

Through December 31, 2016, we have raised an aggregate of $728.7 million to fund our operations, of which $207.8 million was non-equity funding through our collaboration agreements, $444.9 million was from the sale of common stock in our public offerings and $76.0 million was from the sale of redeemable convertible preferred stock. As of December 31, 2016, we had $242.2 million in cash, cash equivalents and marketable securities.

We commenced active operations in early 2008, and since inception, have incurred significant operating losses. As of December 31, 2016, our accumulated deficit totaled $353.7 million. As a clinical stage company, 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 expect our expenses to increase in connection with our ongoing activities, including our continued execution on our clinical development plans for tazemetostat.

Collaborations

Refer to Item 1, *Collaborations* and Note 9, *Collaborations*, of the notes to our consolidated financial statements in Item 15 of this Annual Report on Form 10-K for a description of the key terms of our arrangements with Eisai, Celgene and GSK, as well as the related accounting and revenue recognition considerations.

Table of Contents

Results of Operations for the Years Ended December 31, 2016, 2015 and 2014

Collaboration Revenue

The following is a comparison of collaboration revenue for the years ended December 31, 2016, 2015 and 2014:

	Year Ended December 31,		
	2016	2015	2014
	(In millions)		
Collaboration revenue	$ 8.0	$ 2.6	$ 41.4

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

The following table summarizes our collaboration revenue, by collaboration, for the years ended December 31, 2016, 2015 and 2014:

	Year Ended December 31,		
	2016	2015	2014
	(In millions)		
Collaboration Partner			
GSK:			
Upfront revenue	$	$ 1.0	$ 11.5
Milestone revenue	6.0		3.0
Research and development revenue		0.4	11.0
Celgene:			
Upfront revenue	1.9	1.1	9.6
Eisai:			
Upfront revenue			1.6
Research and development revenue			4.7
Other	0.1	0.1	
	$ 8.0	$ 2.6	$ 41.4

Collaboration revenue for the year ended December 31, 2016 increased $5.4 million as compared to the year ended December 31, 2015, primarily as a result of the achievement of a $6.0 million milestone under our agreement with GSK during 2016. Collaboration revenues for the year ended December 31, 2015 decreased $38.8 million as compared to the year ended December 31, 2014, primarily as a result of the completion of a significant portion of our performance obligations under our collaborations during 2014 and achievement of a $3.0 million milestone under our agreement with GSK during 2014.

GSK. In the year ended December 31, 2016, revenue attributable to the GSK collaboration reflects the $6.0 million milestone earned upon GSK s initiation of patient dosing in a Phase 1 clinical trial of GSK3326595, a PRMT5

inhibitor discovered by us and licensed to GSK under the collaboration agreement. Upfront revenue of $1.0 million and $11.5 million in the years ended December 31, 2015 and 2014, respectively, reflects the recognition of deferred revenue related to upfront payments for licenses under the agreement. Milestone revenue from GSK in the year ended December 31, 2014 represents $3.0 million in preclinical research and development milestones achieved under the agreement. Research and development revenue of $0.4 million and $11.0 million in the years ended December 31, 2015 and 2014, respectively, relates to research and development services performed during the year. Since we have no further performance obligations under the GSK collaboration, future revenues under the collaboration will relate to milestone payments and royalties received under the

Table of Contents

agreement, if any. Upfront and research and development revenue decreased each year as a result of the completion of a significant portion of our performance obligations during 2014.

Celgene. Collaboration revenue attributed to the Celgene collaboration increased in the year ended December 31, 2016, as compared to the year ended December 31, 2015, primarily due to the recognition of deferred revenue attributed to the pinometostat clinical trial services as part of the accounting for the amended and restated Celgene agreement, which was entered into during the third quarter of 2015. Upfront revenue of $1.1 million and $9.6 million in the years ended December 31, 2015 and 2014, respectively, reflects the recognition of deferred revenue related to upfront payments for licenses under the agreement. Upfront revenue decreased from 2014 to 2015 a result of the completion of a significant portion of our performance obligations during 2014.

As of December 31, 2016, all of our deferred revenue relates to our Celgene collaboration. The recognition of deferred revenue under the amended and restated Celgene agreement is dependent on the future development of the non-pinometostat targets that are subject to the collaboration, as all of the $28.8 million deferred revenue as of December 31, 2016 relates to the non-pinometostat targets. We do not expect to recognize any of the remaining $28.8 million of deferred revenue as of December 31, 2016 related to the three non-pinometostat targets for the next twelve months, unless or until Celgene exercises its option rights with respect to those targets or those option rights lapse.

Eisai. Following the execution of the amended and restated collaboration and license agreement with Eisai, we do not expect to recognize any further amounts from Eisai, except for potential royalties on EZH2 product sales in Japan that we may receive in the future. Upfront revenue of $1.6 million in the year ended December 31, 2014 reflects the recognition of deferred revenue related to an upfront payment under the agreement. Research and development revenue of $4.7 million in the year ended December 31, 2014 relates to research and development services performed during the year.

Research and Development

Research and development expenses consist of expenses incurred in performing research and development activities, including clinical trials and related clinical manufacturing expenses, fees paid to external providers of research and development services, third party clinical research organizations, or CROs, compensation and benefits for full-time research and development employees, facilities expenses, overhead expenses, and other outside expenses. Most of our research and development costs are external costs, which we track on a program-by-program basis. Our internal research and development costs are primarily compensation expenses for our full-time research and development employees, including stock-based compensation expense.

In our early-stage research, we identify and prioritize novel CMPs that are implicated in cancer and other diseases, and seek to develop potent and selective small molecule inhibitors of these targets. During this phase of research, our external costs primarily relate to lead discovery, biology, drug metabolism and pharmacokinetics and chemistry services from a multinational network of third party providers of research and development services. As our product candidates progress into preclinical and clinical development, external costs are driven by clinical trial costs, manufacturing expenses, and third-party research and development expenses.

In circumstances where our collaboration and license agreements provide for equally co-funded global development under joint risk sharing collaborations, and where we are the study sponsor, such as our Celgene collaboration, amounts received for co-funding are recorded as a reduction to research and development expense.

81

Table of Contents

The following is a comparison of research and development expenses for the years ended December 31, 2016, 2015 and 2014:

	Year Ended December 31,		
	2016	2015	2014
	(In millions)		
Research and development	$ 91.5	$ 111.2	$ 75.6

During the year ended December 31, 2016, total research and development expenses decreased by $19.7 million compared to the year ended December 31, 2015, primarily due to the $40.0 million upfront payment that we made to Eisai in the first quarter of 2015 to reacquire the worldwide rights, excluding Japan, to tazemetostat. The impact of the prior year upfront payment was partially offset by higher spending on the tazemetostat program and discovery/preclinical and internal research and development costs in the year ended December 31, 2016 compared to the year ended December 31, 2015.

During the year ended December 31, 2015 total research and development expenses increased by $35.6 million compared to the year ended December 31, 2014, primarily due to the $40.0 million upfront payment that we made to Eisai to reacquire the worldwide rights, excluding Japan, to the EZH2 program, including tazemetostat, and the related costs to accelerate the development of tazemetostat. These cost increases were partially offset by reduced spending on pinometostat and related DOT1L programs and on our discovery and preclinical programs.

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

Product Program	Year Ended December 31,		
	2016	2015	2014
	(In millions)		
External research and development expenses:			
Tazemetostat and related EZH2 programs	$ 39.9	$ 63.1	$ 3.8
Pinometostat and related DOT1L programs	2.6	5.3	15.2
Discovery and preclinical stage product programs, collectively	18.9	16.3	31.5
Internal research and development expenses	30.1	26.5	25.1
Total research and development expenses	$ 91.5	$ 111.2	$ 75.6

External research and development costs related to tazemetostat include ongoing clinical trial costs, preclinical research in support of the tazemetostat program, expenses associated with our companion diagnostic program, and external manufacturing costs related to the acquisition of active pharmaceutical ingredient and manufacturing of clinical drug supply. External research and development expenses for tazemetostat decreased $23.2 million during the year ended December 31, 2016 compared to the year ended December 31, 2015. The decrease in tazemetostat related spending in the year ended December 31, 2016 is primarily a result of the $40.0 million upfront payment made to Eisai in the prior year, offset by a significant increase in tazemetostat clinical trial activities in the year ended December 31, 2016. External research and development expenses for tazemetostat during 2015 include the costs associated with our reacquisition of worldwide rights, excluding Japan, to the EZH2 program, including tazemetostat, from Eisai during the first quarter of 2015. External research and development expenses for tazemetostat in 2015 include Phase 1/2 clinical trial costs, discovery and preclinical research in support of the tazemetostat program,

expenses associated with our companion diagnostic program, and external manufacturing costs related to the acquisition of active pharmaceutical ingredient and manufacturing of clinical drug supply. External research and development expenses for tazemetostat increased $59.3 million during the year ended December 31, 2015 compared to the year ended December 31, 2014, primarily due to the upfront payment made to Eisai and the significant expansion of our tazemetostat clinical activities in 2015. In the year ended December 31, 2014, external research and development expenses of $3.8 million for tazemetostat related to the Phase 1 clinical trial costs and exploratory research costs incurred pursuant to our original agreement with Eisai.

Table of Contents

External research and development expenses for pinometostat decreased by $2.7 million for the year ended December 31, 2016 compared to 2015. The decline in program spending reflects our completion of enrollment in the pinometostat adult and pediatric clinical trials and the associated reduction in costs. We completed enrollment in our pinometostat adult Phase 1 clinical trial in the third quarter of 2015 and the pediatric Phase 1 clinical trial in the first quarter of 2016. The costs incurred related to pinometostat in year ended December 31, 2016 are primarily associated with study closeout and final reporting activities on the Phase 1 clinical trials, as well as costs attributed to the CRADA with the NCI. External research and development expenses for pinometostat for the year ended December 31, 2015 decreased by $9.9 million compared to the year ended December 31, 2014. The decline in program spending in 2015 reflects reduced enrollment in the pinometostat adult and pediatric clinical trials and the associated reduction in costs to support the preclinical and research programs. Research and development expenses for pinometostat for the years ended December 31, 2016, 2015 and 2014 are net of less than $0.1 million, $1.1 million and $3.9 million, respectively, of global development co-funding from Celgene.

External research and development expenses for discovery and preclinical stage product programs increased $2.6 million for the year ended December 31, 2016 as compared to the year ended December 31, 2015, due to increased spending on high priority discovery programs. External research and development expenses for discovery and preclinical stage product programs decreased by $15.2 million for the year ended December 31, 2015 as compared to the year ended December 31, 2014. This decrease reflected our reallocation of resources to support the expansion of the tazemetostat programs and our reprioritization of our discovery and preclinical development programs.

Internal research and development expenses are primarily compensation expenses for our full-time research and development employees. Internal research and development expenses increased $3.6 million for year ended December 31, 2016 as compared to the year ended December 31, 2015. The increase in internal research and development costs in the year ended December 31, 2016 was primarily due to the expansion of our development organization to support expanded tazemetostat clinical trials, chemistry, manufacturing and controls, translational medicine, data analytics and regulatory activities. Internal research and development expenses increased by $1.4 million for the year ended December 31, 2015 compared to the year ended December 31, 2014. The increase in 2015 resulted from the expansion of our internal clinical development team to support ongoing and new clinical programs and evaluations of tazemetostat, drug manufacturing, and regulatory filings following the reacquisition of tazemetostat from Eisai.

We expect research and development expenses to increase significantly in 2017, as we progress and expand our development program for tazemetostat, expand our regulatory activities, and potentially advance a preclinical program into later stage preclinical testing.

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 and general legal services.

The following is a comparison of general and administrative expenses for the years ended December 31, 2016, 2015 and 2014:

	Year Ended December 31,		
	2016	2015	2014
	(In millions)		
General and administrative	$ 28.4	$ 23.9	$ 20.9

Table of Contents

For the year ended December 31, 2016, our general and administrative expenses increased $4.5 million compared to the year ended December 31, 2015, primarily due to higher compensation-related expenses associated with additions to the senior leadership team in the first half of 2016, as well as increased investment in business development activities and pre-commercial activities related to tazemetostat. For the year ended December 31, 2015, our general and administrative expenses increased by $3.0 million, or 14%, compared to the year ended December 31, 2014, primarily related to additional intellectual property and related legal costs and compensation-related expenses.

We expect that general and administrative expenses will increase in 2017, as we plan to increase our pre-commercial activities, including the continued buildout of our medical affairs and commercial organizations.

Other Income, Net

The following is a comparison of other income, net for the years ended December 31, 2016, 2015 and 2014:

	Year Ended December 31,		
	2016	2015	2014
	(In millions)		
Other income, net			
Interest income, net	$ 1.5	$ 0.1	$ 0.1
Other income, net	0.1	0.1	0.1
Other income, net	$ 1.6	$ 0.2	$ 0.2

Other income, net consists of interest income earned on our cash equivalents and marketable securities, net of imputed interest expense paid under our capital lease obligation, and other income recorded from a tax incentive award received in 2013. Net interest income increased $1.4 million for the year ended December 31, 2016 compared to the year ended December 31, 2015, primarily due to an increased cash balance as a result of the January 2016 follow-on offering and the purchases of short term interest bearing securities in 2016.

Income Tax Expense

We maintain a full valuation allowance against our deferred tax assets and therefore did not recognize an income tax benefit for the year ended December 31, 2016 or December 31, 2015. Income tax expense for the year ended December 31, 2014 reflects adjustments identified in 2014 related to the year ended December 31, 2013 in the course of preparing the 2013 income tax returns.

Liquidity and Capital Resources

Through December 31, 2016, we have raised an aggregate of $728.7 million to fund our operations, of which $207.8 million was non-equity funding through our collaboration agreements, $444.9 million was from the sale of common stock in our public offerings and $76.0 million was from the sale of redeemable convertible preferred stock. As of December 31, 2016, we had $242.2 million in cash, cash equivalents and marketable securities.

On April 15, 2016, we entered into a Sales Agreement with Cowen and Company, LLC, or Cowen, to sell, from time to time, shares of our common stock having an aggregate sales price of up to $50.0 million through an at the market offering as defined in Rule 415 under the Securities Act of 1933, as amended, under which Cowen would act as sales

agent, which we refer to as the ATM Offering. The shares that may be sold under the Sales Agreement, if any, would be issued and sold pursuant to our $250.0 million universal shelf registration statement on Form S-3 that was declared effective by the SEC on April 29, 2016. Through March 10, 2017, we sold 155,834 shares of Common Stock under the Sales Agreement, resulting in net proceeds of $1.9 million related to the ATM Offering. We terminated the Sales Agreement with Cowen, effective March 10, 2017.

Table of Contents

In addition to our existing cash, cash equivalents and marketable securities, we may receive research and development co-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.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, clinical trial costs, third party research and development services, compensation and related expenses, laboratory and related supplies, our potential future milestone payment obligations to Eisai and Roche Molecular under the amended Eisai collaboration agreement and Roche Molecular companion diagnostic agreement, legal and other regulatory expenses and general overhead costs.

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 make license, milestone or royalty payments under our agreements with them, we do 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 may be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. 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 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 our existing cash, cash equivalents and marketable securities as of December 31, 2016, will be sufficient to fund our planned operating expenses and capital expenditure requirements into at least the third quarter of 2018, without giving effect to any potential option exercise fees or milestone payments we may receive under our collaboration agreements. We have based this estimate 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, 2016, 2015 and 2014:

	Year Ended December 31,		
	2016	**2015**	**2014**

		(In millions)	
Net cash used in operating activities	$ (96.4)	$ (72.9)	$ (35.4)
Net cash used in investing activities	(165.4)	(40.2)	(2.2)
Net cash provided by financing activities	131.4	131.3	104.1

Table of Contents

Net Cash Used in Operating Activities

Net cash used in operating activities was $96.4 million during the year ended December 31, 2016 compared to $72.9 million during the year ended December 31, 2015. The increase in net cash used in operating activities during year ended December 31, 2016 as compared to 2015 primarily relates to the net loss in the period, after adjusting for the $40.0 million payment made to Eisai in the prior year, which is classified as an investing cash outflow.

Net cash used in operating activities for year ended December 31, 2016 primarily relates to our net loss of $110.2 million, partially offset by non-cash stock-based compensation of $10.6 million and depreciation of $1.6 million. The most significant items affecting working capital in the year ended December 31, 2016 include increased accrued expenses and prepaid expenses associated with the expansion of our clinical activities and the recognition of deferred revenue associated with the Celgene arrangement.

Net cash used in operating activities was $72.9 million during the year ended December 31, 2015 compared to $35.4 million during the year ended December 31, 2014. The increase in net cash used in operating activities for the year ended December 31, 2015 primarily resulted from higher non-equity cash receipts from our collaborations of $53.2 million in 2014 compared to $10.0 million in 2015. Net cash used in operating activities for fiscal year 2015 primarily relates to our net loss of $132.4 million less the impact of the $40.0 million upfront payment made to Eisai upon the execution of our amended and restated collaboration and license agreement in March 2015, which is classified as an investing activity in the consolidated statement of cash flows, the $10.0 million payment from Celgene as part of the July 2015 amended and restated agreement and non-cash stock-based compensation and depreciation, which increased $3.7 million to $11.3 million compared to fiscal 2014.

Net Cash Used in Investing Activities

Net cash used in investing activities during the year ended December 31, 2016 reflects $229.9 million of purchases of available for sale securities, maturities/sales of available for sale securities of $65.1 million and $0.6 million of purchases of property and equipment during the period.

Net cash used in investing activities during the year ended December 31, 2015, reflects the $40.0 million upfront payment made to Eisai upon the execution of our amended and restated collaboration and license agreement, under which we reacquired worldwide rights, excluding Japan, to tazemetostat, as well as purchases of property and equipment. Net cash used in investing activities for 2014 related solely to the purchase of property and equipment. Purchases of property and equipment in 2014 consisted principally of purchases to support expansion of and improvements in our technology infrastructure.

Net Cash Provided by Financing Activities

Net cash provided by financing activities of $131.4 million during the year ended December 31, 2016 primarily reflects net cash received from our January 2016 public offering of our common stock of $129.7 million as well as cash received from stock option exercises, cash proceeds from our ATM Offering and purchase of shares under our employee stock purchase plan. This amount was offset in part by the payment of $0.6 million of principal on our capital lease obligation.

Net cash provided by financing activities of $131.3 million during the year ended December 31, 2015 primarily reflects net cash received from our March 2015 public offering of our common stock of $130.3 million as well as cash received from stock option exercises and the purchase of shares under our employee stock purchase plan. This amount was offset in part by the payment of $0.4 million of principal on our capital lease obligation during the year ended

December 31, 2015.

Table of Contents

Contractual Obligations and Contingent Liabilities

The following summarizes our significant contractual obligations as of December 31, 2016:

Contractual Obligations	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
			(In thousands)		
Real estate leases (1)	$ 4,100	$ 2,898	$ 1,202	$	$
Capital leases (2)	776	665	111		
Total obligations	$ 4,876	$ 3,563	$ 1,313	$	$

(1) ***Real Estate Leases.*** Real estate leases represent future minimum lease payments under non-cancelable operating leases in effect as of December 31, 2016.
(2) ***Capital leases*** relate to lease of computer hardware and related equipment. The minimum lease payments above do not include common area maintenance charges or real estate taxes to the extent applicable.

In addition to commitments under leasing arrangements described in the table above, as of December 31, 2016, we have committed to fund $12.0 million of remaining development costs payable to Roche Molecular, expected to be paid through 2019 upon certain development and regulatory milestones, under an amended companion diagnostic agreement. In addition, the contractual obligations table does not include potential future milestones or royalties that we may be required to make under license and collaboration agreements, including potential future milestones or royalties payable to Eisai under the amended collaboration and license agreement, due to the uncertainty of the occurrence of the events requiring payment under these agreements.

We enter into contracts in the normal course of business with CROs for clinical and preclinical research studies, external manufacturers for product for use in our clinical trials, and other research supplies and other services as part of our operations. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments.

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

Table of Contents

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.

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

Table of Contents

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 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

Table of Contents

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.

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. Research and development costs are expensed as incurred if no planned alternative future use exists for the technology and if the payment is not payment for future services. We defer and capitalize our nonrefundable advance payments that are for research and development activities until the related goods are delivered or the related services are performed. In circumstances where our collaboration and license agreements provide for equally co-funded global development under joint risk sharing collaborations, amounts received from collaboration partners for such co-funding are recorded as a reduction to research and development expense.

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses as of each balance sheet date. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- contract research organizations in connection with clinical trials;
- investigative sites in connection with clinical trials;
- vendors in connection with non-clinical development activities; and
- vendors related to product manufacturing, development and distribution of clinical supplies.

We generally accrue expenses related to research and development activities based on the services received and efforts expended pursuant to contracts with multiple contract research organizations that conduct and manage clinical trials on our behalf as well as other vendors that provide research and development services. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a

prepayment of the expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we would adjust the accrual or prepaid accordingly.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed we may report amounts that are too high or too low in any particular period. To date, there have been no material differences from our estimates to the amount actually incurred.

Table of Contents

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 using a blended approach encompassing our historical experience and the historical volatility of a peer group of comparable publicly traded companies with product candidates in similar stages of development;
- the expected risk-free interest rate based on the U.S. Treasury zero coupon rate with a remaining term approximating the expected term; and
- the expected dividend yield of zero.

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.

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.

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 our board of directors believes represents the fair value of our common stock.

Going Concern

We implemented Financial Accounting Standards Board Accounting Standards Update No. 2014-15, *Disclosure of Uncertainties About an Entity s Ability to Continue as a Going Concern*, beginning with this 2016 Annual Report on Form 10-K. We continually evaluate our ability to continue as a going concern within one year of the date of issuance of financial statements in both our Quarterly Reports on Form 10-Q and Annual Reports on Form 10-K. Our evaluation entails analyzing forward looking budgets and forecasts for expectations of our cash needs, and comparing those needs to our current cash, cash equivalent and marketable security balances.

Acquired In-Process Research and Development

We record upfront payments that relate to the acquisition of a development-stage product candidate as research and development expense in the period in which they are incurred, provided that the acquired development-stage product candidate did not also include processes or activities that would constitute a business, the product candidate has not achieved regulatory approval for marketing and, absent obtaining such approval, has no alternative future use. In the first quarter of 2015, we accounted for the upfront payment paid to Eisai in connection with the amended and restated collaboration and license agreement, pursuant to which we reacquired the worldwide rights, excluding Japan, to tazemetostat, as an acquisition of in-process research and development.

Table of Contents

Recent Accounting Pronouncements

For detailed information regarding recently issued accounting pronouncements and the expected impact on our consolidated financial statements, see Note 2, *Summary of Significant Accounting Policies Recent Accounting Pronouncements*, in the accompanying Notes to Consolidated Financial Statements included in Item 15. of Part IV of this Annual Report on Form 10-K.

Item 7A. 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 December 31, 2016, we had cash equivalents and available for sale securities of $242.2 million consisting of money market funds, corporate bonds, commercial paper and government-related obligations. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. We estimate that a hypothetical 100-basis point change in market interest rates would impact the fair value of our investment portfolio as of December 31, 2016 by $0.5 million.

We contract with CROs and manufacturers globally. 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.

Item 8. Financial Statements and Supplementary Data

The information required by this item may be found on pages F-2 through F-32 as listed below, including the quarterly information required by this item.

INDEX

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act) as of December 31, 2016. In designing and evaluating our disclosure controls and procedures, management recognized that any controls and procedures, no

matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and our management necessarily applied its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our principal executive officer and principal financial officer concluded that as of December 31, 2016, our disclosure controls and procedures were (1) designed to ensure that material information relating to us is made known to our management including our

Table of Contents

principal executive officer and principal financial officer by others, particularly during the period in which this report was prepared and (2) effective, in that they provide reasonable assurance that information required to be disclosed by us in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC s rules and forms.

Management s Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of our company;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2016. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO, in *Internal Control Integrated Framework (2013)*. Based on its assessment, management believes that, as of December 31, 2016, our internal control over financial reporting is effective based on those criteria.

Changes in Internal Controls over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2016 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

Pursuant to an agreement with Cowen, we terminated the Sales Agreement dated April 15, 2016 to which we were a party with Cowen, effective March 10, 2017. The Sales Agreement provided for the sale, from time to time, of shares of our common stock having an aggregate sales price of up to $50.0 million through an at the market offering as defined in Rule 415 under the Securities Act of 1933, as amended.

On March 9, 2017, we announced that Robert Copeland, our President of Research and Chief Scientific Officer, will be retiring from the company on a date to be determined in the second quarter of 2017 to pursue advisory and other opportunities within the industry.

Table of Contents

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K and is incorporated by reference from our definitive proxy statement relating to our 2017 annual meeting of stockholders, pursuant to Regulation 14A of the Securities Exchange Act of 1934, as amended, also referred to in this Annual Report on Form 10-K as our 2017 Proxy Statement, which we expect to file with the SEC within 120 days of the end of the fiscal year ended December 31, 2016.

Item 10. Directors, Executive Officers and Corporate Governance

Information regarding our directors, including the audit committee and audit committee financial experts, and executive officers and compliance with Section 16(a) of the Exchange Act will be included in our 2017 Proxy Statement and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics for all of our directors, officers and employees as required by NASDAQ governance rules and as defined by applicable SEC rules. Stockholders may locate a copy of our Code of Business Conduct and Ethics on our website at www.epizyme.com or request a copy without charge from:

Epizyme, Inc.

Attention: Investor Relations

400 Technology Square, 4th Floor

Cambridge, MA 02139

We will post to our website any amendments to the Code of Business Conduct and Ethics, and any waivers that are required to be disclosed by the rules of either the SEC or NASDAQ.

Item 11. Executive Compensation

The information required by this item regarding executive compensation will be included in our 2017 Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item regarding security ownership of certain beneficial owners and management and securities authorized for issuance under equity compensation plans will be included in our 2017 Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item regarding certain relationships and related transactions and director independence will be included in our 2017 Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item regarding principal accounting fees and services will be included in our 2017 Proxy Statement and is incorporated herein by reference.

Table of Contents

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are included in this Annual Report on Form 10-K:

1. The following Report and Consolidated Financial Statements of the Company are included in this Annual Report:

Report of Independent Registered Public Accounting Firm

Consolidated Balance Sheets

Consolidated Statements of Operations and Comprehensive Loss

Consolidated Statements of Cash Flows

Consolidated Statements of Stockholders Equity

Notes to Consolidated Financial Statements

2. All financial schedules have been omitted because the required information is either presented in the consolidated financial statements or the notes thereto or is not applicable or required.

3. The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the exhibits and are incorporated herein.

Item 16. Form 10-K Summary

None.

Table of Contents

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Epizyme, Inc.

By: /s/ Robert B. Bazemore
Robert B. Bazemore
President and Chief Executive Officer

Dated: March 13, 2017

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Name	Title	Date
/s/ Robert B. Bazemore Robert B. Bazemore	President, Chief Executive Officer, Director *(Principal Executive Officer)*	March 13, 2017
/s/ Andrew E. Singer Andrew E. Singer	Executive Vice President of Finance and Administration, Chief Financial Officer and Treasurer *(Principal Financial and Accounting Officer)*	March 13, 2017
/s/ Andrew R. Allen Andrew R. Allen, M.D., Ph.D.	Director	March 13, 2017
/s/ Kenneth Bate Kenneth Bate	Director	March 13, 2017
/s/ Kevin T. Conroy Kevin T. Conroy	Director	March 13, 2017
/s/ Carl Goldfischer Carl Goldfischer, M.D.	Director	March 13, 2017
/s/ David M. Mott David M. Mott	Director	March 13, 2017
/s/ Richard F. Pops Richard F. Pops	Director	March 13, 2017

/s/ Beth Seidenberg Beth Seidenberg, M.D.	Director	March 13, 2017

Table of Contents

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
3.1	Restated Certificate of Incorporation of the Registrant (1)
3.2	Amended and Restated Bylaws of the Registrant (2)
4.2	Amended and Restated Investor Rights Agreement dated as of April 2, 2012 (4)
10.1+	2008 Stock Incentive Plan (4)
10.2+	Form of Incentive Stock Option Agreement under 2008 Stock Incentive Plan (4)
10.3+	Form of Nonstatutory Stock Option Agreement under 2008 Stock Incentive Plan (4)
10.4+	Form of Restricted Stock Agreement under 2008 Stock Incentive Plan (4)
10.5+	2013 Stock Incentive Plan (2)
10.6+	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan (2)
10.7+	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan (2)
10.8+	Form of Restricted Stock Agreement under 2013 Stock Incentive Plan (2)
10.9+	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (12)
10.10+	2013 Employee Stock Purchase Plan (2)
10.11+	Executive Severance and Change in Control Plan (as amended February 25, 2016 (16)
10.12+	Employment Offer Letter dated April 3, 2013 by and between the Registrant and Robert J. Gould, Ph.D. (2)
10.13+	Employment Offer Letter dated April 3, 2013 by and between the Registrant and Robert A. Copeland, Ph.D. (2)
10.14+	Employment Offer Letter dated September 8, 2014 by and between the Registrant and Peter T.C. Ho, M.D., Ph.D. (10)
10.15+	Employment Offer Letter dated January 28, 2015 by and between the Registrant and Andrew E. Singer (11)
10.16+	Employment Offer Letter dated between the Registrant and Robert Bazemore, dated August 5, 2015 (14)
10.17+	Employment Offer Letter between the Company and Matthew E. Ros, dated April 15, 2016 (18)
10.18+	Employment Offer Letter between the Company and Susan Graf, dated April 25, 2016 (21)
10.19	Form of Director and Officer Indemnification Agreement (2)
10.20	Collaboration and License Agreement dated as of April 1, 2011 by and between the Registrant and Eisai Co., Ltd. (3)
10.21	License and Collaboration Agreement dated as of April 2, 2012 by and between the Registrant and Celgene International Sàrl and Celgene Corporation (3)

10.22	Companion Diagnostics Agreement dated as of December 18, 2012 between the Registrant and Eisai Co., Ltd. on the one side and Roche Molecular Systems, Inc. on the other side (3)
10.23	First Amendment to the Companion Diagnostics Agreement dated October 23, 2013 between the Registrant and Eisai Co. Ltd. On the one side and Roche Molecular Systems, Inc. on the other side (6)

Table of Contents

Exhibit Number	Description of Exhibit
10.24	Second Amendment to the Companion Diagnostics Agreement dated November 16, 2015 between the Registrant and Eisai Co. Ltd. on the one side and Roche Molecular Systems, Inc. on the other side (16)
10.25	Letter Agreement by and between the Registrant and Eisai Co., Ltd. dated as of December 21, 2012 relating to Companion Diagnostics Agreement (4)
10.26	Amended and Restated Letter Agreement dated as of March 12, 2015 by and between the Registrant and Eisai Co., Ltd. relating to the Companion Diagnostics Agreement (13)
10.27	Amended and Restated Collaboration and License Agreement dated as of March 12, 2015, by and between the Registrant and Eisai Co. Ltd. (13)
10.28	Lease Agreement dated as of June 15, 2012 between the Registrant and ARE-TECH Square, LLC (4)
10.29	Non-Employee Director Compensation Program (19)
10.30	Amendment to Lease Agreement dated as of September 30, 2013 between the Registrant and ARE-TECH Square, LLC (5)
10.31	Second Amendment to Lease Agreement dated as of May 18, 2016 between the Registrant and ARE-TECH Square, LLC (20)
10.32	Amended and Restated Collaboration and License Agreement dated as of July 8, 2015 by and between the Registrant and Celgene Corporation and Celgene RIVOT Ltd. (15)
10.33	Collaboration and License Agreement dated as of January 8, 2011 by and between the Registrant and Glaxo Group Limited (3)
10.34	Amendment to Collaboration and License Agreement dated as of July 23, 2013 by and between the Registrant and Glaxo Group Limited (7)
10.35	Amendment to Collaboration and License Agreement dated as of February 24, 2014 by and between the Registrant and Glaxo Group Limited (8)
10.36	Amendment to Collaboration and License Agreement dated as of March 18, 2014 by and between the Registrant and Glaxo Group Limited (8)
10.37	Amendment to Collaboration and License Agreement dated as of April 17, 2014 by and between the Registrant and Glaxo Group Limited (9)
10.38	Amendment to Collaboration and License Agreement dated as of October 1, 2014 by and between the Registrant and Glaxo Group Limited (12)
10.39	Consulting Agreement dated August 5, 2015 by and between the Registrant and Robert J. Gould, Ph.D. (14)
10.40	Sales Agreement dated as of April 15, 2016, by and between the Company and Cowen and Company, LLC (17)
21.1	Subsidiaries of the Registrant (4)
23.1	Consent of Ernst & Young LLP (21)
31.1	Certification of Chief Executive Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities

	Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. (21)
31.2	Certification of Chief Financial Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. (21)

Table of Contents

Exhibit Number	Description of Exhibit
32.1	Certifications pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of The Sarbanes-Oxley Act of 2002, by Robert B. Bazemore, President and Chief Executive Officer of the Company, and Andrew E. Singer, Executive Vice President of Finance and Administration, Chief Financial Officer and Treasurer of the Company. (21)
101.INS	XBRL Instance Document
101.SCH	XBRL Schema Document
101.CAL	XBRL Calculation Linkbase Document
101.LAB	XBRL Labels Linkbase Document
101.PRE	XBRL Presentation Linkbase Document
101.DEF	XBRL Definition Linkbase Document

+ Management compensatory agreement.
Confidential treatment has been granted as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.
Confidential treatment requested as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

(1) Incorporated by reference to the Registrant s Current Report on Form 8-K (File No. 001-35945) filed with the Securities and Exchange Commission on June 7, 2013.
(2) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-187892) filed with the Securities and Exchange Commission on April 26, 2013.
(3) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-187982) filed with the Securities and Exchange Commission on May 13, 2013.
(4) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-187982) filed with the Securities and Exchange Commission on April 18, 2013.
(5) Incorporated by reference to the Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on October 23, 2013.
(6) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-193569) filed with the Securities and Exchange Commission on January 27, 2014.
(7) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-193569) filed with the Securities and Exchange Commission on January 28, 2014.
(8) Incorporated by reference to the Registrant s Current Report on Form 8-K (File No. 001-35945) filed with the Securities and Exchange Commission on April 22, 2014.
(9) Incorporated by reference to the Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 14, 2014.
(10) Incorporated by reference to the Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 6, 2014.
(11) Incorporated by reference to the Registrant s Current Report on Form 8-K (File No. 001-35945) filed with the Securities and Exchange Commission on February 3, 2015.
(12) Incorporated by reference to the Registrant s Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 12, 2015.

(13) Incorporated by reference to the Registrant s Current Report on Form 8-K (File No. 001-35945) filed with the Securities and Exchange Commission on March 16, 2015.
(14) Incorporated by reference to the Registrant s Current Report on Form 8-K (File No. 001-35945) filed with the Securities and Exchange Commission on August 1, 2015.
(15) Incorporated by reference to the Registrant s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 9, 2015.

Table of Contents

(16) Incorporated by reference to the Registrant s Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 9, 2016.
(17) Incorporated by reference to the Registration Statement on Form S-3 (File No. 333-210774) filed with the Securities and Exchange Commission on April 15, 2016.
(18) Incorporated by reference to the Registrant s Current Report on Form 8-K (File No. 001-35945) filed with the Securities and Exchange Commission on May 6, 2016.
(19) Incorporated by reference to the Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 9, 2016.
(20) Incorporated by reference to the Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 8, 2016.
(21) Filed with this Annual Report on Form 10-K.

Table of Contents

EPIZYME, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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, 2016 and 2015, and the related consolidated statements of operations and comprehensive loss, cash flows and stockholders equity for each of the three years in the period ended December 31, 2016. 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 the 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, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts

March 13, 2017

Table of Contents

EPIZYME, INC.

CONSOLIDATED BALANCE SHEETS

(Amounts in thousands except per share data)

	December 31, 2016	December 31, 2015
ASSETS		
Current Assets:		
Cash and cash equivalents	$ 77,895	$ 208,323
Marketable securities	164,297	
Accounts receivable	23	262
Prepaid expenses and other current assets	6,457	4,478
Total current assets	248,672	213,063
Property and equipment, net	3,124	4,089
Restricted cash and other assets	645	751
Total Assets	$ 252,441	$ 217,903
LIABILITIES AND STOCKHOLDERS EQUITY		
Current Liabilities:		
Accounts payable	$ 4,994	$ 4,653
Accrued expenses	16,007	11,335
Current portion of capital lease obligation	620	561
Current portion of deferred revenue		1,900
Total current liabilities	21,621	18,449
Capital lease obligation, net of current portion	110	730
Deferred revenue, net of current portion	28,809	28,809
Other long-term liabilities	201	383
Commitments and contingencies (Note 7)		
Stockholders Equity:		
Common stock, $0.0001 par value; 125,000 shares authorized; 58,050 shares and 41,786 shares issued and outstanding, respectively	6	4
Additional paid-in capital	555,473	412,989
Accumulated other comprehensive loss	(106)	
Accumulated deficit	(353,673)	(243,461)
Total stockholders equity	201,700	169,532
Total Liabilities and Stockholders Equity	$ 252,441	$ 217,903

See notes to consolidated financial statements.

F-3

Table of Contents

EPIZYME, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(Amounts in thousands except per share data)

	Year Ended December 31,		
	2016	**2015**	**2014**
Collaboration revenue	$ 8,007	$ 2,560	$ 41,411
Operating expenses:			
Research and development	91,461	111,209	75,595
General and administrative	28,372	23,900	20,866
Total operating expenses	119,833	135,109	96,461
Operating loss	(111,826)	(132,549)	(55,050)
Other income, net:			
Interest income, net	1,531	94	95
Other income, net	83	79	59
Other income, net	1,614	173	154
Loss before income taxes	(110,212)	(132,376)	(54,896)
Income tax expense			109
Net loss	$ (110,212)	$ (132,376)	$ (55,005)
Other Comprehensive loss:			
Unrealized loss on available for sale securities	(106)		
Comprehensive loss	$ (110,318)	$ (132,376)	$ (55,005)
Loss per share allocable to common stockholders:			
Basic	$ (1.93)	$ (3.32)	$ (1.67)
Diluted	$ (1.93)	$ (3.32)	$ (1.67)
Weighted average shares outstanding:			
Basic	57,126	39,839	33,027
Diluted	57,126	39,839	33,027

See notes to consolidated financial statements.

Table of Contents

EPIZYME, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(Amounts in thousands)

	Year Ended December 31,		
	2016	**2015**	**2014**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net loss	$ (110,212)	$ (132,376)	$ (55,005)
Adjustments to reconcile net loss to net cash used in operating activities:			
Acquired in-process research and development		40,000	
Depreciation and amortization	1,589	1,419	742
Stock-based compensation	10,568	9,849	6,864
Amortization of discount on investments	(51)		
Loss on disposal of property and equipment		27	2
Changes in operating assets and liabilities:			
Accounts receivable	239	1,813	31,592
Prepaid expenses and other current assets	(1,542)	(1,638)	(419)
Accounts payable	341	(3,647)	3,611
Accrued expenses	4,673	4,292	411
Deferred revenue	(1,900)	7,558	(23,721)
Restricted cash and other assets	106	(178)	606
Other long-term liabilities	(182)	(44)	(46)
Net cash used in operating activities	(96,371)	(72,925)	(35,363)
CASH FLOWS FROM INVESTING ACTIVITIES:			
Purchases of available for sale securities	(229,887)		
Proceeds from sales/maturities of available for sale securities	65,097		
Acquisition of in-process research and development		(40,000)	
Purchases of property and equipment	(624)	(183)	(2,216)
Net cash used in investing activities	(165,414)	(40,183)	(2,216)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Proceeds from public offering of common stock, net of commissions	130,438	130,712	101,283
Payment of common stock offering costs	(483)	(367)	(649)
Proceeds from reimbursement of common stock offering costs			269
Payment under capital lease obligation	(561)	(441)	
Proceeds from stock options exercised	1,589	996	2,736
Issuance of shares under employee stock purchase plan	374	436	454
Excess tax benefit from stock option plan			17
Net cash provided by financing activities	131,357	131,336	104,110

Net (decrease) increase in cash and cash equivalents	(130,428)	18,228	66,531
Cash and cash equivalents, beginning of period	208,323	190,095	123,564
Cash and cash equivalents, end of period	$ 77,895	$ 208,323	$ 190,095
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:			
Equipment acquired under capital lease		1,732	
Cash paid for income taxes			963

See notes to consolidated financial statements.

Table of Contents

EPIZYME, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS EQUITY

(Amounts in thousands except share data)

	Common Stock							
	Shares	Amount	Treasury Stock	Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Total Stockholders Equity
Balance at December 31, 2013	28,494,447	$ 3	$	$ 160,390	$ (56,080)	$	$ 104,313
Issuance of common stock (net of commissions and offering costs of $380)	3,673,901			100,903			100,903
Exercise of stock options	2,239,643			2,736			2,736
Stock-based compensation				6,864			6,864
Excess tax benefit from stock option plan				17			17
Issuance of shares under employee stock purchase plan	18,021			454			454
Net loss					(55,005)		(55,005)
Balance at December 31, 2014	34,426,012	$ 3	$	$ 271,364	$ (111,085)	$	$ 160,282
Issuance of common stock (net of commissions and offering costs of $367)	6,701,448	1		130,344			130,345
Exercise of stock options	634,760			996			996
Stock-based compensation				9,849			9,849
Issuance of shares under employee stock purchase plan	23,554			436			436
Net loss					(132,376)		(132,376)
Balance at December 31, 2015	41,785,774	$ 4	$	$ 412,989	$ (243,461)	$	$ 169,532
Issuance of common stock (net of commissions and offering costs of $483)	15,420,220	2		129,953			129,955
Exercise of stock options	788,097			1,589			1,589
Stock-based compensation				10,568			10,568
Issuance of shares under employee stock purchase plan	56,189			374			374
Unrealized loss on available for sale securities						(106)	(106)
Net loss					(110,212)		(110,212)
Balance at December 31, 2016	58,050,280	$ 6	$	$ 555,473	$ (353,673)	$ (106)	$ 201,700

See notes to consolidated financial statements.

Table of Contents

EPIZYME, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. The Company

Epizyme, Inc. (collectively referred to with its wholly owned, controlled subsidiary, Epizyme Securities Corporation, as Epizyme or the Company) is a clinical stage biopharmaceutical company that discovers, develops and plans to commercialize novel epigenetic therapies for patients with cancer and other diseases. The Company s lead product candidate, tazemetostat, is a potent and selective inhibitor of the EZH2 HMT, an enzyme that plays an important role in various cancers. The Company owns the global development and commercialization rights to tazemetostat outside of Japan. Eisai Co. Ltd (Eisai) holds the rights to develop and commercialize tazemetostat in Japan, and holds a limited right of first negotiation for the rest of Asia.

The Company has additional programs in development, including pinometostat, a clinical program that is subject to a collaboration with Celgene Corporation and Celgene RIVOT Ltd., an affiliate of Celgene Corporation (Celgene) (refer to Note 9, *Collaborations*), three preclinical programs for small molecule HMT inhibitors that are subject to a collaboration with Celgene, one clinical and two preclinical programs for small molecule HMT inhibitors that are subject to a collaboration with Glaxo Group Limited, an affiliate of GlaxoSmithKline (GSK) (refer to Note 9, *Collaborations*), and multiple novel targets for which the Company retains worldwide global development and commercialization rights.

Through December 31, 2016, the Company has raised an aggregate of $728.7 million to fund its operations, of which $207.8 million was non-equity funding through its collaboration agreements, $444.9 million was from the sale of common stock in the Company s public offerings and $76.0 million was from the sale of redeemable convertible preferred stock in private financings prior to the Company s initial public offering in May 2013. As of December 31, 2016, the Company had $242.2 million in cash, cash equivalents and marketable securities.

The Company commenced active operations in early 2008. Since its inception, the Company has generated an accumulated deficit of $353.7 million through December 31, 2016 and will require substantial additional capital to fund its research and development. The Company is subject to risks common to companies in the biotechnology industry, including, but not limited to, risks of failure of clinical trials and preclinical studies, the need to obtain additional financing to fund the future development of tazemetostat and the rest of its pipeline, the need to obtain marketing approval for its product candidates, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations and ability to transition from pilot-scale manufacturing to large-scale production of products.

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 transactions and balances of subsidiaries have been eliminated in consolidation.

Use of Estimates

The preparation of these consolidated financial statements in accordance with accounting principles generally accepted in the United States requires management 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 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.

Table of Contents

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 these financial statements were filed with the Securities and Exchange Commission.

Cash and cash equivalents

The Company considers all highly liquid securities with original final maturities of three months or less from the date of purchase to be cash equivalents. Cash and cash equivalents are comprised of funds in money market accounts, commercial paper and corporate notes.

Marketable securities

The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available for sale. The Company considers all available for sale securities, including those with maturity dates beyond 12 months, as available to support current operational liquidity needs and therefore classifies all securities with maturity dates beyond 90 days at the date of purchase as current assets within the consolidated balance sheets. Available for sale securities are maintained by the Company s investment managers and may consist of commercial paper, high-grade corporate notes, U.S. Treasury securities, U.S. government agency securities, and certificates of deposit. Available for sale securities are carried at fair value with the unrealized gains and losses included in other comprehensive income (loss) as a component of stockholders equity until realized. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense over the life of the instrument. Realized gains and losses are determined using the specific identification method and are included in other income (expense).

If any adjustment to fair value reflects a decline in value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is other-than-temporary and, if so, mark the investment to market through a charge to the Company s statement of operations and comprehensive loss.

The following table summarizes the available for sale securities held at December 31, 2016 (in thousands):

Description	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Commercial paper	$ 68,407	$	$ (32)	$ 68,375
Corporate notes	70,489		(81)	70,408
U.S. Treasuries	25,507	7		25,514
Total	$ 164,403	$ 7	$ (113)	$ 164,297

The Company did not hold any available for sale securities prior to the second quarter of 2016. Certain short-term debt securities with original maturities of less than 90 days are included in cash and cash equivalents within the consolidated balance sheets and are not included in the tables above.

The amortized cost of available for sale securities is adjusted for amortization of premiums and accretion of discounts to maturity. At December 31, 2016, the balance in the Company s accumulated other comprehensive loss was

composed solely of activity related to the Company s available for sale marketable securities. There was less than $0.1 million of realized losses recognized on the sale of available for sale securities during the year ended December 31, 2016.

The aggregate fair value of available for sale securities held by the Company in an unrealized loss position for less than twelve months as of December 31, 2016 was $128.8 million. The aggregate unrealized loss for those

Table of Contents

securities in an unrealized loss position for less than twelve months as of December 31, 2016 was $0.1 million. The Company determined that there was no material change in the credit risk of any of its investments. As a result, the Company determined it did not hold any investments with any other-than-temporary impairment as of December 31, 2016. The weighted average maturity of the Company s portfolio was approximately three months at December 31, 2016.

Fair Value Measurements

The Financial Accounting Standards Board (FASB) Codification Topic 820, *Fair Value Measurements and Disclosures,* requires the use of valuation techniques that are consistent with the market approach, the income approach and/or the cost approach. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets and liabilities. The income approach uses valuation techniques to convert future amounts, such as cash flows or earnings, to a single present amount on a discounted basis. The cost approach is based on the amount that currently would be required to replace the service capacity of an asset (replacement cost). Valuation techniques should be consistently applied. GAAP also establishes a fair value hierarchy which requires an entity to maximize the use of observable inputs, where available, and minimize the use of unobservable inputs when measuring fair value. The standard describes three levels of inputs that may be used to measure fair value:

Level 1 Quoted prices in active markets for identical assets or liabilities.

Level 2 Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

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.

The Company s financial instruments as of December 31, 2016 consisted primarily of cash and cash equivalents, marketable securities and accounts receivable and accounts payable. The Company s financial instruments as of December 31, 2015 consisted primarily of cash and cash equivalents, accounts receivable and accounts payable. As of December 31, 2016 and December 31, 2015, the Company s financial assets recognized at fair value consisted of the following:

	Fair Value as of December 31, 2016			
	Total	Level 1	Level 2	Level 3
	(In thousands)			
Cash equivalents	$ 62,854	$ 59,862	$ 2,992	$
Marketable securities:				
Commercial paper	68,375		68,375	
Corporate notes	70,408		70,408	
U.S. government agency securities and treasuries	25,514		25,514	
Total	$ 227,151	$ 59,862	$ 167,289	$

	Fair Value as of December 31, 2015			
	Total	Level 1	Level 2	Level 3
	(In thousands)			
Cash equivalents	$ 197,023	$ 197,023	$	$
Total	$ 197,023	$ 197,023	$	$

Cash equivalents and marketable securities have been initially valued at the transaction price and subsequently valued, at the end of each reporting period, utilizing third-party pricing services or other market observable data.

Table of Contents

The Company measures its cash equivalents at fair value on a recurring basis. The Company classifies its cash equivalents within Level 1 of the fair value hierarchy because they are valued using observable inputs that reflect quoted prices for identical assets in active markets. The Company measures its marketable securities at fair value on a recurring basis and classifies those instruments within Level 2 of the fair value hierarchy. The pricing services used by management utilize industry standard valuation models, including both income and market based approaches and observable market inputs to determine the fair value of marketable securities.

Going Concern

The Company adopted the requirements of FASB Accounting Standards Update (ASU) No. 2014-15, *Disclosure of Uncertainties About an Entity s Ability to Continue as a Going Concern*, on December 31, 2016. At each reporting period, the Company evaluates whether there are conditions or events that raise substantial doubt about the Company s ability to continue as a going concern within one year after the date that the financial statements in both its Quarterly Reports on Form 10-Q and Annual Reports on Form 10-K are issued. The Company is required to make certain additional disclosures if it concludes substantial doubt exists and it is not alleviated by the Company s plans or when its plans alleviate substantial doubt about the Company s ability to continue as a going concern.

The Company s evaluation entails analyzing prospective operating budgets and forecasts for expectations of the Company s cash needs, and comparing those needs to the current cash, cash equivalent and marketable security balances. After considering the Company s current research and development plans and the timing expectations related to the progress of its programs, and after considering its existing cash, cash equivalents and marketable securities as of December 31, 2016, the Company did not identify conditions or events that raise substantial doubt about the Company s ability to continue as a going concern within one year from the date these financial statements were issued.

Accounts Receivable

Accounts receivable are amounts due from collaboration partners as a result of research and development services provided, reimbursements 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, 2016 or 2015, 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, cash equivalents, marketable securities and accounts receivable. The Company attempts to minimize the risks related to cash, cash equivalents and marketable securities 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 of collection.

Acquired In-Process Research and Development

The Company records upfront payments that relate to the acquisition of a development-stage product candidate as research and development expense in the period in which they are incurred, provided that the acquired

Table of Contents

development-stage product candidate did not also include processes or activities that would constitute a business, the product candidate has not achieved regulatory approval for marketing and, absent obtaining such approval, has no alternative future use. In the first quarter of 2015, the Company accounted for the upfront payment paid to Eisai Co., Ltd. (Eisai) in connection with the amended and restated collaboration and license agreement, pursuant to which the Company reacquired the worldwide rights, excluding Japan, to tazemetostat, as in-process research and development expense.

Property and Equipment

The Company records property and equipment at cost. Property and equipment acquired under a capital lease is recorded at the lesser of the present value of the minimum lease payments under the capital lease or the fair value of the leased property at lease inception. The Company calculates depreciation and amortization using the straight-line method over the following estimated useful lives:

Asset Category	**Useful Lives**
Laboratory equipment	5 - 20 years
Office furniture and equipment	3 - 10 years
Leasehold improvements	3 - 10 years or term of respective lease, if shorter

Amortization of capital lease assets is included in depreciation expense. 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.

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. No such impairments were recorded during 2016, 2015 or 2014.

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

Table of Contents

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 6, *Income Taxes*, for additional information regarding the Company s income taxes.

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 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

Table of Contents

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-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

Table of Contents

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.

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 are expensed as incurred. Research and development expenses are comprised of costs incurred in providing research and development activities, including salaries and benefits, facilities costs, overhead costs, contract research and development services, and other outside costs. Nonrefundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

External research and development expenses associated with the Company s programs include clinical trial site costs, clinical manufacturing costs, costs incurred for consultants and other outside services, such as data management and statistical analysis support, and materials and supplies used in support of the clinical and preclinical programs. Internal costs of the Company s clinical programs include salaries, stock-based compensation, and the portion of the Company s facility costs allocated to research and development expense. When third-party service providers billing terms do not coincide with the Company s period-end, the Company is required to make estimates of its obligations to those third parties, including clinical trial and pharmaceutical development costs, contractual services costs and costs for supply of its drug candidates incurred in a given accounting period and record accruals at the end of the period. The Company bases its estimates on its knowledge of the research and development programs, services performed for the period, past history for related activities and the expected duration of the third-party service contract, where applicable.

The Company generally accrues expenses related to research and development activities based on the services received and efforts expended pursuant to contracts with multiple contract research organizations that conduct and manage clinical trials, as well as other vendors that provide research and development services. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical trial milestones. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from estimates, the Company would adjust the accrual or prepaid accordingly in future periods.

Table of Contents

Stock-Based Compensation

The Company measures employee stock-based compensation based on the grant date fair value of the stock-based compensation award. The Company grants stock options at exercise prices equal to the fair value of the Company s common stock on the date of grant, based on observable market prices.

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 shares of common stock 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 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.

Segment Information

The Company operates as one reportable business segment: the discovery and development of novel epigenetic therapies for patients with cancer and other diseases.

Recent Accounting Pronouncements

In May 2014, the FASB issued ASU No. 2014-09, *Revenue From Contracts With Customers*. ASU 2014-09 amends Accounting Standards Codification (ASC) 605, *Revenue Recognition*, by outlining a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers. In addition, the FASB recently issued ASUs 2016-10 and 2016-12, which provide clarifying amendments to ASU 2014-09. ASU 2014-09 and its related amendments will be effective for the Company for interim and annual periods beginning after December 15, 2017, with early adoption permitted for periods beginning after December 15, 2016. The Company expects to adopt ASU 2014-09, as amended, effective January 1, 2018. The Company plans on utilizing the modified prospective approach to implementing this standard and is in the process of evaluating its collaboration agreements with Celgene, GSK and Eisai (as it relates to the receipt of royalties on the sale of any EZH2 product in Japan) to determine the impact the adoption of these ASUs may have on its consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)*, which requires lessees to recognize a right-of-use asset and lease liability for most lease arrangements. The new standard is effective for annual reporting

periods beginning after December 15, 2018 with early adoption permitted. The Company is currently evaluating the potential changes from this ASU to the Company s future financial reporting and disclosures.

Table of Contents

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*. The standard will revise accounting for share-based compensation arrangements, including the accounting for income taxes, forfeitures, and statutory tax withholding requirements, as well as classification in the statement of cash flows. Under this guidance, a company recognizes all excess tax benefits and tax deficiencies as income tax expense or benefit in the income statement when the awards vest or are settled. The amendments also remove the requirement to delay the recognition of an excess tax benefit until it reduces current taxes payable. In addition, cash flows related to excess tax benefits will no longer be separately classified as a financing activity apart from other income tax cash flows. The standard also allows the Company to repurchase more of an employee s shares for tax withholding purposes without triggering liability accounting, clarifies that all cash payments made on an employee s behalf for withheld shares should be presented as a financing activity on the cash flows statement, and provides an accounting policy election to account for forfeitures as they occur. ASU 2016-09 is effective for public companies for annual reporting periods beginning after December 15, 2016, including interim periods within those annual reporting periods with all adjustments to be reflected as of the beginning of the fiscal year of adoption; however, early adoption is permitted. The Company has evaluated the impact of ASU 2016-09 and expects that when it adopts this standard for the annual reporting period beginning January 1, 2017, it will recognize previously unrecognized excess tax benefits using the modified retrospective transition method, which the Company expects will result in a cumulative increase of approximately $23.0 million to $27.0 million to deferred tax assets and the valuation allowance. The Company does not expect the implementation of the standard to materially impact its future stock-based compensation expense.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments (Topic 230)*. The new standard clarifies certain aspects of the statement of cash flows, including the classification of contingent consideration payments made after a business combination, the clarification of restricted cash, and several clarifications not currently applicable to the Company. The new standard also clarifies that an entity should determine each separately identifiable source or use within the cash receipts and cash payments on the basis of the nature of the underlying cash flows. In situations in which cash receipts and payments have aspects of more than one class of cash flows and cannot be separated by source or use, the appropriate classification should depend on the activity that is likely to be the predominant source or use of cash flows for the item. The new standard will be effective for the Company on January 1, 2018. The adoption of this standard is not expected to have a material impact on the Company s consolidated statements of cash flows.

In November 2016, the FASB issued ASU 2016-18, *Restricted Cash*, or ASU 2016-18. The amendments in ASU 2016-18 require an entity to reconcile and explain the period-over-period change in total cash, cash equivalents and restricted cash within its statements of cash flows. ASU 2018-18 is effective for fiscal years, and interim periods within, beginning after December 15, 2017. Early adoption is permitted. A reporting entity must apply the amendments in ASU 2016-18 using a full retrospective approach. The Company is currently evaluating the impact the adoption of the ASU will have on its consolidated financial statements.

Table of Contents

3. Property and Equipment, net

Property and equipment, net consists of the following:

	December 31,	
	2016	2015
	(In thousands)	
Laboratory equipment	$ 3,691	$ 3,468
Computer and office equipment, furniture (1)	4,495	4,848
Leasehold improvements	464	473
Property and equipment	8,650	8,789
Less: accumulated depreciation and amortization	(5,526)	(4,700)
Property and equipment, net	$ 3,124	$ 4,089

(1) In 2015, the Company acquired $1.7 million of computer hardware and equipment, pursuant to a capital lease, the term of which expires in February 2018. Accumulated depreciation related to these assets totaled $1.1 million and $0.5 million as of December 31, 2016 and 2015, respectively.

Depreciation and amortization expense was $1.6 million, $1.4 million and $0.7 million for the years ended December 31, 2016, 2015 and 2014, respectively.

4. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following:

	December 31,	
	2016	2015
	(In thousands)	
Prepaid clinical and manufacturing costs	$ 3,666	$ 2,400
Interest receivable on available for sale securities	295	
Other prepaid expenses and other receivables	2,496	2,078
Total prepaid expenses and other current assets	$ 6,457	$ 4,478

5. Accrued Expenses

Accrued expenses consisted of the following:

	December 31,

	2016	2015
	(In thousands)	
Employee compensation and benefits	$ 4,100	$ 3,314
Research and development expenses	10,925	6,518
Professional services and other	982	1,503
Accrued expenses	$ 16,007	$ 11,335

6. Income Taxes

The Company s losses before income taxes consist solely of domestic losses. The Company did not have income tax expense for the years ended December 31, 2016 and 2015. Income tax expense for the year ended December 31, 2014 reflects adjustments identified in 2014 related to the year ended December 31, 2013 in the course of preparing the 2013 income tax returns. The Company had no deferred income tax expense for the years ended December 31, 2016, 2015 or 2014.

Table of Contents

A reconciliation of the federal statutory income tax rate and the Company s effective income tax rate is as follows:

	Year Ended December 31,		
	2016	2015	2014
Federal statutory income tax rate	34.0%	34.0%	34.0%
State income taxes	4.5	5.2	4.9
Research and development and other tax credits	3.3	1.8	13.6
Permanent items	(1.9)	(1.2)	(5.2)
Change in valuation allowance	(40.1)	(40.0)	(44.3)
Return-to-provision adjustments			(3.1)
Change in deferred taxes	0.2	0.2	
Other	0.0		(0.1)
Effective income tax rate	0.0%	0.0%	(0.2)%

Deferred Tax Assets (Liabilities)

The Company s deferred tax assets (liabilities) consist of the following:

	December 31,	
	2016	2015
	(In thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 94,390	$ 57,005
Research and development and other credit carryforwards	18,055	14,112
Capitalized start-up costs	1,899	2,111
Capitalized research and development costs	154	258
Deferred revenue	11,231	8,475
Accruals and allowances	1,435	1,233
Eisai license payment	14,035	15,155
Other	5,607	4,275
Gross deferred tax assets	146,806	102,624
Deferred tax asset valuation allowance	(146,548)	(102,370)
Total deferred tax assets	258	254
Deferred tax liabilities:		
Depreciation and other	(258)	(254)
Total deferred tax liabilities	(258)	(254)
Net deferred tax asset (liability)	$	$

The Company evaluated the expected recoverability of its net deferred tax assets as of December 31, 2016 and 2015 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, 2016 and 2015. The valuation allowance increased by $44.2 million in 2016 compared to 2015.

As of December 31, 2016, the Company had operating loss carryforwards of approximately $305.6 million and $302.5 million available to offset future taxable income for United States federal and state income tax purposes,

Table of Contents

respectively. The U.S. federal tax operating loss carryforwards expire commencing in 2029. The state tax operating loss carryforwards expire commencing in 2030. Additionally, as of December 31, 2016 the Company had research and development tax credit carryforwards of approximately $5.2 million and $1.9 million available to be used as a reduction of federal income taxes and state income taxes, respectively, which expire at various dates from 2024 through 2036, as well as federal orphan drug tax credit carryforwards of $11.6 million, which would expire at various dates from 2033 through 2036, and a $0.4 million federal alternative minimum tax credit carryforward, which comprises approximately $0.4 million related to excess tax benefits that have been included in the gross deferred tax asset reflected for research and development and other credit carryforwards. This amount will be recorded as an increase to additional paid-in capital on the consolidated balance sheet when the excess benefits are realized. 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 U.S. 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 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.

Uncertain Tax Positions

The following is a rollforward of the Company s unrecognized tax benefits:

	December 31,	
	2016	2015
	(In thousands)	
Unrecognized tax benefits - as of beginning of year	$ 3,480	$ 3,062
Gross increases - tax positions of prior periods		(43)
Gross increases - current period tax positions	726	461
Unrecognized tax benefits - as of end of year	$ 4,206	$ 3,480

None of the Company s unrecognized tax benefits would result in income tax expense or impact the Company s effective tax rate if recognized. The Company had no accrued tax-related interest or penalties as of December 31, 2016 or 2015.

The Company files income tax returns in the U.S. federal tax jurisdiction and Massachusetts, North Carolina and Colorado state tax jurisdictions. 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.

7. Commitments and Contingencies

Commitments

The Company leases office and laboratory space at Technology Square in Cambridge, Massachusetts under an operating lease agreement with a term through May 31, 2018, 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. The lease extension notice date is August 31, 2017. An extension fee of $0.2 million will be due and payable on November 30, 2017 if the Company has

not (i) exercised its five-year option to renew the headquarter lease or (ii) signed a lease with its existing landlord for a new location with increased square footage.

The Company has a $0.5 million letter of credit as a security deposit for this lease and 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.

Table of Contents

In addition, the Company has a capital lease related to computer hardware equipment, an operating lease for storage space in Colorado and an operating lease for office space in North Carolina.

Rent expense was $2.8 million, $2.7 million and $2.5 million for the years ended December 31, 2016, 2015, and 2014, respectively.

The Company s contractual commitments under these leases, excluding common area maintenance charges and real estate taxes, as of December 31, 2016 are as follows:

	Total	2017	2018	2019
		(In thousands)		
Operating leases	$ 4,100	$ 2,898	$ 1,202	$
Capital lease, including amounts representing interest	776	665	111	
Total commitments	$ 4,876	$ 3,563	$ 1,313	$

In addition to commitments under leasing arrangements, as of December 31, 2016 the Company has committed to $12.0 million of remaining development costs payable to Roche Molecular, expected to be paid through 2019 upon certain development and regulatory milestones, under an amended companion diagnostic agreement. In addition, the contractual commitments table above does not include potential future milestones or royalties that the Company may be required to make under license and collaboration agreements, including potential future milestones or royalties payable to Eisai under the amended collaboration and license agreement, due to the uncertainty of the occurrence of the events requiring payment under these agreements. Refer to Note 9, *Collaborations*.

Additionally, the Company enters into contracts in the normal course of business with clinical research organizations for clinical and preclinical research studies, external manufacturers for product for use in clinical trials, and other research supplies and other services as part of the Company s operations. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in the contractual commitments table above.

Contingencies

In October 2013, the Company entered into a license agreement with a third party to obtain a non-exclusive license to a patent related to an excipient in the formulation of pinometostat. During the term of this license agreement, the Company may be required to make a 0.3 million milestone payment upon the first approval of a new drug application for pinometostat and pay royalties in the low single digits on commercial net sales of pinometostat.

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.

In January 2016, the Company issued an additional 15,333,334 shares of common stock in connection with a public offering. The issuance of these shares contributed to a significant increase in the Company s shares outstanding as of December 31, 2016 and in the weighted average shares outstanding for the year ended December 31, 2016 when compared to the comparable prior year periods. During the year ended December 31, 2016, the Company also sold

23,581 shares of Common Stock under an at the market program (ATM Facility) with Cowen and Company, LLC (Cowen) acting as sales agent during the year ended December 31, 2016. Cowen was compensated at a fixed commission rate of 3.0%. Transactions under the ATM Facility resulted in net proceeds of $0.3 million in the year ended December 31, 2016. The Company also incurred other

Table of Contents

issuance related costs of $0.1 million associated with the ATM Facility in the fourth quarter of 2016, which have been accounted for as an offset to additional paid in capital. Through March 10, 2017, including sales in the year ended December 31, 2016, the Company sold 155,834 shares of Common Stock under the sales agreement with Cowen, resulting in net proceeds of $1.9 million related to the ATM Facility. The Company terminated the sales agreement with Cowen, effective March 10, 2017.

As of December 31, 2016, a total of 6,952,359 shares of common stock were reserved for issuance upon (i) the exercise of outstanding stock options and vesting of restricted stock units and (ii) the issuance of stock awards under the Company s 2013 Stock Incentive Plan and 2013 Employee Stock Purchase Plan.

9. Collaborations

Celgene

In April 2012, the Company entered into a collaboration and license agreement with Celgene. On July 8, 2015, the Company entered into an amendment and restatement of the collaboration and license agreement with Celgene.

Original Agreement Structure

Under the original agreement, the Company granted Celgene an exclusive license, for all countries other than the United States, to small molecule HMT inhibitors targeting the DOT1L HMT, including pinometostat, and an option, on a target-by-target basis, to exclusively license, for all countries other than the United States, rights to small molecule HMT inhibitors targeting any HMT targets, other than the EZH2 HMT, including tazemetostat, and targets covered by the Company s collaboration and license agreement dated January 8, 2011 with GlaxoSmithKline (GSK). Under the original agreement, Celgene s option was exercisable during an option period that would have expired on July 9, 2015.

Under the original agreement, the Company received a $65.0 million upfront payment and $25.0 million from the sale of its series C redeemable convertible 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 has received a $25.0 million clinical development milestone payment and $7.0 million of global development co-funding through December 31, 2016. The Company was also eligible to receive $35.0 million in an additional clinical development milestone payment and up to $100.0 million in regulatory milestone payments related to DOT1L as well as up to $65.0 million in payments, including a combination of clinical development milestone payments and an option exercise fee for each available target to which Celgene had the right to exercise its option during an initial option period that would have ended in July 2015 (each a selected target), and up to $100.0 million in regulatory milestone payments for each selected target. As to DOT1L and each selected target, the Company retained all product rights in the United States and was 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.

The Company was obligated to conduct and solely fund research and development costs of the Phase 1 clinical trials for pinometostat. For all remaining DOT1L program development costs, Celgene and the Company were to equally co-fund global development and each party was to solely fund territory-specific development costs for its territory.

Amended and Restated Agreement Structure

Under the amended and restated collaboration and license agreement:

Celgene retains its exclusive license to small molecule HMT inhibitors targeting DOT1L, including pinometostat,

Table of Contents

Celgene s other option rights have been narrowed to small molecule HMT inhibitors targeting three predefined targets (the Option Targets),

The exclusive licenses to HMT inhibitors targeting two of the Option Targets that Celgene may acquire have been expanded to include the United States, with the exclusive license to HMT inhibitors targeting the third Option Target continuing to be for all countries other than the United States,

Celgene s option period has been extended for each of the Option Targets and Celgene s option is exercisable at the time of the Company s investigational new drug application (IND) filing for an HMT inhibitor targeting the applicable Option Target, upon the payment by Celgene at such time of a pre-specified development milestone-based license payment,

Celgene s license may be maintained beyond the end of Phase 1 clinical development for each of the Option Targets, upon payment by Celgene at such time of a pre-specified development milestone-based license payment, and

The Company s research and development obligations with respect to each Option Target under the amended and restated agreement have been extended for at least an additional three years, subject to Celgene exercising its option with respect to such Option Target at IND filing. Subject to the Company s opt-out rights, the Company s research and development obligations have been expanded to include the completion of a Phase 1 clinical trial as to each Option Target following Celgene s exercise of its option at IND filing.

Under the amended and restated agreement, the Company received a $10.0 million upfront payment in exchange for the Company s extension of Celgene s option rights to the Option Targets and the Company s research and development obligations. In addition, the Company is eligible to earn an aggregate of up to $75.0 million in development milestones and license payments, up to $365.0 million in regulatory milestone payments and up to $170.0 million in sales milestone payments related to the three Option Targets. The Company is also eligible to receive royalties on each of the Option Targets as specified in the amended and restated agreement. The Company is also eligible to earn $35.0 million in an additional clinical development milestone payment and up to $100.0 million in regulatory milestone payments related to DOT1L. 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 Celgene. Due to the varying stages of development of each target, the Company is not able to determine the next milestone that might be earned, if any.

The amended and restated agreement eliminated the right of first negotiation that the Company had granted to Celgene under the original agreement with respect to business combination transactions that the Company may desire to pursue with third parties.

The Company is primarily responsible for the research strategy under the collaboration. During each applicable option period the Company is required to use commercially reasonable efforts to carry out a mutually agreed-upon research plan for each Option Target. Subject to the Company s opt-out right, for the DOT1L target and each of the Option Targets, the Company is required to conduct and solely fund development costs of the Phase 1 clinical trials for HMT inhibitors directed to such targets, including for pinometostat. After the completion of Phase 1 development, as to DOT1L and the Option Target for which the Company retains U.S. rights, Celgene and the Company will equally co-fund global development and each party will solely fund territory-specific development costs for its respective

territory; and, as to the other two Option Targets, after the completion of Phase 1 development, Celgene will solely fund all development costs on a worldwide basis.

Accounting Considerations of the Amended and Restated Agreement

The Company determined that the amended and restated agreement represented a modification of the original agreement. Accordingly, the Company determined that the remaining deferred revenue of $21.6 million attributable to the original agreement should be combined with the $10.0 million upfront payment received from

Table of Contents

Celgene upon execution of the amended and restated agreement. This combined amount, along with any development milestone-based license fees associated with those Option Targets where Celgene s option rights are determined to be non-substantive, will be recognized on a prospective basis after (i) identifying the deliverables and units of accounting included in the amended and restated agreement, (ii) allocating the total arrangement fee among the units of accounting and (iii) determining the revenue recognition for each unit of accounting.

The Company evaluated the deliverables in the amended and restated agreement and determined that the deliverables included its obligation to provide research and development services for DOT1L and the three Option Targets. In addition, the Company concluded that Celgene s option rights are not substantive and the licenses to HMT inhibitors targeting each Option Target were therefore considered to be deliverables. As a result, the Company has determined the deliverables in the amended and restated arrangement to be:

Research and development services for DOT1L and the three Option Targets

Licenses to HMT inhibitors targeting the Option Targets

The Company evaluated the nature of the deliverables to determine the units of accounting. At a program level (that is, for DOT1L and each Option Target), the Company believes there is standalone value. Therefore, the identified deliverables were evaluated on a program by program basis to determine the units of accounting.

The Company determined the research services related to DOT1L have stand-alone value as the services are delivered and therefore represent a single unit of accounting. There are no other deliverables related to the DOT1L program. For two of the Option Targets, the Company concluded the licenses and related research services should be accounted for as a combined unit of accounting up until an IND filing. Prior to an IND filing, the delivered research services do not have standalone value from the remaining undelivered elements because Celgene could not resell the research services and no other vendor has the specialized skills and know-how related to HMT inhibitors necessary to provide the research services. After an IND filing, for these two Option Targets, the Company concluded the delivered pre-IND research services and licenses, once delivered, would have standalone value from the remaining research services because Celgene, or other market participants, would have the ability to execute human clinical trials on the identified compound. After an IND filing, the remaining research services represent a separate unit of accounting which has standalone value upon delivery. With respect to the third Option Target where the Company retains U.S. rights, because the license terms restrict Celgene s access to information through the completion of a Phase 1 trial that would otherwise be necessary for Celgene, or other market participants, to execute human clinical trials on the identified compound, the Company determined the licenses did not have standalone value apart from the research services Accordingly, for the third Option Target, the licenses and research services will be accounted for as a combined unit of accounting.

Because Celgene s option rights with respect to the Option Targets are not considered substantive, any development milestone-based license fees associated with the Option Targets would be considered to be part of the total consideration for purposes of allocating the arrangement consideration. Accordingly, the Company has identified the total allocable arrangement consideration to be $106.6 million, as follows: (i) the remaining $21.6 million of deferred revenue under the original agreement, (ii) the $10.0 million upfront payment made in connection with the amended and restated agreement, and (iii) the $75.0 million of aggregate development milestone-based license fees associated with the Option Targets.

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 license deliverable for each Option Target using management s best estimate of selling price after considering potential future cash flows under each license and industry benchmarks on the probability of achieving development milestones. The Company then discounted these probability-weighted cash flows to their present value. The Company estimated the selling price of the research services to be provided in connection with the DOT1L Phase 1 clinical trial and related to each Option Target using management s best estimate of selling price based on the Company s estimated cost of providing

Table of Contents

the services plus an applicable profit margin of 10%, which is commensurate with observable market data for similar services.

Due to the stage of development of each of the option programs and considering the expected timing of delivery for those deliverables associated with each Option Target, the Company does not expect to recognize revenue related to the Option Targets in 2017. The Company expects to recognize the allocated arrangement consideration as follows, subject to the limitation described in ASC 605-25-30-5:

Research and development services for DOT1L: The arrangement consideration allocated to the DOT1L program will be recognized as the research and development services are performed. The Company allocated $2.8 million to the remaining research services under the DOT1L program, and this amount was recognized through December 31, 2016, the period over which the related research services were provided.

Two Option Targets: The arrangement consideration allocated to these Option Targets of $70.2 million in the aggregate will be deferred until an IND filing. The Company does not expect to recognize any revenue related to the Option Targets during 2017.

Third Option Target: The licenses and the research services provided through completion of a Phase 1 trial represent a single combined unit of accounting. Therefore, because a license is the last delivered item in this unit of accounting, the Company will defer all consideration allocated to this unit of accounting, $33.6 million, until the delivery of the license upon completion of a Phase 1 clinical trial. The Company does not expect to recognize any revenue related to the Option Target during 2017.

If any of the programs are terminated in accordance with the amended and restated agreement, any remaining deferred revenue will be reallocated among the undelivered items based upon their relative selling prices.

Collaboration Revenue

Through December 31, 2016, in addition to amounts allocated to Celgene s purchase of shares of the Company s series C redeemable convertible preferred stock, the Company had recorded a total of $110.0 million in cash and accounts receivable under the Celgene agreement, as amended, including the $3.0 million implied premium on Celgene s purchase of shares of the Company s series C redeemable convertible preferred stock.

Through December 31, 2016, the Company has recognized $74.3 million of total collaboration revenue since the inception of the collaboration, including $1.9 million, $1.1 million and $9.6 million in the years ended December 31, 2016, 2015, and 2014, respectively. In addition, the Company has recognized $0.1 million, $1.1 million and $3.9 million of total global development co-funding as a reduction to research and development expense in the years ended December 31, 2016, 2015, and 2014, respectively. As of December 31, 2016 and December 31, 2015, the Company had deferred revenue of $28.8 million and $30.7 million, respectively, related to this agreement.

GSK

In January 2011, the Company entered into a collaboration and license agreement with 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 agreement, the Company granted GSK exclusive worldwide license rights to HMT inhibitors directed to three targets. Additionally, as part of the research collaboration, the Company agreed to provide research and development services related to the licensed targets pursuant to agreed upon research plans during a research term that ended January 8, 2015. In March 2014, the Company and GSK amended certain terms of this agreement for the third licensed target, revising the license terms with respect to candidate compounds and amending the corresponding financial terms, including reallocating milestone payments and increasing royalty rates as to the third target. The Company substantially completed all research obligations

Table of Contents

under this agreement by the end of the first quarter of 2015 and completed the transfer of the remaining data and materials for these programs to GSK in the second quarter of 2015.

Agreement Structure

Under the agreement, the Company has recorded a $20.0 million upfront payment, a $3.0 million payment upon the execution of the March 2014 agreement amendment, $6.0 million of fixed research funding, $15.0 million of preclinical research and development milestone payments and $9.0 million for research and development services. In addition, in the third quarter of 2016, the Company recognized a $6.0 million clinical milestone following GSK s initiation of patient dosing in a Phase 1 clinical trial of a PRMT5 inhibitor that was discovered by the Company and licensed to GSK. The Company is eligible to receive up to $18.0 million in additional preclinical research and development milestone payments, up to $103.0 million in clinical development milestone payments, up to $278.0 million in regulatory milestone payments and up to $218.0 million in sales-based milestone payments. In addition, GSK is required to pay the Company 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 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 payments from GSK. The next potential milestone that the Company might receive under this agreement would be a $10.0 million payment for the commencement of a good laboratory practices, or GLP, toxicity study by GSK for the second licensed target under the agreement. GSK became solely responsible for development and commercialization for each licensed target in the collaboration when the research term ended on January 8, 2015.

Accounting Analysis. For each selected target in the collaboration, the Company was primarily responsible for research until the earlier of the selection of a development candidate for the target or January 8, 2015, 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. GSK was obligated to provide research funding equal to 100.0% of research and development costs, subject to specified limitations, during the fourth year of the research term.

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 could not 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 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 therefore accounted 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 probabilities of success and the research services in each unit of accounting were initially expected to 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, was recognized as collaboration revenue, on a target-by-target basis, ratably 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. In December 2013, the Company and GSK agreed to the

selection of a development candidate for one of the three targets under the agreement, earning the Company a $4.0 million milestone payment and reducing the period over which the Company was recognizing revenue for this target by nine months. Accordingly, the Company recognized the remaining deferred revenue related to this target during the first quarter of 2014. As to this target, GSK is solely responsible for subsequent development and commercialization.

The $3.0 million upfront payment received in connection with the March 2014 amendment was allocated equally to the remaining two targets for which the Company was actively providing research and development services, as these remaining two targets were at similar stages of development, had equal probabilities of success and the remaining research services were expected to be performed concurrently on a ratable basis over the research term. The $3.0 million was recognized as collaboration revenue, on a target-by-target basis, ratably from the execution of the amendment, in March 2014, through the end of the research term. In the fourth quarter of 2014, the Company agreed to perform additional preclinical research and development studies related to the third target under the agreement, which extended the research term for this target through June 2015. Accordingly, the Company recognized the remaining deferred revenue related to this deliverable, of approximately $1.2 million as of December 31, 2014, in 2015.

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 was combined with the upfront payment and fixed research funding and was 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 2014, the Company achieved $3.0 million in preclinical research and development milestones upon the selection of lead candidates for the second and third targets under the agreement. In the fourth quarter of 2013, the Company achieved a $4.0 million preclinical research and development milestone upon the selection of a development candidate for one of the three targets under the agreement. 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 2014, 2013 and 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 milestones were recognized as revenue upon achievement.

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

Table of Contents

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.

Collaboration Revenue

Through December 31, 2016, the Company has earned a total of $59.0 million under the GSK agreement, which the Company recognized as collaboration revenue in the condensed consolidated statements of operations and comprehensive loss, including $6.0 million, $1.4 million and $25.5 million in the years ended December 31, 2016, 2015 and 2014, respectively. The Company did not have any deferred revenue related to this agreement as of December 31, 2016 or 2015 and any future revenues will relate to any milestone payments and royalties received under the agreement, if any

Eisai

In April 2011, the Company entered into a collaboration and license agreement with 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 tazemetostat, while retaining an opt-in right to co-develop, co-commercialize and share profits with Eisai as to licensed products in the United States.

As of December 31, 2014, the Company had completed its performance obligations under the original agreement.

In March 2015, the Company entered into an amended and restated collaboration and license agreement with Eisai, under which the Company reacquired worldwide rights, excluding Japan, to its EZH2 program, including tazemetostat. Under the amended and restated agreement, the Company is responsible for global development, manufacturing and commercialization outside of Japan of tazemetostat and any other EZH2 product candidates, with Eisai retaining development and commercialization rights in Japan, as well as a right to elect to manufacture tazemetostat and any other EZH2 product candidates in Japan.

Under the original agreement, Eisai was solely responsible for funding all research, development and commercialization costs for EZH2 compounds. Under the amended and restated agreement, the Company is solely responsible for funding global development, manufacturing and commercialization costs for EZH2 compounds outside of Japan, including the remaining development costs due under a Roche Molecular companion diagnostic agreement, and Eisai is solely responsible for funding Japan-specific development and commercialization costs for EZH2 compounds.

The Company recorded the reacquisition of worldwide rights, excluding Japan, to the EZH2 program, including tazemetostat, under the amended and restated agreement with Eisai as an acquisition of an in-process research and development asset. As this asset was acquired without corresponding processes or activities that would constitute a business, had not achieved regulatory approval for marketing and, absent obtaining such approval, had no alternative future use, the Company recorded the $40.0 million upfront payment made to Eisai in March 2015 as research and development expense in the consolidated statements of operations and comprehensive loss. The Company has also agreed to pay Eisai up to $20.0 million in clinical development milestone payments, up to $50.0 million in regulatory milestone payments and royalties at a percentage in the mid-teens on worldwide net sales of any EZH2 product, excluding net sales in Japan. The Company is eligible to receive from Eisai royalties at a percentage in the mid-teens on net sales of any EZH2 product in Japan.

LYSA

In May 2016, the Company entered into a collaboration agreement with the Lymphoma Academic Research Organisation (LYSARC), for the first planned combination trial of tazemetostat. LYSARC is the operational arm of the Lymphoma Study Association (LYSA), a premier cooperative group in France dedicated to clinical and translational research for lymphoma. This Phase 1b/2 study is evaluating tazemetostat in combination with

Table of Contents

R-CHOP, the standard of care front-line combination treatment for diffuse large B-cell lymphoma (DLBCL), as a front-line treatment in elderly, high-risk patients with DLBCL and is being sponsored by LYSARC. LYSA is managing the study operations for the trial, and the Company is recognizing its share of the related expenses as those costs are incurred over the duration of the trial.

Genentech

In June 2016, the Company entered into a collaboration agreement with Genentech Inc. (Genentech), a member of the Roche Group, to conduct a Phase 1b clinical trial to investigate the anti-cancer effects of the Company s EZH2 inhibitor, tazemetostat, and Genentech s anti-PD-L1 cancer immunotherapy, Tecentriq (atezolizumab), when used in combination. The trial is evaluating this combination regimen for the treatment of patients with relapsed or refractory DLBCL. Under the agreement, each company is supplying its respective anti-cancer agent to support the trial and sharing equally in the trial costs. Genentech is managing the study operations for the trial, and the Company is recognizing its share of the related expenses as those costs are incurred over the duration of the trial.

Companion Diagnostics

Roche Molecular. In December 2012, Eisai and the Company entered into an agreement with Roche Molecular under which Eisai and the Company engaged Roche Molecular to develop a companion diagnostic to identify patients who possess certain activating mutations of EZH2. In October 2013, this agreement was amended to include additional mutations in EZH2. The development costs due under the amended agreement with Roche Molecular were the responsibility of Eisai until the execution of the amended and restated collaboration and license agreement with Eisai in March 2015, at which time the Company assumed responsibility for the remaining development costs due under the agreement. In December 2015, the Company entered into the second amendment to the companion diagnostic agreement with Roche Molecular. As of December 31, 2016, the Company is responsible for the remaining development costs of $12.0 million due under the second amendment. The Company expects the remaining development costs under the second amendment to be incurred and paid through 2019.

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

The agreement with Roche Molecular will expire when the Company is no longer developing or commercializing tazemetostat. The Company may terminate the agreement by giving Roche Molecular 90 days written notice if the Company discontinues development and commercialization of tazemetostat or determines, in conjunction with Roche Molecular, that the companion diagnostic is not needed for use with tazemetostat. Either the Company or Roche Molecular 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 Molecular may become entitled to specified termination fees.

10. Employee Benefit Plans

Stock Incentive Plans

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. 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

Table of Contents

stock incentive awards to employees, members of the Company s board of directors and non-employee consultants, advisors or other service providers. 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. Initial non-qualified stock options granted to members of the Company s board of directors generally vest over the recipient s term of Board service. Annual non-qualified stock options granted to members of the Company s board of directors vest on the one-year anniversary of the grant.

Stock-Based Compensation

Stock-based compensation expense is classified in the consolidated statements of operations and comprehensive loss as follows:

	Year Ended December 31,		
	2016	2015	2014
	(In thousands)		
Research and development	$ 5,352	$ 5,155	$ 3,299
General and administrative	5,216	4,694	3,565
Total	$ 10,568	$ 9,849	$ 6,864

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,		
	2016	2015	2014
Risk-free interest rate	1.2%	1.6%	1.6%
Expected life of options	6.0 years	6.0 years	6.0 years
Expected volatility of underlying stock	78.5%	83.6%	92.1%
Expected dividend yield	0.0%	0.0%	0.0%

There were no stock option awards granted to non-employees in 2016, 2015 or 2014.

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 using a blended approach encompassing its historical experience and 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

Table of Contents

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, 2016:

	Number of Options (In thousands)	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Term (In years)	Aggregate Intrinsic Value (In thousands)
Outstanding at December 31, 2015	3,100	$ 15.20		
Granted	2,213	9.50		
Exercised	(788)	2.02		
Forfeited or expired	(466)	18.08		
Outstanding at December 31, 2016	4,059	$ 14.32	8.4	$ 8,724
Exercisable at December 31, 2016	1,162	$ 18.39	6.9	$ 3,106
Vested and expected to vest	3,695	$ 14.53	8.3	$ 8,001

During the years ended December 31, 2016, 2015 and 2014, the Company granted stock options to purchase an aggregate of 2,212,668 shares, 1,289,755 shares and 876,385 shares, respectively, at weighted average grant date fair values per option share of $6.42, $14.57 and $21.73, respectively. The total grant date fair value of options that vested during the years ended December 31, 2016, 2015 and 2014 was $12.0 million, $9.3 million and $4.9 million, respectively. The aggregate intrinsic value of stock options exercised was $7.1 million in 2016, $11.9 million in 2015 and $59.4 million in 2014.

As of December 31, 2016, there was $19.2 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 following is a summary of restricted stock unit activity for the year ended December 31, 2016:

	Number of Units (In thousands)	Weighted Average Grant Date Fair Value per Unit

Outstanding at December 31, 2015	37	$	18.49
Granted	81		9.29
Vested	(54)		12.20
Outstanding at December 31, 2016	64	$	12.20

In February 2016, the Company granted 80,732 restricted stock units with a grant date fair value of $9.29 per unit, in accordance with the Company s chief financial officer s employment agreement. One quarter of these restricted stock units vested on February 9, 2016 and the remaining three quarters are vesting on a straight line basis over 36 months. As of December 31, 2016 there was $0.8 million of unrecognized compensation cost related to restricted stock units that are expected to vest. These costs are expected to be recognized over a weighted average remaining vesting period of 2.1 years. The intrinsic value of restricted stock that vested during the years ended December 31, 2016, 2015 and 2014 was $0.5 million, $0.0 million and $0.1 million, respectively.

Table of Contents

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. During the year ended December 31, 2014, the Company implemented a matching contribution to the 401(k) Plan, matching 50% of an employee s contribution up to a maximum of 3% of the participant s compensation. Company contributions to the 401(k) plan totaled $0.4 million, $0.4 million and $0.2 million in the years ended December 31, 2016, 2015 and 2014, respectively.

11. Loss 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). The two-class method was not applied for the years ended December 31, 2016, 2015 and 2014 due to the net loss recognized in each of those periods.

Basic and diluted loss per share allocable to common stockholders are computed as follows:

	Year Ended December 31,		
	2016	2015	2014
	(In thousands except per share data)		
Net loss	$ (110,212)	$ (132,376)	$ (55,005)
Weighted average shares outstanding	57,126	39,839	33,027
Basic and diluted loss per share allocable to common stockholders	$ (1.93)	$ (3.32)	$ (1.67)

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:

	Year Ended December 31,		
	2016	2015	2014
	(In thousands)		
Stock options	4,059	3,100	2,960
Unvested restricted stock	64	37	
Shares issuable under employee stock purchase plan	46	8	6
	4,169	3,145	2,966

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. Refer to Note 9, *Collaborations*, for additional information

regarding this collaboration agreement. In the second quarter of 2013, in connection with the Company s 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 December 31, 2013. In the first quarter of 2014, in connection with the Company s public offering of common stock, Celgene made an additional investment in the Company, acquiring an additional 340,000 shares of the Company s common stock. As of December 31, 2016, Celgene s ownership percentage represented 6.3% of the Company s outstanding common stock.

Under the Celgene collaboration agreement, the Company recognized $1.9 million, $1.1 million and $9.6 million of collaboration revenue in the years ended December 31, 2016, 2015 and 2014, respectively, and as of

Table of Contents

December 31, 2016 and 2015, had recorded $28.8 million and $30.7 million of deferred revenue related to the Celgene collaboration arrangement, respectively. Additionally, in the years ended December 31, 2016, 2015 and 2014, the Company recorded $0.1 million, $1.1 million and $3.9 million, respectively, in global development co-funding from Celgene. As of December 31, 2016 and 2015, the Company had accounts receivable of less than $0.1 million and $0.1 million, respectively, related to this collaboration arrangement.

13. Unaudited Quarterly Results

The results of operations on a quarterly basis for the years ended December 31, 2016 and 2015 are set forth below:

	Quarter Ended			
	March 31, 2016	June 30, 2016	September 30, 2016	December 31, 2016
	(In thousands, except per share data)			
Collaboration revenue	$ 472	$ 473	$ 6,584	$ 478
Operating expenses:				
Research and development	17,740	21,450	23,888	28,383
General and administrative	5,846	7,424	7,522	7,580
Total operating expenses	23,586	28,874	31,410	35,963
Operating loss	(23,114)	(28,401)	(24,826)	(35,485)
Other income, net	235	420	490	469
Net loss	$ (22,879)	$ (27,981)	$ (24,336)	$ (35,016)
Loss per share allocable to common stockholders:				
Basic	$ (0.41)	$ (0.49)	$ (0.42)	$ (0.60)
Diluted	$ (0.41)	$ (0.49)	$ (0.42)	$ (0.60)
Weighted average shares outstanding:				
Basic	55,149	57,352	57,970	58,016
Diluted	55,149	57,352	57,970	58,016

	Quarter Ended			
	March 31, 2015	June 30, 2015	September 30, 2015	December 31, 2015
	(In thousands, except per share data)			
Collaboration revenue	$ 911	$ 736	$ 358	$ 555
Operating expenses:				
Research and development	57,051	20,551	16,788	16,819
General and administrative	5,237	5,970	6,676	6,017
Total operating expenses	62,288	26,521	23,464	22,836
Operating loss	(61,377)	(25,785)	(23,106)	(22,281)

Other income, net	51	26	41	55
Net loss	$ (61,326)	$ (25,759)	$ (23,065)	$ (22,226)
Loss per share allocable to common stockholders:				
Basic	$ (1.75)	$ (0.63)	$ (0.56)	$ (0.53)
Diluted	$ (1.75)	$ (0.63)	$ (0.56)	$ (0.53)
Weighted average shares outstanding:				
Basic	34,992	41,087	41,461	41,725
Diluted	34,992	41,087	41,461	41,725