



# Meeting Information Package

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**Advisory Committee Briefing Document**

**Tazemetostat for the Treatment of Pediatric Subjects with  
Malignant Rhabdoid Tumors and Other INI1-Negative Tumors**

**Epizyme, Inc.**

**Pediatric Oncology Subcommittee of the Oncologic  
Drugs Advisory Committee**

**Date of Meeting: June 28, 2016**

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## LIST OF ABBREVIATIONS

AE	Adverse event
ATRT	Atypical teratoid rhabdoid tumor
BID	Twice a day
CAP	College of American Pathology
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CLIA	Clinical laboratory improvement amendments
CNS	Central nervous system
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DLBCL	Diffuse large B-cell lymphoma
ES	Epithelioid sarcoma
EMC	Extraskeletal myxoid chondrosarcoma
EMPNST	Epithelial malignant peripheral nerve sheath tumor
EZH2	Enhancer of zeste homolog 2
FISH	Fluorescent in situ hybridization
FTIH	First-time-in-human
FL	Follicular lymphoma
GCB	Germinal center origin
H3K27	Lysine 27 of histone H3
H3K27Me3	Trimethylated form of lysine 27 of histone H3
HMT	Histone methyltransferases
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
INI1	Integrase interactor 1
MATCH	Molecular Analysis for Therapeutic Choice
MRT	Malignant rhabdoid tumor
MRTO	Malignant rhabdoid tumor of the ovary
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate

OS	Overall survival
PFS	Progression-free survival
PD	Pharmacodynamics
PK	Pharmacokinetics
PR	Partial response
PRC2	Polycomb Repressive Complex 2
R-CHOP	Rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RMC	Renal medullary carcinoma
RP2D	Recommended Phase 2 Dose
RTK	Rhabdoid tumor of kidney
SAE	Serious adverse event
SAM	S-adenosyl methionine
SD	Sprague Dawley
SCCOHT	Small cell carcinoma of the ovary, hypercalcemic type
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 2
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1
SWI/SNF	SWItch/Sucrose NonFermentable
TEAE	Treatment-emergent adverse event
WT	Wild type

## EXECUTIVE SUMMARY

Epizyme is participating in the Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee to provide the Agency with an opportunity to seek input from the Subcommittee on the issuance of a Written Request to facilitate tazemetostat development in pediatric patients. Tazemetostat (EPZ-6438) is a selective, reversible, SAM-competitive small molecule inhibitor of the EZH2 HMT enzymatic activity. Aberrant EZH2 activity has been implicated as an oncogenic driver (through presence of activating mutations in EZH2) in non-Hodgkin lymphoma (NHL), providing a rationale for clinical investigation of tazemetostat in Diffuse Large B-Cell (DLBCL) and Follicular Lymphoma (FL). In addition to genetic alterations in EZH2 itself, distal genetic changes in other proteins can lead to an oncogenic dependency on EZH2 activity, specifically those affecting proteins of the SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex. At many gene loci, PRC2 and SWI/SNF antagonize each other and loss of the core subunit INI1 or the ATPase subunit SMARCA4, have been demonstrated to generate sensitivity to EZH2 inhibition in select indications.

Loss of INI1 or SMARCA4 expression either through direct or indirect genetic mechanisms is a hallmark of several life-threatening rare tumors such as rhabdoid tumors, epithelioid sarcomas and synovial sarcomas that affect children and young adults. There is a high unmet need for novel effective therapies in subjects with these tumors as standard approaches are only marginally useful. For example, current treatment of malignant rhabdoid tumors (MRT), an integrase interactor 1 (INI1)-negative tumor, consists of multi-modality combinations consisting of surgery, chemotherapy and radiation therapy, which are associated with limited efficacy and significant treatment-related morbidity. Overall, INI1-negative or certain SMARCA4-negative tumors are characterized as aggressive cancers with no specifically approved treatments to date. To address the unmet medical need for INI1-negative tumors, Epizyme is developing tazemetostat for the treatment of pediatric (phase 1) and adult (phase 2) subjects with advanced or metastatic MRT and other tumors bearing a deficiency of INI1.

The adult phase 2 global multicenter study includes subjects with advanced or metastatic MRT and other tumors bearing a deficiency of INI1, is ongoing and will enroll up to 150 subjects in five cohorts. The first cohort will be comprised of subjects with MRT, rhabdoid tumor of the kidney (RTK), atypical teratoid rhabdoid tumor (ATRT), and select tumors with

rhabdoid features (including malignant rhabdoid tumor of the ovary, also referred to as small cell carcinoma of the ovary, hypercalcemic type), all of which are characterized by INI1- or SMARCA4-negativity. The second cohort will be comprised of subjects with synovial sarcoma in which INI1 is dysregulated by a reciprocal translocation between chromosome 18 and the X chromosome. The third cohort will be comprised of subjects with non-rhabdoid INI1-negative tumors including but not limited to epithelioid malignant peripheral nerve sheath tumor (EMPNST), extraskeletal myxoid chondrosarcoma (EMC), myoepithelial carcinoma and other INI1-negative tumors such as dedifferentiated chordoma. Patients with renal medullary carcinoma (RMC) or epithelioid sarcoma (ES), which are both characterized as non-rhabdoid INI1-negative tumors, will be excluded from cohort three and instead will each have their own disease specific cohorts (four and five, respectively).

Adult subjects will be dosed with tazemetostat at 800 mg twice daily with tablets taken orally. The primary endpoint is overall response rate (ORR) for subjects with INI1-negative tumors and progression-free survival (PFS) for subjects with synovial sarcoma. Secondary endpoints include duration of response, overall survival (OS), and PFS for subjects with INI1-negative tumors, as well as safety and pharmacokinetics (PK).

For children with these deadly diseases, tazemetostat potentially represents a meaningful option. The ongoing pediatric phase 1 global, multicenter study is enrolling children with cancers such as malignant rhabdoid tumors, based on unique genetic defects that appear to result in biological sensitivity to EZH2 inhibition. The study will enroll approximately 24 subjects in a dose escalation design, followed by dose expansion treating approximately 60 subjects, with an oral suspension of tazemetostat. The study is enrolling subjects with the same INI1-negative tumors, SMARCA4-negative tumors or synovial sarcoma as in the adult study. The primary endpoint of the study is safety, with the objective of establishing the recommended phase 2 dose in pediatric subjects. Secondary endpoints include PK, ORR, duration of response, PFS, and OS.

Epizyme proposes that the ongoing trial, EZH-102 “A Phase 1 Study of Tazemetostat in Pediatric Subjects with Relapsed/Refractory INI1-negative Tumors or Synovial Sarcomas” (see Section 8) can be used as the basis for a Written Request from the FDA. Epizyme is evaluating tazemetostat in subjects with these cancers since the molecular mechanism is compelling, especially with the recent identification of mutations in INI1 or SMARCA4 as genetic drivers across these cancers. Because of the rarity of these tumors within the general population, patient numbers may be limited within each specific tumor type. Nevertheless,



Epizyme believes this approach provides the optimal mechanism to evaluate tazemetostat in a pediatric population with these rare fatal diseases and very limited treatment options. In conjunction with a larger safety and PK database from concurrent clinical trials in adults, the results of these investigations will adequately describe the safety, pharmacokinetic and efficacy profile of tazemetostat in the pediatric population.



## 1.0 DISEASE BACKGROUND

### 1.1 Overview of Malignant Rhabdoid Tumors and Other INI1-Negative Tumors in Adults and Children

Malignant rhabdoid tumors and other INI1-negative tumors are a group of tumors which are rare and poorly treated by existing therapies. This is particularly true for malignant rhabdoid tumors (MRT) which arise in the brain, kidney, and other soft tissues including the ovary. These are rare, but rapidly progressive tumors, and of the non-ovarian subtypes 98% are INI1-negative resulting from homozygous deletion or mutation of the INI1 gene (also known as SNF5 or SMARCB1) [Biegel 1999; Jackson 2009], with rare cases of deletion or mutation of SMARCA4 [Schneppenheim 2010; Chun 2016]. In comparison, malignant rhabdoid tumors of the ovary are characterized by biallelic genetic loss of SMARCA4 with a concomitant epigenetic suppression of the redundant subunit SMARCA2 [Bailey 2015; Jelinic 2015; Kupryjańczyk 2013; Ramos 2014]. These different rhabdoid tumors are diagnosed in children or young adults, have rapid onset, are highly resistant to all treatment and are characterized by aberrant chromatin remodeling due to the loss of INI1 or SMARCA4 from the SWI/SNF complex.

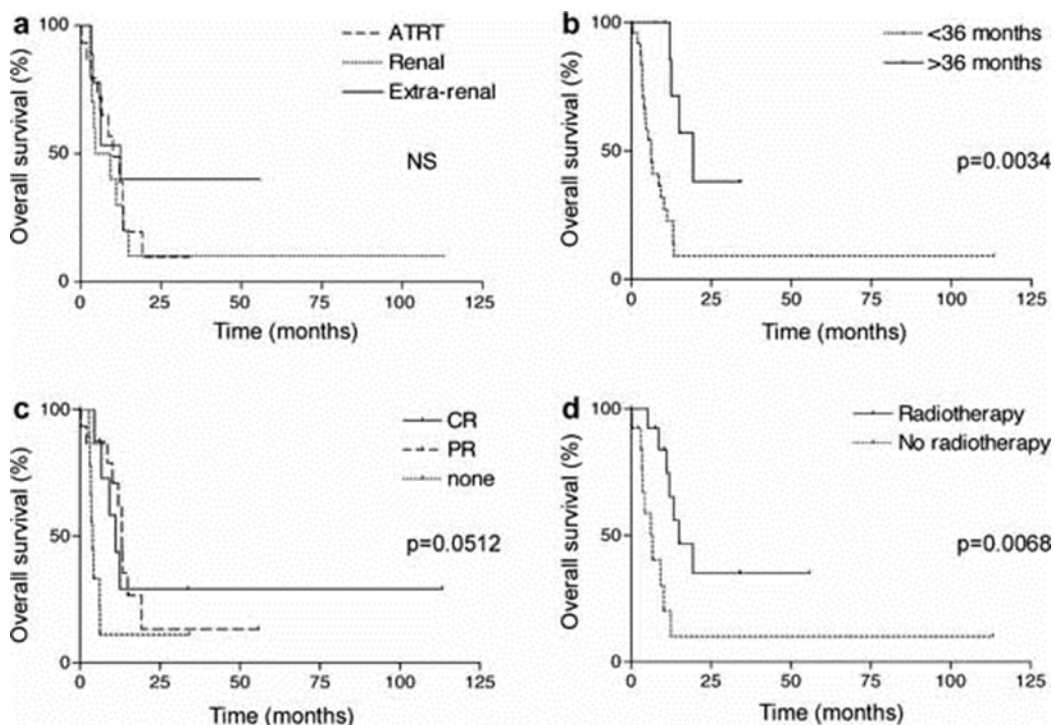
Other rare tumors characterized by genetic deletions or mutations of INI1 rendering cells INI1-negative include epithelioid sarcoma (ES), epithelioid malignant peripheral nerve sheath tumor (EMPNST), extraskeletal myxoid chondrosarcoma (EMC); myoepithelial carcinoma, renal medullary carcinoma (RMC). Synovial sarcoma, while having wild-type INI1 expressed, are functionally INI1-negative as a result of its characteristic translocation [t(X;18)(p11;q11)] resulting in formation of the SS18-SSX fusion protein which displaces INI1 from SWI/SNF complexes.

Epizyme proposes to study this patient population which includes several tumors for which there are currently no effective treatment options, specifically, MRT and several rare tumor types that are characterized by INI1-negativity. There exists preliminary clinical activity observed from the phase 1 trial with ongoing objective responses in adult subjects with INI1- and SMARCA4-deficient tumors treated with tazemetostat. In adult subjects with INI1-negative tumors, objective responses (1 CR and 3 PRs) were observed in 4 of 11 response evaluable subjects with INI1- and SMARCA4-negative cancers. In detail the objective responses are: 2 of 5 in MRT; 1 of 3 in ES; 1 of 2 in malignant rhabdoid tumor of the ovary (MRTO).

The results are supported by pre-clinical studies, conducted by Epizyme and other investigators, in which EZH2 inhibitors have demonstrated anti-tumor activity in multiple INI1-deficient tumor models (in particular MRT and synovial sarcoma) as well as SMARCA4-deficient models (MRTO).

As shown in Figure 1, MRTs and their CNS counterpart, ATRT, are rare, have historically poor OS and have no established standard treatment approaches in children and adults [Morgenstern 2010; Sultan 2010].

**Figure 1.** Overall Survival, by Site of Disease (A), Age at Presentation (B), Initial response (C), and Following Radiotherapy (D)



The historical 5-year OS in children is estimated to be 17% to 33% [Ginn 2012]. The median age at diagnosis is 6 years; however, subjects are diagnosed well into adulthood. The clinical course of the disease is characterized by frequent and late local or metastatic recurrence, resulting in poor long-term prognosis. The median survival following recurrence in children has been reported to be 0.3 years with the majority of subjects who recur dying of their

disease [Tekautz 2005; Chi 2009]. Though current standard treatment at the time of presentation for MRT consists of attempted surgical resection, followed by intensive chemotherapy and radiotherapy [Chi 2009], at the recent Rhabdoid Tumor Symposium in 2014, the authors concluded “currently, no standard approaches are available for the treatment of rhabdoid tumors, regardless of tumor location” [Bourdeaut 2014]. At time of recurrence, treatment is based upon anecdotal reports of response to chemotherapy [Chi 2009; Wetmore 2015].

Current standard of care for other rare INI1-negative tumors is likewise not been well established due to their rarity. The incidence of INI1-negativity in subjects with ES was recently reported to be 90% with homozygous deletion of the INI1 gene found for 83% of these subjects [Sullivan 2013]. ES is an unusual tumor of young adults with a local recurrence rate of 35% and often requires radical excisions and amputations with local radiation as the tumor has a predilection for extremities with nodal metastasis [Chbani 2009]. At time of recurrence there is no standard of care. EMPNST is another rare soft tissue sarcoma that is treated with surgery at time of diagnosis and demonstrates variable response to chemotherapy [Minagawa 2011]. Again, due to the rarity and aggressive nature of the tumors at time of recurrence, there are only anecdotal reports of long-term treatment success. EMC is another soft tissue sarcoma of intermediate malignant potential and case reports discuss treatment with wide local resection [Kawaguchi 2003]. Myoepithelial carcinoma is yet another soft tissue tumor with an aggressive course with median survival of 9 months [Mahdi 2014]. Finally, RMC is a highly aggressive and extremely rare tumor that often affects younger subjects with sickle cell trait or disease with fatality approaching 100% within several weeks to months of diagnosis [Cheng 2008]. As these tumors are very rare, there are no reported controlled clinical trials specific to these INI1-negative populations.

Synovial sarcoma is a highly aggressive soft tissue sarcoma of childhood and young adults, representing 10% of soft tissue sarcomas in all age groups and 15-20% of young adult sarcomas. In the metastatic setting responses to chemotherapy are transient and this malignancy is universally fatal. The mechanism of INI1 deficiency in synovial sarcomas is distinct compared to those tumors that are characterized by INI1 loss such as MRT, ES or RMC. Tumors harbor characteristic translocations of chromosome X and 18, resulting in the fusion genes (SS18-SSX1, 2 and 4). The resulting fusion proteins integrate into the SWI/SNF complex evicting wild-type SS18 and INI1 leading to proteolytic degradation of INI1, generating a state of low INI1 levels without mutations in the *INI1* gene itself [Kadoch 2013; Arnold 2013]. Treatment of synovial sarcoma involves surgical excision of primary and metastatic tumors, irradiation, and adjuvant chemotherapy with ifosfamide, doxorubicin

and cisplatin-based regimens, although clinical data on the benefit of chemotherapy in the adjuvant setting are conflicting [Fisher 1998; Guadagnolo 2007]. At time of recurrence, combinations with gemcitabine and docetaxel, trabectedin or pazopanib are used with 40% progression-free survival (PFS) at 3 months [Sleijfer 2009; van der Graaf 2012]. Additional therapeutic options for subjects with these selected advanced tumors are needed.

## 2.0 MECHANISM OF ACTION

### 2.1 Histone Methyltransferases in Cancer with Focus on EZH2

Post-translational modifications of histones, the core proteins of chromatin, play an important role in controlling the fidelity of cellular gene transcription patterns. One of the critical transcription-controlling histone modifications is methylation of specific lysine and arginine residues, catalyzed by histone methyltransferases (HMTs) which all use S-adenosyl methionine (SAM) as a cofactor for the methylation reaction [Copeland 2013]. Genetic alterations in a number of HMTs or associated regulatory proteins have been identified in several human cancers where they are purported to be oncogenic. EZH2 (enhancer of zeste homolog 2) is the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono-, di-, and trimethylation of lysine 27 of histone H3 (H3K27) [Margueron and Reinberg 2011]. EZH2 mutation and/or over-expression have been observed in several cancer types, leading to an aberrant H3K27 trimethylation (H3K27Me3) state which is oncogenic [Chase and Cross 2011]. For instance, somatic gain of function mutations within EZH2, found within subsets of non-Hodgkin lymphoma (NHL), result in production of abnormally high H3K27Me3 levels, resultant transcriptional reprogramming of the cell, and an oncogenic dependency on EZH2 [Morin 2010; Sneeringer 2010].

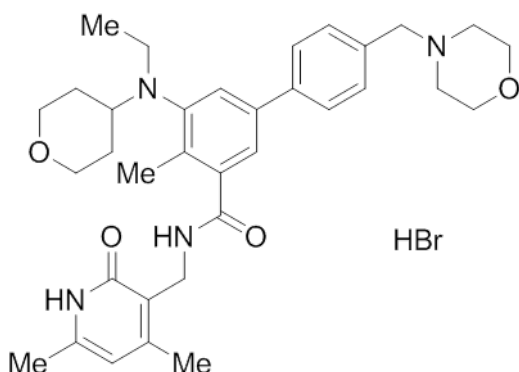
In addition to genetic alterations in EZH2 itself, distal genetic changes in other proteins can lead to an oncogenic dependency on EZH2 activity, specifically those affecting proteins of the SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex. SWI/SNF mutations are observed in nearly all cancer types, with loss-of-function mutations in the core subunit INI1 as the predominant drivers in MRT [Biegel 1999, Chun 2016] and SMARCA4 in MRTO [Bailey 2015; Jelinic 2015; Kupryjańczyk 2013; Ramos 2014]. At many gene loci, PRC2 and SWI/SNF antagonize each other and loss of the SWI/SNF component INI1 has been demonstrated to generate an over-activation of the PRC2 pathway and tumor cell proliferation [Wilson 2010]. Genetic loss of INI1 has been described in many human malignancies, for example MRT, ATRT, RTK, and other rare tumors such as, ES, EMPNST, EMC; myoepithelial carcinoma, RMC, and atypical chordoma [Margol and Judkins 2014]. As described earlier, synovial sarcoma is also considered an INI1-deficient tumor as it contains a recurrent chromosomal translocation that generates a state of low INI1 levels without mutations within the *INI1* gene itself [Kadoch 2013; Arnold 2013]. MRTO is characterized by SMARCA4 loss with concomitant epigenetic suppression of the redundant subunit SMARCA2. Inhibition of EZH2 activity by either knock-down or small molecule inhibition suppresses cell proliferation and induces durable tumor regressions in preclinical

models of both rhabdoid tumors and synovial sarcoma [Alimova 2013; Knutson 2013; Shen 2016]. Select tumors with mutations in other SWI/SNF subunits (ARID1A, PBRM1) have also been theorized to be sensitive to EZH2 inhibition [Bitler 2015; Kim 2015], however given the weight of preclinical evidence and the unmet medical need in pediatric malignant rhabdoid tumors and other INI-deficient tumors, Epizyme has prioritized clinical development in these indications.

## 2.2 Tazemetostat Mechanism of Action

Based on the contribution of EZH2 in specific genetically defined cancer types, efforts were undertaken by Epizyme to discover small molecule inhibitors of EZH2. Tazemetostat (EPZ-6438) is a selective, reversible, SAM-competitive small molecule inhibitor of the EZH2 HMT enzymatic activity (Figure 2). Tazemetostat inhibits both wild-type EZH2 and mutated EZH2 residues Y641, A677G and A687 with half maximal inhibitory concentrations (IC<sub>50</sub>) ranging from 2-38 nmol/L. The compound has 35-fold selectivity over the most closely related HMT, EZH1, and greater than a 4500-fold selectivity over other HMTs. Tazemetostat selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective cell killing of cell lines that depend on EZH2 activity, such as INI1-negative tumors.

**Figure 2. Chemical Structure of Tazemetostat (EPZ-6438)**



### **3.0 REGULATORY HISTORY**

An investigational new drug (IND) application for tazemetostat for the treatment of INI1-negative solid tumors went into effect in August 2015. A clinical study specific to pediatrics (Study EZH-102) and a study in adults (Study EZH-202) with INI1-negative tumors was initiated in January 2016 and December 2015, respectively, in the United States (US). Since that time, additional study sites have been activated in the European Union (EU), Canada and Australia. Under separate INDs, CTAs or CTN, a total of three clinical trials in adults (see Section 5.0) and one study in pediatrics (see Section 8.0) have been initiated in the US, EU, and other countries worldwide in multiple hematologic and solid tumor malignancy indications.

Epizyme received orphan drug designation for tazemetostat in the US for treatment of MRTs in February 2016 (orphan application number: 15-5084).

Epizyme intends to conduct a global pediatric program for the indication of INI1-negative tumors and is actively screening and recruiting subjects in US, Canada, Denmark, France, Germany, Italy, Netherlands, UK and Australia as part of a global pediatric study.

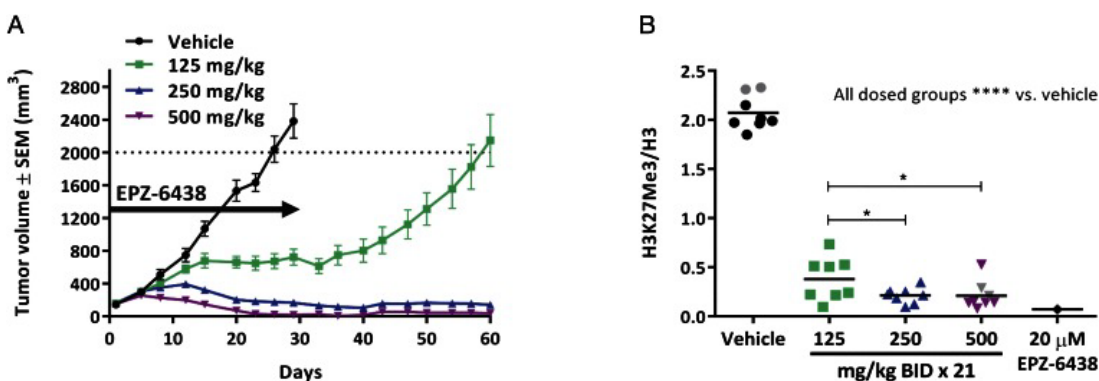
Tazemetostat is not approved for marketing in the US or any other country worldwide.

## 4.0 PRECLINICAL DATA SUPPORTING CLINICAL STUDIES

### 4.1 Tazemetostat Efficacy in Malignant Rhabdoid Tumors

The effects of EZH2 inhibition by tazemetostat were evaluated in preclinical models of INI1-negative MRT. Tazemetostat demonstrated dose dependent anti-proliferative effects in human MRT cell lines derived from pediatric patients with IC50s in the nanomolar range, with a concomitant induction of apoptosis and differentiation [Knutson 2013]. This is consistent with the effects seen in MRT cell lines upon EZH2 genetic knockdown [Wilson 2010]. In vivo, tazemetostat induced tumor regressions in a xenograft model of pediatric MRT, with no regrowth after cessation of dosing. There was a robust decrease in H3K27me3 levels in the tumor that correlated with anti-tumor activity [Figure 3] [Knutson, 2013].

**Figure 3. Tazemetostat in INI1-Negative MRT Xenografts in SCID Mice**



A) Tumor regressions in the G401 model of pediatric MRT induced by twice daily (BID) administration of tazemetostat for 28 d at the indicated doses. Compound administration was stopped on day 28, and tumors were allowed to regrow until they reached 2,000 mm<sup>3</sup> (data shown as mean values ± SEM; n = 8).

B) EZH2 target inhibition in G401 xenograft tumor tissue collected from mice euthanized on day 21. Each point shows the ratio of H3K27Me3 to total H3, measured by ELISA. The horizontal lines represent group mean values; gray symbols are values outside of the ELISA standard curve.



## 4.2 Tazemetostat Efficacy in MRTO and Other INI1-Negative Tumors

The effects of EZH2 inhibition were also tested in additional tumor models with select SWI/SNF mutations, including synovial sarcoma and malignant rhabdoid tumor of the ovary. As described earlier, synovial sarcoma contains either the SS18-SSX1 or SS18-SSX2 fusion that induces INI1 exclusion from the SWI/SNF complex and its subsequent proteolytic degradation. Tazemetostat treatment of human synovial sarcoma cell lines dose dependently and potently inhibited the in vitro proliferation of all synovial sarcoma cell lines tested (either SS18-SSX1 or SS18-SSX2 fusion positive). In vivo, dose-dependent tumor growth inhibition was observed with tazemetostat treatment in 2 patient-derived xenograft (PDX) models and the Fuji cell line xenograft model, which all contain the SS18-SSX2 fusion. Tazemetostat also inhibited the in vitro proliferation of four human cell line models of MRTO.

In support of the current pediatric clinical study Epizyme plans to investigate ATRT in preclinical models (single agent tazemetostat and in combination with SOC) both internally as well as through academic collaborations.

## 4.3 Nonclinical Pharmacokinetics

The plasma pharmacokinetics of tazemetostat in rats and monkeys was characterized by high-to-moderate clearance, a moderate-to-large volume of distribution, and a short half-life of 0.4 to 1.6 hours. Low-to-moderate accumulation of tazemetostat in plasma was observed after repeated doses in male rats. In contrast, there was a 3- to 5-fold decrease in systemic exposure between Day 1 and Day 28 in monkeys. In vitro, cytochrome P450 (CYP)3A4 is the predominant enzyme responsible for the hepatic metabolism of tazemetostat. The desethyl metabolite, EPZ-6930, was the major metabolite formed in vitro in all species and no metabolite unique to humans has been observed. Low renal excretion of tazemetostat was observed in rats.

## 4.4 Nonclinical Toxicity and Development Plan

The overall nonclinical safety program for tazemetostat is consistent with the ICH S9 guidance. The toxicity profile of tazemetostat has been evaluated in adult (rat and monkey) and juvenile (rat) animal studies of up to 3 months in duration (pivotal studies) to support

global clinical development and registration in adults and pediatrics. No additional studies are planned to support pediatric development.

The nonclinical safety profile of tazemetostat supports further development of tazemetostat in ongoing clinical trials in:

1. adult subjects with relapsed/refractory B-cell lymphomas with and without activating mutations in EZH2
2. adult subjects with genetically defined BAP1-deficient relapsed/refractory malignant mesothelioma
3. pediatric and adult subjects with rare, but genetically defined INI1-negative or SMARCA4-negative tumors

## 5.0 CLINICAL TRIAL EXPERIENCE IN ADULTS

### 5.1 Overview

Tazemetostat is currently being assessed in three ongoing studies in adult subjects. These studies focus on subjects with NHL (DLBCL and FL), solid tumors and mesothelioma.

- Study 101: Phase 1/2 in NHL and Advanced Solid Tumors (NCT 01897571)  
“An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects with Advanced Solid Tumors or With B-cell Lymphomas”
- Study EZH-202: Phase 2 in Advanced Solid Tumors (NCT 02601950)  
“A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma”
- Study EZH-203: Phase 2 in Mesothelioma  
“A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 Loss of Function”

### 5.2 Study 101: Phase 1/2 in NHL and Solid Tumors

In 2013, the first-time-in-human (FTIH), single-agent, phase 1/2 safety and PK study E7438-G000-101 (101) of tazemetostat in adult subjects with advanced B cell lymphomas and solid tumors was initiated in France. In the dose escalation part of the study, subjects with advanced solid tumors or B-cell lymphomas for which there is no known effective therapy were recruited. All subjects received oral tazemetostat BID until disease progression or a dose-limiting toxicity (DLT). The phase 1 data were most recently presented at the 2015 American Society of Hematology (ASH) Annual Meeting; as of November 7, 2015, 58 subjects have been enrolled and treated at 5 dose levels of 100, 200, 400, 800, and 1600 mg BID. The diagnoses for the 21 subjects with B-cell NHL included follicular lymphoma, diffuse large B-cell lymphoma including one subject with primary mediastinal lymphoma and one subject with marginal zone lymphoma. The diagnoses for the 37 subjects with solid tumors included 5 subjects with MRT, 3 subjects with ES, and 2 subjects with in malignant rhabdoid tumor of the ovary (MRTO). At the 2015 European Cancer Congress, Epizyme reported four objective responses (1 CR and 3 PRs) were observed in 4 of 11 response evaluable subjects with INI1- and SMARCA4-negative cancers. In detail the objective

responses are: 2 of 5 in MRT; 1 of 3 in ES; 1 of 2 in MRTO. The median age of subjects enrolled is 59 years (range: 19 to 84 years).

The dose escalation portion of Study 101 has been completed. The protocol-defined maximum tolerated dose (MTD) was not reached. The highest evaluated dose of 1600 mg BID was safe with only one DLT (Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 Grade 4 thrombocytopenia) observed in 6 subjects. There was one other Grade 4 SAE (SAE) of possible treatment-related neutropenia reported in a subject in the expansion cohort. The RP2D of 800 mg BID represents 50% of the highest evaluated safe dose and was determined by the Sponsor and ratified by the Independent Data Monitoring Committee (IDMC) for use in the proposed phase 2 study in adults with INI1-negative tumors and the phase 2 study in NHL adult subjects.

Additionally, within this study, evaluation of the effect of food on the bioavailability of tazemetostat and the effect of tazemetostat on exposure of midazolam, a CYP3A4 substrate, were evaluated in separate food effect and drug-drug interaction (DDI) cohorts.

The phase 2 component of Study 101, restricted to relapsed or refractory B-cell lymphomas, is underway in Europe, Australia and North America with additional countries planned. This study will evaluate the clinical efficacy of tazemetostat in NHL subjects. Subjects with B-cell lymphoma will be enrolled to determine preliminary efficacy and safety of tazemetostat in advanced B-cell NHL with cohorts determined by centralized testing of both cell-of-origin histology and EZH2 status. The five cohorts include: diffuse large B cell lymphoma (DLBCL) germinal center (GCB) subtype with and without EZH2 mutation, DLBCL non-GCB sub-type and FL with and without EZH2 mutation. Initially, the planned enrollment was for up to 150 subjects with futility analysis at predetermined points (first ten subjects of each cohort) subject to IDMC review. This design allows parallel evaluations of tazemetostat in DLBCL and FL subjects with or without an activating mutation of EZH2.

The phase 2 component of Study 101 in the U.S. will enroll subjects with diffuse large B-cell lymphoma (DLBCL) in the following three cohorts: a) germinal center DLBCL with mutant EZH2, b) germinal center DLBCL with wild-type EZH2 and c) non-germinal center DLBCL.

Epizyme will present initial data from the ongoing phase 2 study in subjects with relapsed or refractory non-Hodgkin lymphoma (NHL) at the 2016 ASH Meeting on Lymphoma Biology in June 2016. This presentation will include a progress update on the study enrollment, safety experience for all subjects enrolled and an initial assessment of clinical activity in the patient populations that have surpassed their futility hurdle as confirmed by the IDMC. The

three arms confirmed to have surpassed the futility hurdle are: germinal center diffuse large B-cell lymphoma (DLBCL) with an EZH2 mutation; germinal center DLBCL with wild-type EZH2; and non-germinal center DLBCL. Responses have been observed in the two arms enrolling subjects with follicular lymphoma; however, neither arm has yet reached its pre-specified futility hurdle.

The IDMC recently approved Epizyme's proposed expansion of enrollment in all five arms of the phase 2 study in subjects with NHL. The total population will increase to 270 subjects from 150. The three arms enrolling subjects with DLBCL will now enroll 60 subjects each, and the two arms enrolling subjects with follicular lymphoma will now enroll 45 subjects each. This expansion will enable greater precision around the efficacy endpoints in each B-cell lymphoma population, which will provide guidance for determining next steps for each population and for the statistical design of potential subsequent studies.

### **5.3 Study EZH-202: Phase 2 in INI1-Negative Tumors or Synovial Sarcoma**

This study initially included three cohorts of adult subjects: Cohort 1 - MRT, RTK and ATRT; Cohort 2 - synovial sarcoma; and Cohort 3 - other rare INI1-negative tumors (ES, EMPNST, EMC, myoepithelial carcinoma, RMC, dedifferentiated chordoma as representative examples.

Epizyme recently expanded the number of arms in this study in adult subjects with certain genetically defined solid tumor (INI1-negative tumors, SMARCA4-negative tumors or synovial sarcomas) from three arms to five arms due to a higher accrual of subjects with certain types of INI1-negative tumors than originally anticipated. The two arms enrolling subjects with rhabdoid tumors and synovial sarcomas remain unchanged. A third arm will continue to enroll subjects with other INI1-negative tumors, and Epizyme has now separated out two specific INI1-negative cohorts from the third arm. One arm will enroll subjects with RMC and another will enroll subjects with ES.

The current recruitment plans in the adult study of 5 cohorts of 30 subjects in each is as follows:

- Cohort 1: malignant rhabdoid tumor (MRT), rhabdoid tumor of kidney (RTK), atypical teratoid rhabdoid tumor (ATRT) and select tumors with rhabdoid features
- Cohort 2: synovial sarcoma

- Cohort 3: other rare INI1-negative tumors: epithelioid malignant peripheral nerve sheath tumor (EMPNST), extraskeletal myxoid chondrosarcoma (EMC), myoepithelial carcinoma and other INI1-negative tumors such as dedifferentiated chordoma
- Cohort 4: renal medullary carcinoma (RMC)
- Cohort 5: epithelioid sarcoma (ES)

The subjects must have disease that has advanced or is metastatic with progression after treatment with approved therapies or disease for which there are no standard therapies available. In addition to enable cohort allocation patients must have locally determined histopathological disease diagnosis and evidence of loss of tumor expression of INI1 or SMARCA4 or for synovial sarcoma presence of an SS18-translocation. The primary objective of the study is based upon the tumor type: cohorts 1, 3, 4, and 5 is to assess the objective response rate in adult subjects with selected INI1-deficient tumors following administration of tazemetostat orally at 800 mg BID; and for cohort 2, to assess progression-free rate at the week 16 assessment as evaluated by RECIST 1.1 when tazemetostat is administered orally at 800 mg BID. The study is designed as a Green-Dahlberg two-stage study with approximately 150 subjects to be enrolled.

As of May 2016, subjects have been enrolled in the US, Belgium, France, and Italy. Additional sites planned in the Canada, Germany, UK, Australia, and Taiwan.

#### **5.4 Study EZH-203: Phase 2 in Malignant Mesothelioma**

The preclinical antitumor activity of EZH2 inhibition in BAP1 mutant mesothelioma xenograft models highlights the potential clinical benefit of tazemetostat in BAP1 mutant mesothelioma, disease with an highly unfavorable prognosis and high unmet need, especially for patients with relapsed or refractory disease.

In May 2016, the IND for tazemetostat for the treatment of adult subjects with mesothelioma characterized by BAP1 loss-of-function was accepted. Epizyme plans to initiate a phase 2 trial in subjects with mesothelioma in the third quarter of 2016. This is a multi-center, open-label, 2-part, single-arm, 2-stage study of tazemetostat 800 mg BID administered orally that will be conducted in the US, France and the UK.

In Part 1, 12 subjects with relapsed or refractory malignant mesothelioma, regardless of BAP1 status, will be treated and undergo PK blood sample collection using a new 400 mg

tablet formulation. Part 2 will include 55 subjects with BAP1-deficient relapsed or refractory malignant mesothelioma who will receive orally administered tazemetostat 800 mg BID. A two-stage Green-Dahlberg design will be utilized. Treatment with tazemetostat will continue until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study. Response assessment will be evaluated after 6 weeks of treatment and then every 6 weeks thereafter while on the study.

## 5.5 Clinical Pharmacokinetics

Tazemetostat was administered orally at doses of 100, 200, 400, 800, and 1600 mg twice daily (BID) in subjects with advanced solid tumors or with B-cell lymphomas. Tazemetostat was absorbed rapidly with a time to maximum plasma concentration (t<sub>max</sub>) of approximately 1 to 2 hours after administration and a mean terminal phase half-life of 3 to 5 hours. There was a decrease in systemic exposure to tazemetostat on Day 15 of twice daily dosing relative to administration of a single dose. However, systemic exposure at steady-state did not change beyond Day 15. The tazemetostat maximum concentration (C<sub>max</sub>) and area under the plasma concentration-time curve (AUC) increased in a greater than dose-proportional fashion after a single dose and in an approximately dose-proportional fashion at steady state. Administration of tazemetostat with food decreased the rate of oral absorption with no relevant effect on the total systemic exposure compared to administration in the fasted state. Administration of oral midazolam with tazemetostat 800 mg BID resulted in an approximately 40% and 22% decrease in midazolam AUC and C<sub>max</sub>, respectively, relative to administration of midazolam alone, which demonstrates that tazemetostat is a weak inducer of CYP3A4/5-mediated metabolism. Therefore, potential interactions with concomitantly administered medications that are substrates for CYP3A4/5 will be mild.

## 5.6 Safety Database from Ongoing Clinical Studies

To date, there are four ongoing clinical studies with tazemetostat. As of January 15, 2016, 78 of 89 (88%) subjects experienced at least one treatment-emergent adverse event (TEAE) and 51 of 89 (57%) subjects experienced TEAEs that were considered by the investigator to be related to tazemetostat. The majority of the TEAEs were Grade 1 or 2 (92%) with 7 subjects (8%) experiencing Grade 3 or 4 TEAEs. No clear pattern of dose-related increase in toxicity (all Grades and Grade 3 or 4) was identified (see Table 1).

**Table 1. Summary of Treatment-Emergent Adverse Events Occurring in  $\geq 5\%$  of Subjects by Severity and Relationship to Study Drug**

Preferred Term	Overall (Independent of Causality) (N = 89) <sup>a</sup> n (%)		Related to Treatment (N = 89) <sup>a</sup> n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Subjects with at least 1 TEAE	78 (88)	22 (25)	51 (57)	7 (8)
Asthenia	31 (35)	0 (0)	19 (21)	0 (0)
Nausea	14 (16)	0 (0)	12 (14)	0 (0)
Thrombocytopenia	13 (15)	4 (5)	10 (11)	1 (1)
Decreased appetite	12 (14)	1 (1)	5 (6)	0 (0)
Anemia	11 (12)	3 (3)	7 (8)	0 (0)
Constipation	11 (12)	0 (0)	2 (2)	0 (0)
Dysgeusia	7 (8)	1 (1)	6 (7)	0 (0)
Vomiting	7 (8)	0 (0)	5 (6)	0 (0)
Diarrhea	6 (7)	0 (0)	5 (6)	0 (0)
Dry skin	6 (7)	0 (0)	5 (6)	0 (0)
Dyspnea	6 (7)	0 (0)	0 (0)	0 (0)
Muscle spasms	6 (7)	0 (0)	3 (3)	0 (0)
Abdominal pain	5 (6)	1 (1)	1 (1)	0 (0)
Neutropenia	5 (6)	2 (2)	5 (6)	2 (2)

<sup>a</sup> One EZH-202 subject is included.

Percentages are based on the total number of subjects.

Subjects with multiple instances of a Preferred Term are counted only once in each applicable cell.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0.



## **6.0 OTHER CLINICAL TRIALS THAT ARE PLANNED, ONGOING OR COMPLETED IN ADULTS**

### **6.1 Planned Trials**

EZH-103: “An Open-Label, Single-Center, Two-Part, Phase 1 Study to Characterize the Pharmacokinetics of an Intravenous Micro-Dose of Tazemetostat (EPZ-6438) and the Absorption, Distribution, Metabolism and Elimination of an Oral [<sup>14</sup>C]-Labeled Dose of Tazemetostat in Subjects with B-Cell Lymphomas”

NCI (National Cancer Institute) MATCH (“Molecular Analysis for Therapeutic Choice”): NCI-sponsored multi-center precision medicine clinical trial that is exploring the treatment of patients based on the molecular profiles of their tumors. A number of targeted therapies from a variety of pharmaceutical sponsors are being evaluated in separate arms of this trial. Tazemetostat has been requested for inclusion in this study which will be conducted through a planned collaboration between Epizyme and the NCI.

### **6.2 Ongoing or Completed Trials**

No other tazemetostat clinical trials sponsored by Epizyme or conducted in collaboration with partners are ongoing or have been completed at this time.

## 7.0 CURRENT DRUG DEVELOPMENT PLAN FOR OTHER INDICATIONS IN ADULTS

Beyond the current global phase 2 studies in subjects with both newly diagnosed and recurrent NHL, solid tumors and mesothelioma, Epizyme's future development activities include or may include:

- EZH-104: "A Phase Ib-II Study of Tazemetostat (EPZ-6438) in newly diagnosed Diffuse Large B Cell Lymphoma (DLBCL) subjects with poor prognosis treated by R-CHOP." Epizyme announced in May 2016 that it has entered into a collaboration agreement with the Lymphoma Academic Research Organization (LYSARC) for the first planned combination trial of tazemetostat. LYSARC is the operational arm of the Lymphoma Study Association, a premier cooperative French lymphoma group.
- Evaluating the additional potential of tazemetostat to enhance the clinical activity of immuno-oncology therapies by combining with an anti-PD1 or PDL-1 agent. Preclinical studies in the field show that EZH2 inhibitors, including tazemetostat, may potentially prime tumor cells and the microenvironment for synergy with immune checkpoint inhibitors.
- Identifying new hematologic malignancy or solid tumor indications where tazemetostat may provide clinical benefit. This will be accomplished through Epizyme-sponsored or NCI-sponsored (in collaboration with Epizyme) proof-of-concept studies based on strong preclinical evidence of tumor sensitivity to EZH2 inhibition in clearly defined patient populations determined through internal Epizyme research as well as academic collaborations and partnerships.

## 8.0 PROPOSED PEDIATRIC PLAN

### 8.1 Introduction

A pediatric phase 1 dose escalation safety and tolerability study with an expansion cohort to determine safety, pharmacokinetics and preliminary efficacy in INI1-negative tumors is the only study currently active in pediatrics. Epizyme designed this phase 1 study with 24 subjects in dose escalation and 60 subjects at RP2D (approximately 20 subjects for each of the three cohorts described below) to assess efficacy in this rare population and potentially to use the data for registration.

Epizyme also plans to participate in the NCI-sponsored Pediatric MATCH multi-center trial through a planned CRADA collaboration with NCI. This pediatric counterpart to the NCI-MATCH trial in adults will evaluate molecularly targeted therapies such as tazemetostat in children with advanced cancers who have few other treatment options. Pediatric MATCH which will be led by the Children's Oncology Group is under currently under development and expected to start dosing in 2016. Tazemetostat will be incorporated into Pediatric MATCH as one of the initial investigational agents to be tested.

### 8.2 EZH-102: Phase 1 in Pediatric INI1-Negative Tumors or Synovial Sarcoma

A pediatric phase 1 dose escalation safety and tolerability study with an expansion cohort to determine preliminary efficacy in INI1-negative tumors is ongoing: EZH-102 "A Phase 1 Study of Tazemetostat in Pediatric Subjects with Relapsed/Refractory INI1-negative Tumors or Synovial Sarcomas". The study will include subjects with relapsed or refractory tumors of the histologies listed below:

- Cohort 1: atypical teratoid rhabdoid tumor (ATRT)
- Cohort 2: malignant rhabdoid tumor (MRT), rhabdoid tumor of kidney (RTK) and select tumors with rhabdoid features
- Cohort 3: other rare INI1-negative tumors (ES, EMPNST, EMC, myoepithelial carcinoma, RMC) and synovial sarcoma

The primary objective of the dose escalation study is to determine the MTD and/or RP2D of tazemetostat when administered as a single agent oral suspension BID continuously in

pediatric subjects 6 months to 21 years of age. Following determination of the MTD or RP2D, dose expansion cohorts will be opened for subjects with rhabdoid tumors, INI1-negative tumors, and synovial sarcoma, to evaluate anti-tumor activity as assessed by objective response rate (ORR: complete response [CR] + partial response [PR]) in pediatric subjects. Inclusive of the expansion cohort, a total of up to 84 subjects may be enrolled to this study.

As of May 2016, the phase 1 dose-escalation and expansion study of tazemetostat in pediatric subjects with certain INI1-negative tumors, including rhabdoid tumors and synovial sarcomas, has enrolling 14 subjects and the study has escalated to the second dose level (300 mg/m<sup>2</sup> po BID).

### 8.3 Objectives of the Pediatric Study

#### Primary Objectives:

Dose Escalation:

- To determine the maximum tolerated dose (MTD) or the Recommended Phase 2 Dose (RP2D) of tazemetostat when administered as an oral suspension twice daily (BID) in pediatric subjects with relapsed/refractory integrase interactor 1 (INI1)-negative tumors or synovial sarcoma

Dose Expansion:

- To evaluate the anti-tumor activity of tazemetostat as assessed by overall response rate (ORR) in pediatric subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), and INI1-negative tumors or synovial sarcoma (Cohort 3) using disease appropriate standardized response criteria

#### Secondary Objectives:

Dose Escalation:

- To evaluate the preliminary anti-tumor activity of tazemetostat as assessed by ORR using disease appropriate standardized response criteria

Dose Expansion:

- To determine the progression-free survival (PFS) and overall survival (OS) at 24 and 56 weeks and overall for subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), and INI1-negative tumors or

synovial sarcoma (Cohort 3) using disease-appropriate standardized response criteria in selected pediatric subjects

#### All Subjects:

- To assess the safety and tolerability of tazemetostat administered as an oral suspension BID
- To assess the pharmacokinetics (PK) of tazemetostat in pediatric subjects
- To evaluate the duration of response in subjects achieving a complete response (CR) or partial response (PR) according to a disease appropriate standardized response criteria

#### Exploratory Objective (All Subjects):

- To assess the PK and pharmacodynamic (PD) relationship for tazemetostat in pediatric subjects
- To assess the effects of tazemetostat on H3K27 methylation in peripheral blood mononuclear cell (PBMC) subsets
- To assess tumor tissue and/or blood for somatic mutations, messenger ribonucleic acid (mRNA) and proteins as candidate markers of clinical response to tazemetostat

## 8.4 Investigators/Institutions

As of May 2016, 22 sites have been activated for pediatric enrollment in the U.S., Denmark, Australia and U.K. Additional study sites in the U.S., Canada, France, Germany, Italy, Netherlands and Australia are planned to be added over the upcoming months. Updated list of study locations can be found at: [ClinicalTrials.gov: A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects With Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma](#)

## 8.5 Study Population

Enrollment to the clinical trial will be based upon locally determined histopathological disease diagnosis and evidence of loss of tumor expression of INI1 or SMARCA4 or for synovial sarcoma presence of an SS18-translocation. Epizyme will, however, centrally confirm pathology, IHC and FISH (if applicable), which are both considered standard of care for diagnosis of INI1 and SMARCA4-negative tumors.

## 8.6 Number of Subjects to Be Enrolled

**Dose Escalation:** For the ongoing pediatric study, it is expected that up to 24 subjects with relapsed/refractory rhabdoid tumors (MRT/ATRT/RTK), INI1-negative tumors, and synovial sarcoma will be enrolled using a “Rolling 6” dose escalation design.

**Dose Expansion:** It is expected that approximately 20 subjects with ATRT (Cohort 1), approximately 20 subjects with MRT/RTK/select tumors with rhabdoid features (Cohort 2), and approximately 20 subjects with INI1-negative non-rhabdoid tumors and synovial sarcoma (Cohort 3) will be enrolled in an expansion cohort.

The subject composition and projected sample size of any additional expansion cohort(s) will be the subject of an amendment to the protocol.

## 8.7 Main Inclusion and Exclusion Criteria

### 8.7.1 Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for enrollment in this study.

1. Age (at the time of consent/assent):  $\geq 6$  months to  $\leq 21$  years
2. Performance Status:
  - If  $< 12$  years of age: Lansky Performance Status  $> 50\%$
  - If  $\geq 12$  years of age: Karnofsky Performance Status  $> 50\%$
3. Has relapsed or refractory disease and no standard treatment options as determined by locally or regionally available standards of care and treating physician's discretion
4. Is ineligible or inappropriate for other treatment regimens known to have effective potential
5. Has a documented local diagnostic pathology of original biopsy confirmed by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) or equivalent laboratory certification
6. Has adequate hematologic (bone marrow and coagulation factors), renal and hepatic function

7. For subjects with CNS involvement: Subjects must have:
- deficits that are stable for a minimum of 14 days prior to first dose of study drug, or
  - seizures that are stable, not increasing in frequency or severity and controlled on current anti-seizure medication(s) for a minimum of 7 days prior to first dose of study drug

NOTE: Subjects with leptomenigeal disease or brain tumors with positive cerebral spinal fluid cytology are eligible for this study. Subjects may receive glucocorticoids (at stable or tapering dose) to control CNS symptoms prior to enrollment; however, subjects should receive a stable or tapering dose for at least 7 days prior to first dose of study drug.

8. Has a shortening fraction of  $>27\%$  or an ejection fraction of  $\geq 50\%$  by echocardiogram or multi-gated acquisition scan and New York Heart Association Class  $<2$
9. Has a QT interval corrected by Fridericia's formula (QTcF)  $\leq 480$  msec
10. Has evaluable disease as defined as lesions that can be accurately measured at least in one dimension by radiographic examination or physical examination and other lesions such as bone lesions, leptomenigeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis or hepatosplenomegaly from disease.

NOTE: Measurable disease is required for the dose expansion cohorts

11. Has one of the following histologically confirmed tumors:
- Rhabdoid tumor:
    - ATRT
    - MRT
    - RTK
    - Select tumors with rhabdoid features
  - INI1-negative tumor:
    - Epithelioid sarcoma
    - Epithelioid malignant peripheral nerve sheath tumor
    - Extraskelatal myxoid chondrosarcoma
    - Myoepithelial carcinoma

- Renal medullary carcinoma
- Other INI1-negative malignant tumors (e.g., dedifferentiated chordoma) with Sponsor approval
- Synovial sarcoma with SS18-SSX rearrangement

NOTE: Evidence of diagnostic pathology of original biopsy confirmed by a CLIA/CAP certified laboratory must be available.

12. For subjects with ATRT, MRT or RTK and select tumors with rhabdoid features only: The following test results must be available:
  - Morphology and immunophenotypic panel consistent with rhabdoid tumor, and
  - Loss of INI1 or SMARCA4 confirmed by IHC, or
  - Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss/mutation when INI1 or SMARCA4 IHC is equivocal or unavailable
13. For subjects with INI1 negative tumor only: The following test results must be available:
  - Morphology and immunophenotypic panel consistent with INI1-negative tumors, and
  - Loss of INI1 confirmed by IHC, or
  - Molecular confirmation of tumor bi-allelic INI1 loss/mutation when INI1 IHC is equivocal or unavailable
14. For subjects with synovial sarcoma only: The following test results must be available:
  - Morphology consistent with synovial sarcoma, and
  - Cytogenetics or FISH and/or molecular confirmation (e.g., deoxyribonucleic acid [DNA] sequencing) of SS18 rearrangement t(X;18)(p11;q11)

### **8.7.2 Main Exclusion Criteria**

Subjects meeting ANY of the following criteria must NOT be enrolled in this study:

1. Has had prior exposure to tazemetostat or other inhibitor(s) of enhancer of zeste homologue-2 (EZH2)



2. Is being actively treated for another concurrent malignancy or is less than five years from completion of treatment for another malignancy
3. Has participated in another interventional clinical study and received investigational drug within 30 days or 5 half-lives, whichever is longer, prior to the planned first dose of tazemetostat
4. Has had major surgery within 2 weeks prior to enrolment

NOTE: Minor surgery (e.g., minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 2 weeks prior to enrollment.

5. Has clinically active heart disease including prolonged corrected QT interval
6. Has an active infection requiring systemic treatment
7. Is immunocompromised, including subjects known history of infection with human immunodeficiency virus
8. Has known history of chronic infection with hepatitis B virus (hepatitis B surface antigen positive) or hepatitis C virus (anti-hepatic C virus positive)
9. Has had a symptomatic venous thrombosis within the 3 months prior to study enrollment

NOTE: Subjects with a history of a deep vein thrombosis >3 months prior to study enrollment who are on anticoagulation therapy with low molecular weight heparin are eligible for this study

10. For subjects with CNS involvement (primary tumor or metastatic disease): Have any active bleeding, or new intratumoral hemorrhage of more than punctate size on Screening MRI obtained within 14 days of starting study drug, or known bleeding diathesis or treatment with anti-platelet or anti-thrombotic agents

## 8.8 Pediatric Dose Selection

Physiologically based PK modeling of the existing adult exposure data obtained in the FTIH study E7438-G000-101 informed the selection of the starting dose for this pediatric study. Systemic exposure data in adults together with in vitro data on the absorption, distribution,

and metabolism of tazemetostat were used to build a PK model that accurately described the concentration-time data from adults. This model was then transformed accounting for known age and developmental changes in physiological parameters, such as organ size and blood flows, as well as biochemical factors, e.g., the maturation of drug metabolizing enzyme expression and activity, to derive a series of age-based pediatric models for the PK of tazemetostat.

Tazemetostat doses that resulted in predicted AUC at steady-state (AUC<sub>ss</sub>) within the range of values observed in adults were identified. For children 1 year to 18 years of age, the starting dose of 240 mg/m<sup>2</sup>/dose is predicted to result in AUC<sub>ss</sub> values that are 64% and 36% of the AUC<sub>ss</sub> observed in adults at 800 mg/dose and 1600 mg/dose, respectively. For children 6 months to 1 year of age, the starting dose of 240 mg/m<sup>2</sup>/dose is predicted to result in AUC<sub>ss</sub> values that are 80% and 45% of the AUC<sub>ss</sub> observed in adults at 800 mg/dose and 1600 mg/dose, respectively. The 1600 mg/dose, which did not meet protocol-specified criteria for the MTD, is the highest dose level administered in the adult FTIH study, E7438-G000-101.

In this pediatric clinical study, subjects will receive BID oral treatment every day. Tazemetostat may be administered, assuming subject and/or parent/guardian and Investigator consent, until disease progression (treatment failure) or unacceptable toxicity occurs.

## 8.9 Methodology

Subjects will visit the study site and be screened for eligibility within 14 days of the planned first dose of tazemetostat. Subjects will receive tazemetostat as an oral agent BID. Response assessment will be evaluated after 8 weeks of treatment and subsequently every 8 weeks while on study. Treatment may continue, assuming subject and/or parent/guardian and Investigator consent, until disease progression or unacceptable toxicity.

Subjects will be dosed daily in continuous 28-day cycles for a maximum duration of 2 years, with weekly evaluations during the first cycle, and every other week in subsequent cycles. If treatment with study drug is discontinued prior to completing 2 years, subjects will be followed for a maximum duration of 2 years from start of study drug dosing.

The starting dose for the dose escalation will be 240 mg/m<sup>2</sup>/dose given BID for a total daily dose of 480 mg/m<sup>2</sup>/day. Dose escalation will proceed in increments of 25-33% and dose de-escalation will proceed in decrements of 50% as per Table 2.

**Table 2. Dose Escalation**

Dose level	Dose of Tazemetostat
Level 0	120 mg/m <sup>2</sup> BID = 240 mg/m <sup>2</sup> /day
Level 1 (starting dose)	240 mg/m <sup>2</sup> BID (starting dose) = 480 mg/m <sup>2</sup> /day
Level 2	300 mg/m <sup>2</sup> BID = 600 mg/m <sup>2</sup> /day
Level 3	400 mg/m <sup>2</sup> BID = 800 mg/m <sup>2</sup> /day
Level 4	520 mg/m <sup>2</sup> BID = 1040 mg/m <sup>2</sup> /day

Dose escalation will be performed using a “Rolling 6” design. The starting dose is derived from physiologically-based PK modeling of observed PK data in adult subjects.

## 8.10 Safety Assessment

Adverse events, laboratory profiles, physical exams, ECGs, echocardiogram (at screening and off study visits), and vital signs will be assessed throughout the study.

During the dose escalation period, a Clinical Safety Review Committee (CSRC) will review safety data, available PK data, AEs including dose limiting toxicities (DLTs), laboratory parameters, treatment delays, study agent dosing records, treatment reductions, and treatment discontinuations from each cohort and will make recommendations regarding escalation of dosage in subsequent cohorts. Any treatment-related death will be reviewed. The CSRC will be composed of the Investigators, the Medical Monitor, Epizyme Chief Medical Officer, and/or their designees.

The CSRC will review safety data from the first study visit following initiation of dosing through Day 28 of dosing from each cohort. The CSRC will review the following safety data:

- AEs/SAEs, including DLTs and any actions taken with the study drug (e.g., dose reduction, dose interruption, dose withdrawal)
- Clinical laboratory values
- Cycle 1, Days 1 and 15 electrocardiograms (ECGs) (over-read by central reader, if available)
- Vital signs
- PK data, if available

The CSRC will also review safety data as outlined in the dose escalation phase for aggregate AEs after every 6-8 cycles of treatment given during the Dose Expansion part of the study. Based on the review of the data, the CSRC will recommend that the study continue as planned, or may alternatively recommend that the study be placed on hold, that the dose of study drug be de-escalated, or that the study be terminated. A recommendation of study hold, study treatment dose de-escalation, or study termination would be made in the event of the discovery of an unexpected, serious, or unacceptable risk to the subjects in the study.

In Dose Escalation, the MTD and/or RP2D of tazemetostat, when administered as an oral suspension BID in pediatric subjects with selected relapsed or refractory solid tumors and CNS tumors, will be assessed. All DLTs that occur during the first 28 days of exposure to tazemetostat will be summarized by dose level.

## 8.11 Pharmacokinetic Assessment

Pharmacokinetic (PK) Analysis set will include all subjects in the Full Analysis set who have sufficient post-dose samples collected to allow estimation of the PK parameters. The PK Analysis set will be used for population-based analysis.

Plasma concentrations of tazemetostat and its metabolite EPZ-6930 (ER-897387) will be determined by a validated bioanalytical method. Concentrations of tazemetostat and its metabolite will be listed by cohort and nominal time. Standard summary statistics will be calculated (i.e., mean, SD, median, minimum and maximum). All PK parameters will be calculated using actual times, if data are sufficient. Non-compartmental PK parameters  $C_{max}$ ,  $t_{max}$ ,  $AUC(0-t)$ ,  $AUC(0-12)$  and  $t_{1/2}$  will be calculated for tazemetostat and its metabolite on Cycle 1, Day 1 and Cycle 1, Day 15 using the Phoenix WinNonLin software, if data are sufficient. All plasma tazemetostat concentrations will be used to determine population estimates of  $CL/F$ ,  $V_d/F$  and  $K_a$  with a non-linear mixed-effects model using NONMEM 7 software as data warrant. The effect of subject characteristics such as age, weight, body surface area, and gender on tazemetostat PK parameters may be investigated.

## 8.12 Efficacy Assessment

Disease will be evaluated by using the following disease-appropriate standardized response criteria:

- For solid tumors: RECIST 1.1
- For CNS tumors: RANO criteria

To be assigned a status of PR or CR, a confirmatory disease assessment must be performed no less than 4 weeks (28 days) after the criteria for response are first met.

The ORR is defined as the percentage of subjects achieving a confirmed CR or PR (using disease-appropriate standardized response criteria) from the start of tazemetostat treatment until disease progression or the start of subsequent anti-cancer therapy. The calculation of ORR will utilize the Full Analysis set. All subjects who received at least one dose of tazemetostat will be included in the determination of ORR regardless of the number of efficacy assessments performed. Subjects with not evaluable or missing response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage.

In Dose Expansion, the ORR will be summarized by cohort and overall. An exact 80% CI for ORR in each cohort and overall will be calculated.

Progression-Free Survival (PFS) is defined as the interval of time between the date of the first dose of study drug and the earliest date of disease progression or death due to any cause.

For subjects who progressed or died after an extended period without adequate assessment, the time of PFS will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the investigator determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring. Specific rules for identifying extended loss to follow-up or extended time without an adequate assessment are provided in the SAP.

For subjects who receive subsequent anticancer therapy prior to the date of documented progression or death, the time of PFS will be censored at the last adequate assessment (i.e., last assessment of CR, PR or SD) prior to the initiation of that anticancer therapy.

For other subjects who do not progress or die, the time of PFS will be censored at the date of the last adequate tumor assessment.

### **8.13 Pediatric Investigation Plan**

A Pediatric Investigation Plan (PIP) has not been submitted to the European Medicines Agency (EMA), but will be the subject of future discussions with EMA.

## 8.14 Pediatric Formulation

Tazemetostat is available for pediatric administration as an oral suspension during the phase 1 and covers the entire pediatric age range. The amount of suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. Bulk oral suspension is prepared, by the compounding pharmacist, by mixing tazemetostat powder with Ora-sweet® to produce tazemetostat oral suspension at 30 mg/mL. Standard institutional procedures for administering an oral agent by mouth are followed, and a 7-day or 14-day supply is provided with instructions on home administration.

A clinical pharmacology study to determine the bioavailability of the pediatric suspension formulation relative to tablets is also planned to facilitate switching between the suspension and tablet formulations.

A commercial formulation for pediatric subjects is being developed and will be introduced during clinical development.

## 8.15 Current or Potential Challenges that Have Been Identified Regarding Clinical Trials in Children

The ongoing phase 1 study in children is restricted to subjects with genetically-defined INI1-negative and SMARCA4 tumors that are rare in incidence and poorly treated by existing therapies. These tumors include MRTs, ES, EMPNST, EMC, RMC and myoepithelial carcinomas, and are characterized by their rarity and unmet medical need. INI1-negative tumors include several tumors for which there are no established standard of care. MRTs are characterized by primary treatment resistance and by subjects with relapsed or refractory disease. There have been at best, only anecdotal reports of objective responses to unapproved investigational drugs on clinical trials, salvage radiation therapy or combination chemotherapy. As such:

1. Due to the rarity of these diseases, Epizyme proposes to evaluate clinical safety across multiple tumor types by enrolling up to 84 pediatric subjects with genetically-defined INI1-negative and SMARCA4-negative tumors. The safety profile of tazemetostat would be supplemented by the adult safety experience across all indications which currently include B-cell NHL, INI1-negative and SMARCA-4 negative tumors, synovial sarcoma, and mesothelioma. Available safety data for indications to be studied in the future will also be included in an integrated summary of safety.

2. Due to the rarity of these diseases and unmet medical need, Epizyme proposes to discuss with the Agency that this study be considered as adequate and well controlled in order to demonstrate efficacy and safety in this pediatric population.
  
3. Pediatric subjects are enrolled into the trial on the basis of locally determined histopathological disease diagnosis and evidence of either: a) loss of tumor expression of INI1 or SMARCA4; or b) the presence of a t(X;18) translocation in the case of synovial sarcoma. As a result, in the case of (a) Epizyme proposes to define the indication as any tumor independent of histological diagnosis which is INI1-negative or SMARCA4-negative. Thus, the proposed labeled indication would include rhabdoid tumors with either loss of INI1 or SMARCA4 and non-rhabdoid tumors with loss of INI1.

## 9.0 SUMMARY

In vitro and in vivo non-clinical xenograft experiments strongly suggest the potential for clinical anti-tumor activity in INI1-negative tumors, thus providing rationale for the expectation of benefit of tazemetostat in the aforementioned pediatric tumors. Moreover, in the phase 1 study of tazemetostat in adults, objective responses (1 CR and 3 PRs) were observed in 4 of 11 response evaluable adult subjects with INI1- and SMARCA4-negative cancers.

Given the available clinical safety data and initial activity experience of tazemetostat in adult subjects, non-clinical pharmacology and efficacy data in xenograft models, and unmet need in pediatric subjects, there appears to be sufficient potential benefit to evaluating the therapeutic potential tazemetostat in pediatric subjects with INI1-negative tumors.

Epizyme considers the early, but compelling clinical activity observed to date in these rare and fatal tumors in the phase 1 study of tazemetostat in adults, coupled with lack of effective alternate therapeutic options, including those at the investigational level, to warrant a cautious, but systematic, clinical evaluation of tazemetostat in pediatric subjects with this rare, but genetically defined set of tumors with the commonality of INI1 or SMARCA4 loss.



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