EZH-202

A PHASE II, MULTICENTER STUDY OF THE EZH2 INHIBITOR TAZEMETOSTAT IN ADULT SUBJECTS WITH INI1-NEGATIVE TUMORS OR RELAPSED/REFRACTORY SYNOVIAL SARCOMA

Original Protocol:	13 July 2015
Protocol Amendment 1.0:	24 August 2015
Protocol Amendment 2.0:	02 October 2015
Protocol Amendment 2.1:	03 December 2015 (United Kingdom only)
Protocol Amendment 2.2:	17 February 2016 (Germany only)
Protocol Amendment 2.3:	12 February 2016 (France only)
Protocol Amendment 3.0:	02 March 2016
Protocol Amendment 3.1:	11 July 2016 (Germany only)
Protocol Amendment 4.0:	25 October 2016
Protocol Amendment 4.1:	05 December 2016 (Germany only)
Protocol Amendment 5.0:	07 August 2017
Protocol Amendment 5.1:	03 October 2017 (Germany only)
Protocol Amendment 6.0:	28 September 2018
Protocol Amendment 6.1:	18 January 2019 (Germany only)
Protocol Amendment 7.0:	12 September 2019
Protocol Amendment 8.0:	21 October 2019
Protocol Amendment 8.2:	14 January 2020 (France only)
Protocol Amendment 9.0:	17 March 2020
Protocol Amendment 9.1:	17 April 2020 (Germany only)
Protocol Amendment 10.0:	23 July 2021
Protocol Amendment 10.1:	23 July 2021 (France only)
Protocol Amendment 11.0:	**05 October 2022**

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Epizyme, Inc.

Sponsor's Authorized Officer:

PPD

10-Oct-2022 | 02:44 EDT

PPD

Date (dd mmm yyyy)

Epizyme, Inc.
400 Technology Square, 4th floor
Cambridge, MA 02139, USA

Responsible Medical Officer:

PPD

05-Oct-2022 | 14:16 EDT

PPD

Date (dd mmm yyyy)

Epizyme, Inc.
400 Technology Square, 4th floor
Cambridge, MA 02139, USA

INVESTIGATOR'S AGREEMENT

I have read the EZH-202 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (dd mmm yyyy)

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma
Compound Name (Number):	Tazemetostat (EPZ-6438)
Protocol Number:	EZH-202
IND Number:	124608
EudraCT Number:	2015-002469-41
Sponsor:	Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 11	**05 October 2022**
Amendment 10.1	23 July 2021 (France only)
Amendment 10	23 July 2021
Amendment 9.1	17 April 2020 (Germany only)
Amendment 9:	17 March 2020
Amendment 8.2:	14 January 2020 (France only)
Amendment 8:	21 October 2019
Amendment 7	12 September 2019
Amendment 6.1	18 January 2019 (Germany only)
Amendment 6	28 September 2018
Amendment 5.1	03 October 2017 (Germany only)
Amendment 5	07 August 2017
Amendment 4.1	05 December 2016 (Germany only)
Amendment 4	25 October 2016
Amendment 3.1	11 July 2016 (Germany only)
Amendment 3	02 March 2016
Amendment 2.3	12 February 2016 (France only)
Amendment 2.2	17 February 2016 (Germany only)
Amendment 2.1	03 December 2015 (United Kingdom only)
Amendment 2	02 October 2015
Amendment 1	24 August 2015
Original Protocol	13 July 2015

Amendment 11 (05 October 2022)

Overall Rationale for the Amendment:

This amendment is being made primarily for the following reasons:

- To update and align background and clinical information about tazemetostat with the updated Investigator Brochure (IB) for tazemetostat (IB version 12.0)
- To update the Medical Monitor
- To update the exploratory objectives and endpoints regarding pharmacodynamics
- To remove the requirement for central ECG readings
- To remove the requirements for PK sampling for subjects in Cohort 8
- To update the requirements for record retention

In addition, non-substantial changes, minor editorial, and document formatting revisions were made. All changes are visible in the tracked version.

Substantial changes to the protocol are detailed in the table below:

Section # and Name	Description of Substantial Change	Rationale
Sponsor Protocol Approval Page Clinical Study Protocol	Updated to provide the new Medical Monitor.	To ensure the Medical Monitor information is up-to-date and accurate.
Section 2 (Protocol Synopsis) Section 6 (Objectives and Endpoints) Section 17.4.2 (Analysis of Secondary Efficacy Endpoints) Section 17.7 (Exploratory Analysis)	Rephrased objectives and endpoints for clarity. Updated to make investigating the pharmacodynamic effects of tazemetostat in tumor tissue an exploratory endpoint rather than a secondary endpoint.	Tumor tissue sampling was made optional in Amendment 9.0 (17 March 2020), therefore not all subjects will have the samples needed for pharmacodynamics to be a secondary endpoint. The Sponsor will instead analyze available samples collected for pharmacodynamic analysis as an exploratory endpoint.
Section 7.1 (Overall Experimental Plan)	Updated based on current study.	To clarify the history of each cohort.
Section 12.1 (Schedule of Assessments and Procedures)	Removed row for annual assessments	Annual PK assessments are no longer required to be collected for subjects as of Protocol Amendment 10 (July 2021)
Section 12.1 (Schedule of Assessments and Procedures)	Added row for overall survival	To clarify what assessments are performed during survival follow-up.
Section 12.1 (Schedule of Assessments and Procedures) Section 12.5.4 (Electrocardiograms (ECGs))	Updates to remove the need for central ECG readings.	Local reads are sufficient and to align across the tazemetostat program.
Section 12.1 (Schedule of Assessments and Procedures) Section 12.5.7 (Pharmacokinetics)	Update to remove the requirement for collecting PK samples from subjects in Cohort 8.	Based on the number of samples already collected, the Sponsor feels continued collection of PK sample from Cohort 8 subjects would be an unnecessary burden for subjects and sites. PK sampling was stopped in a memo to file dated 14 February 2020.
Section 14.4.2 (MDS/AML/MPN) Section 14.4.3 (Tazemetostat Quarterly Safety Review and External Safety Committee (ESC)) Section 14.4.4 (Dose Modification for Occurrence of AESI)	Updates to align with the current IB.	To provide more up-to-date information
Section 19.1 (Recording and Access to Study Records)	Updates to the requirements for record retention.	To align across the tazemetostat program.

Non-substantial changes to the protocol are detailed in the table below:

Section # and Name	Description of Substantial Change	Rationale
Title Page Signature Page Investigator's Agreement Section 2 (Protocol Synopsis)	Reformatted and rearranged information.	To align with an updated template.
Section 2 (Protocol Synopsis) Section 6 (Objectives and Endpoints)	Rephrased objectives and endpoints for clarity, readability, and accuracy.	The objectives and endpoints of this study have changed since it began in 2015. These editorial updates were made to streamline the future outputs needed for the clinical study report.
Section 8.2 (Inclusion Criteria)	Minor edits	To align with the inclusion criteria listed in the synopsis
Section 12.2 (Timing Window Allowances for ECGs)	Changed "-240 minutes" to "-4 hours."	For clarity
Section 12.5.2 (Comprehensive Physical Examination)	Clarified genitourinary exams are required only if clinically indicated.	For clarity.
Section 17.4 (Efficacy Analyses)	Changed 90% confidence interval (CI) to 95%	To align with the Statistical Analysis Plan
Throughout protocol	Renumbered sections	To better align with the Epizyme protocol template.

2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Epizyme, Inc.		
Name of Investigational Product: Tazemetostat (EPZ-6438)		
Name of Active Ingredient: Tazemetostat		
Protocol Number: EZH-202	**Phase: II**	**Country: Global**
Title of Study: A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma		
Study centers: Approximately 20-30 sites in Europe, North America, Australia, and Taiwan		
Studied period (years): Estimated date first subject enrolled: 3Q 2015 Estimated date last subject completed: 4Q 2022		**Phase of development:** II

Objectives:	**Primary Objectives:** **Cohorts 1 (rhabdoid tumors), 3 (other integrase interactor 1 [INI1]-negative tumors or any solid tumor with enhancer of zeste homolog-2 [EZH2] gain of function [GOF] mutation), 4 (renal medullary carcinoma [RMC]), 5 (epithelioid sarcoma [ES]), Cohort 6 (ES with optional tumor biopsy), and 7 (chordoma):** • To assess the objective response rate (ORR) following oral administration of tazemetostat 800 mg twice daily (BID). **Cohort 2 (relapsed/ refractory [R/R] synovial sarcoma):** • To determine the progression-free survival (PFS) rate following 16 weeks of oral administration of tazemetostat 800 mg BID. **Cohort 8 (ES treated with tazemetostat 1600 mg once daily [QD]):** • To assess the safety and tolerability of tazemetostat 1600 mg QD.
	Secondary Objectives: • To evaluate the duration of response (DOR) in subjects with rhabdoid tumors (Cohort 1), R/R synovial sarcoma (Cohort 2), other INI1-negative tumors or any solid tumor with EZH2 GOF mutation (Cohort 3), RMC (Cohort 4), and ES (Cohort 5), ES undergoing optional biopsy (Cohort 6), chordoma (Cohort 7), and ES receiving 1600 mg tazemetostat QD (Cohort 8) and to evaluate the DOR in Cohorts 1, 3, 4, 5, 6, and 7 combined. • To assess the disease control rate (DCR) in subjects with ES (Cohort 5) and ES undergoing optional biopsy (Cohort 6) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD. • To assess the ORR in subjects with R/R synovial sarcoma (Cohort 2) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD. • To determine the PFS and overall survival (OS) at Weeks 24, 32, and 56 and overall in subjects with rhabdoid tumors (Cohort 1), R/R synovial sarcoma (Cohort 2), other INI1-negative tumors or any solid tumor with EZH2 GOF mutation (Cohort 3), RMC (Cohort 4), ES (Cohort 5), ES undergoing optional biopsy (Cohort 6), and chordoma (Cohort 7) following oral administration of

	tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD.
	Exploratory Objectives: • To explore the relationship between plasma PK and tumor pharmacodynamic (PD) markers as permitted by the data • To assess tumor tissue and blood for somatic mutations, germline variants, messenger ribonucleic acid (mRNA), and/or proteins as candidate markers of response to tazemetostat • **Cohort 6 only:** To assess the effects of tazemetostat on tumor immune priming (e.g., PD-L1 and CD8 IHC) • **Cohort 6 only:** To investigate the PD effects of tazemetostat in tumor tissue, if a post-dose tumor sample is available
Study Design:	This is a Phase II, multicenter, open-label, single-arm, 2-stage study with an oral dose of tazemetostat 800 mg BID and 1600 mg QD. Subjects will be screened for eligibility within 21 days of the planned date of the first dose of tazemetostat and enrolled into 1 of 8 cohorts based on tumor type: **Cohorts using tazemetostat 800 mg BID:** **Cohort 1:** Rhabdoid tumors (malignant rhabdoid tumors [MRT], rhabdoid tumors of the kidney [RTK], atypical teratoid rhabdoid tumors [ATRT], and selected tumors with rhabdoid features, including small cell carcinoma of the ovary hypercalcemic type [SCCOHT], also known as malignant rhabdoid tumor of the ovary [MRTO]) (closed to enrollment) **Cohort 2:** R/R synovial sarcoma with SS18-SSX rearrangement (closed to enrollment) **Cohort 3:** Other INI1-negative tumors or any solid tumor with EZH2 GOF mutation: epithelioid malignant peripheral nerve sheath tumors (EMPNST), extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma, other INI1-negative tumors with Sponsor approval, and any solid tumors including but not limited to Ewing's sarcoma and melanoma (closed to enrollment). **Cohort 4:** RMC (closed to enrollment) **Cohort 5**: ES (closed to enrollment) **Cohort 6:** ES undergoing optional tumor biopsy (closed to enrollment) **Cohort 7:** Poorly differentiated chordoma (or other chordoma with Sponsor approval) (closed to enrollment) **Cohorts using tazemetostat 1600 mg QD:** **Cohort 8:** ES (closed to enrollment) Subjects will receive tazemetostat in continuous 28-day cycles. Subjects may discontinue study treatment at any time due to disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study. Subjects will have an End of Treatment (EOT) visit up to 30 days after last dose of treatment in this study or prior to the start of a new anticancer therapy, whichever occurs first. All subjects will be followed for survival. Response is defined as having documented evidence of complete response (CR) or partial response (PR). Response assessment will be performed every 8 weeks while on treatment and every 8-12 weeks in survival follow-up.

For all cohorts (except Cohorts 6 and 8), statistical analyses of the primary endpoint will be performed at the end of Stage 1 (first 15 subjects in each cohort and end of Stage 2 (all subjects enrolled in each cohort). The data cut-off for Stages 1 and 2 analyses will vary by cohort:

- **For Cohorts 1, 3, 4, and 7:** The data cut-off for the analysis of the primary endpoint will occur when subjects have completed at least the Week 24 assessment, completed the final study visit, or terminated early from the study, whichever is sooner.
- **For Cohort 2:** The data cut-off for the analysis of the primary endpoint will occur when subjects have completed at least the Week 16 assessment, completed the final study visit, or terminated early from the study, whichever is sooner.
- **For Cohort 5:** The data cut-off for the analysis of the primary endpoint will occur when subjects have completed at least the Week 24 assessment, completed the final study visit, or terminated early from the study, whichever is sooner.

  Note the data cut-off for the Stage 1 futility analysis and the Stage 2 analysis opening the expansion cohort occurred when subjects completed at least the Week 24 assessment (or Week 32 assessment, respectively), completed the final study visit, or terminated early from the study, whichever was sooner.
- **For Cohort 6:** The data cut-off for the analysis of the primary endpoint will occur when subjects have completed at least the Week 24 assessment, completed the final study visit, or terminated early from the study, whichever is sooner.
- **For Cohort 8:** The data cut-off for the analysis of the primary endpoint will occur when subjects have completed at least the Cycle 2 Day 1 assessment, completed the final study visit, or terminated early from the study, whichever is sooner.

Rollover Study

All subjects who received tazemetostat in this study (EZH-202) and are eligible to continue receiving tazemetostat or to continue survival follow-up, can transfer to a Rollover Study (EZH-501) for continued study drug and/or continued monitoring at the Investigator and Medical Monitor's discretion.

Number of Subjects:

Each cohort (except Cohorts 6 and 8) will use a two-stage Green-Dahlberg design. The number of subjects expected to be enrolled in each stage are provided in the table below:

	Each Cohort Separately: **Cohort 1** (Rhabdoid tumors) **Cohort 2** (R/R synovial sarcoma) **Cohort 3** (INI1-negative/ EZH2 GOF mutation) **Cohort 4** (RMC) **Cohort 7** (Chordoma)	**Cohort 5** (ES; tazemetostat 800 mg BID)	**Cohort 6** (ES undergoing optional tumor biopsy)	**Cohort 8** (ES; tazemetostat 1600 mg QD)
Stage 1	15	15	NA	NA
Stage 2	15 (Note: Cohorts 4 and 7 were closed prior to Stage 2)	15	NA	NA
Expansion	NA	30	NA	NA
Total	**30**	**60**	**65**	**16** (Note: Cohort 8 was closed prior to reaching this enrollment goal)

Abbreviations: BID twice daily; ES epithelial sarcoma; GOF gain of function; NA not applicable; QD once daily; R/R relapsed/ refractory; RMC renal medullary carcinoma.

	It is expected that approximately 130-291 subjects will be enrolled.
Diagnosis and Main Criteria for Inclusion:	**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): ≥18 years of age 2. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 **NOTE:** If subject is unable to walk due to paralysis, but is mobile in a wheelchair, subject is considered to be ambulatory for the purpose of assessing their performance status. 3. Has provided signed written informed consent 4. Has a life expectancy of >3 months 5. Has a malignancy: • For which there are no standard therapies available (Cohorts 1, 3, 4 & 5) • That is relapsed or refractory, defined as metastatic or non-resectable, locally advanced disease that has previously been treated with and progressed following approved therapy(ies), if therapy(ies) exists (Cohort 2) • That has progressed within 6 months prior to study enrollment (Cohort 5 Expansion, Cohort 6, and Cohort 8 only) 6. Has a documented local diagnostic pathology of original biopsy confirmed by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) or other Sponsor-approved laboratory certification 7. **For Cohort 1 (rhabdoid tumors) only:** The following test results must be available by local laboratory: • Morphology and immunophenotypic panel consistent with rhabdoid tumors, and • Loss of INI1 or SMARCA4 confirmed by IHC, or • Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss or mutation when INI1 or SMARCA4 IHC is equivocal or unavailable 8. **For Cohort 2 (subjects with relapsed/refractory synovial sarcoma) only:** The following test results must be available by local laboratory: • Morphology consistent with synovial sarcomas, and • Cytogenetics or fluorescence in situ hybridization (FISH) and/or molecular confirmation (e.g., DNA sequencing) of SS18 rearrangement t(X;18)(p11;q11) 9. **For Cohorts 3, 4, 5, 7, and 8 (subjects with INI1-negative tumors or any solid tumor with EZH2 GOF mutation) only:** The following test results must be available by local laboratory: • Morphology and immunophenotypic panel consistent with INI1-negative tumors (not applicable for solid tumors with EZH2 GOF mutation), and • Loss of INI1 confirmed by IHC, or • Molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC is equivocal or unavailable, or • Molecular evidence of EZH2 GOF mutation 10. **For Cohort 6 (subjects with ES undergoing optional tumor biopsy) only:** • Morphology and immunophenotypic panel consistent with ES (e.g., CD34,

EMA, Keratin, and INI1)

- If providing optional biopsy: Willingness to provide informed consent to undergo pre- and post-dose biopsy

11. Has all prior treatment (i.e., chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolved to ≤ Grade 1 per CTCAE, version 4.03 or are clinically stable and not clinically significant, at time of enrollment
12. Prior anti-cancer therapy(ies), if applicable, must be completed according to the criteria below:

Prior Therapy	Time from Last Prior Therapy Regimen
Chemotherapy: cytotoxic	At least 14 days since last dose of chemotherapy prior to first dose of tazemetostat
Chemotherapy: nitrosoureas	At least 6 weeks since last dose of nitrosoureas prior to first dose of tazemetostat
Chemotherapy: non-cytotoxic (e.g., small molecule inhibitor)	At least 14 days since last dose of non-cytotoxic chemotherapy prior to first dose of tazemetostat
Monoclonal antibody(ies)	At least 28 days since the last dose of monoclonal antibody prior to first dose of tazemetostat
Immunotherapy (e.g., tumor vaccine)	At least 42 days since last dose of immunotherapy agent(s) prior to first dose of tazemetostat
Radiotherapy (RT)	At least 14 days from last local site RT prior to first dose of tazemetostat At least 21 days from stereotactic radiosurgery prior to first dose of tazemetostat At least 12 weeks from craniospinal, ≥50% radiation of pelvis, or total body irradiation prior to first dose of tazemetostat
High Dose Therapy with autologous or allogeneic hematopoietic cell infusion	At least 60 days from last infusion prior to first dose of tazemetostat
Hematopoietic growth factor in support of anti-cancer therapy	At least 14 days from last dose of hematopoietic growth factor prior to first dose of tazemetostat

13. Has sufficient tumor tissue (slides or blocks) available for central confirmatory testing of IHC and/or cytogenetics/FISH and/or DNA mutation analysis (required for study entry but enrollment based on local results).
14. Has **measurable** disease based on either RECIST 1.1 for solid tumors or RANO for CNS tumors
15. Has adequate hematologic (bone marrow and coagulation factors), renal and hepatic function as defined by criteria below:

System	Laboratory Value
Hematologic (Bone Marrow Function)	
Hemoglobin[a]	≥9 g/dL
Platelets[b]	≥100 000/mm^3 (≥100 ×10^9/L)
ANC[c]	≥1000/mm^3 (≥1.0 × 10^9/L)
Hematologic (Coagulation Factors)	
INR/PT[d]	<1.5 × ULN

PTT	<1.5 × ULN
Renal Function	
Serum creatinine[e]	≤1.5 × ULN
Hepatic Function	
Total bilirubin[f]	<1.5 × ULN
AST[g]	<3 × ULN
ALT[g,h]	<3 × ULN

Abbreviations: ALT alanine aminotransferase; ANC absolute neutrophil count; AST aspartate aminotransferase; CrCl creatinine clearance; LLN lower limit of normal; PT prothrombin time; PTT partial thromboplastin time; ULN upper limit of normal.

a. May receive transfusion
b. Should be evaluated after at least 7 days since last platelet transfusion
c. Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
d. INR is the preferred value to be measured. However, if only PT can be performed in the testing laboratory that is acceptable
e. If creatinine is not <1.5ULN then calculate by Cockcroft-Gault methods or local institutional standard and CrCl must be >50 mL/kg/1.73 m^2
f. If attributed to documented Gilbert's disease, total bilirubin < 2.5 × ULN. Eligibility can be determined by conjugated or total bilirubin
g. If attributed to tumor involvement, AST, and ALT <5×ULN

16. Subjects with a history of hepatitis (Exclusion Criterion No. 13) must have ALT within the normal range

    NOTE: Laboratory results obtained during screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the Investigator may retest the subject and the subsequent within range screening result may be used to determine the subject's eligibility.

17. **For subjects with CNS tumors only:** Subject must have seizures that are stable, not increasing in frequency or severity and controlled on current anti-seizure medication(s) for a minimum of 21 days prior to the planned first dose of tazemetostat

    NOTE: Subjects may receive glucocorticoids (at stable or tapering dose) to control CNS symptoms prior to enrollment; however, should receive stable or tapering dose for at least 7 days prior to planned first dose of tazemetostat

18. Has a shortening fraction of >27% or an ejection fraction of ≥50% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan and New York Heart Association (NYHA) Class ≤2
19. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec
20. **Female subjects of childbearing potential must:**
    - Have a negative beta-human chorionic gonadotropin (β-hCG) pregnancy test at time of screening and within 14 days prior to planned first dose of tazemetostat (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing), **and**
    - Agree to use effective contraception, as defined in Section 12.6.1, from a minimum of 7 days prior to first dose until 6 months following the last dose of tazemetostat and have a male partner who uses a condom, **or**
    - Practice true abstinence (when this is in line with the preferred and usual lifestyle of the subject, see Section 12.6.1), **or**
    - Have a male partner who is vasectomized
21. **Male subjects with a female partner of childbearing potential must:**

	• Be vasectomized, **or** • Agree to use condoms as defined in Section 12.6.2, from first dose of tazemetostat until 3 months following the last dose of tazemetostat, **or** • Have a female partner who is NOT of childbearing potential
	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. 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 3. Has known active CNS or any leptomeningeal metastasis of primary extracranial tumor. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging 4 weeks prior to the first dose of study drug and any neurologic symptoms have stabilized), have no evidence of new or enlarging brain metastases, and are on stable or tapering doses of steroids for at least 7 days prior to first dose of study drug. **NOTE:** Subjects with asymptomatic brain metastases found on screening MRI may be entered into the study without prior radiation therapy to the brain if they do not require immediate surgical or radiation therapy in the opinion of the treating Investigator and in the opinion of a radiation therapy or neurosurgical consultant. 4. Has had a prior malignancy other than the malignancies under study **Exception:** A subject who has been disease-free for 5 years, or a subject with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma is eligible. 5. Has had major surgery within 3 weeks prior to enrollment **NOTE**: Minor surgery (e.g., minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment. 6. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS). Has abnormalities known to be associated with MDS (e.g. del 5q, chr 7 abn) and MPN (e.g. JAK2 V617F) observed in cytogenetic testing and DNA sequencing. **NOTE:** Bone marrow aspirate/biopsy will be conducted following abnormal peripheral blood smear morphology assessment conducted by central laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy. 7. Has a prior history of T-LBL/T-ALL. 8. Is unwilling to exclude grapefruit juice, Seville oranges and grapefruit from the diet and all foods that contain those fruits from time of enrollment to while on study. 9. Has cardiovascular impairment, history of congestive heart failure greater than NYHA Class 2, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of

	tazemetostat; or ventricular cardiac arrhythmia requiring medical treatment 10. Is currently taking any prohibited medication(s) 11. Has an active infection requiring systemic treatment 12. Is immunocompromised (i.e., has a congenital immunodeficiency), including subjects known history of infection with human immunodeficiency virus (HIV) 13. Has known active infection with hepatitis B virus or hepatitis C virus **NOTE:** Subjects with a history of hepatitis B or C with normal ALT and undetectable HBV DNA or HCV RNA are eligible for this study 14. Has had a symptomatic venous thrombosis within the 2 weeks prior to study enrollment. **NOTE:** Subjects with a history of a deep vein thrombosis > 2 weeks prior to study enrollment who are on anticoagulation therapy with low molecular weight heparin are eligible for this study. 15. **For subjects with CNS involvement (primary tumor or metastatic disease):** Have any active bleeding, or new intra-tumoral 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. 16. Has known hypersensitivity to any of the components of tazemetostat or other inhibitor(s) of EZH2 17. Is unable to take oral medications, or has malabsorption syndrome or any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea or vomiting) that might impair the bioavailability of tazemetostat 18. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements. 19. **For female subjects of childbearing potential:** Is pregnant or nursing 20. **For male subjects:** Is unwilling to adhere to contraception criteria from time of enrollment in study to at least 3 months after last dose of tazemetostat.
Dosage and Administration for Tazemetostat:	Subjects will receive tazemetostat 800 mg BID orally over continuous 28-day cycles. Subjects in Cohort 8 only, will receive tazemetostat 1600 mg QD orally over continuous 28-day cycles. Subjects may discontinue at any time due to disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.
Criteria for Evaluation:	**Primary Endpoints:** • **Cohorts 1, 3, 4, 5, 6, and 7:** ORR (confirmed CR+PR) for tazemetostat in subjects with INI1-negative tumors using disease-appropriate standardized response criteria (primary CNS tumors: Response Assessment for Neuro-Oncology [RANO] and all others: RECIST 1.1) • **Cohort 2:** PFS rate after 16 weeks of treatment with tazemetostat. This is the number of subjects with confirmed CR or PR, or stable disease (SD) at the Week 16 assessment. • **Cohort 8:** Safety and tolerability as assessed by AEs and clinical laboratory tests
	Secondary Endpoints: • DOR for each cohort (Cohorts 1-8) and for Cohorts 1, 3, 4, 5, 6, and 7 combined. DOR is defined as the time from the first documented evidence of CR or PR to the

<table>
<tr><td></td><td>time of first documented disease progression or death due to any cause, whichever comes first, using disease-appropriate standardized response criteria
• Cohorts 5, 6, and 8: DCR for tazemetostat. This is defined as the number of subjects who achieve confirmed response (CR+PR) or who have SD lasting at least 32 weeks.
• Cohorts 2 and 8: ORR. This is defined as the number of subjects who achieve confirmed response (CR+PR) per RECIST 1.1
• PFS at Weeks 24, 32, and 56 and overall for each cohort. PFS is defined as the time from the date of first dose of study treatment to the earlier of the date of first documented disease progression or date of death due to any cause
• OS at Weeks 24, 32, and 56 and overall for each cohort. OS is defined as the time from the date of the first dose of study treatment to the date of death due to any cause</td></tr>
<tr><td></td><td>Exploratory Endpoints:
• Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation, and cell proliferation and their correlation with activity
• Somatic mutation analysis of tumor tissue and blood derived circulating DNA
• Germline DNA analysis for INI1 and SMARCA4 variants
• Cohort 6: Assessment of pre- and post-dose biopsies for immune priming (e.g., PD-L1 and CD8 IHC)
• Cohort 6: Assessment of pre- and post-dose biopsies for H3K27me3 and for changes in gene expression.</td></tr>
<tr><td>Statistical Methods:</td><td>Sample Size Rationale: For all cohorts except Cohorts 6 and 8 (ES undergoing optional tumor biopsy and ES 1600 mg QD, described below), each cohort will be evaluated separately using a two-stage Green-Dahlberg design. The sample size of each cohort is calculated on the primary endpoint. Within each cohort the hypothesis will be tested using a one-sided test with α=0.05 and the type II error rate will be controlled at 0.2.
<table>
<tr><td></td><td>Each Cohort Separately:
Cohort 1[a] (Rhabdoid tumors)
Cohort 3[a] (Other INI1-negative tumors or any solid tumor with EZH2 GOF mutation)
Cohort 4[a] (RMC)
Cohort 7[a] (Chordoma)</td><td>Cohort 2[a] (Relapsed/ refractory synovial sarcoma)</td><td>Initial Design: Cohort 5[a] (ES)</td><td>Amended Design: Cohort 5[b] (ES)</td></tr>
<tr><td>Stage 1: Null hypothesis</td><td>CR + PR ≤5%</td><td>CR + PR + SD at Week 16 ≤15%</td><td>CR + PR ≤5%</td><td>DCR ≤5%</td></tr>
<tr><td>Stage 1: Alternative hypothesis</td><td>CR + PR ≥20%</td><td>CR + PR + SD at Week 16 ≥35%</td><td>CR + PR ≥20%</td><td>DCR ≥20%</td></tr>
<tr><td>Stage 1 sample size (n1)[c]</td><td>15</td><td>15</td><td>15</td><td></td></tr>
<tr><td>Stage 1 rejection of study treatment (r1)[c]</td><td>0</td><td>1</td><td>0</td><td></td></tr>
<tr><td>Stage 2 sample size (n2)</td><td>15</td><td>15</td><td>15</td><td>15</td></tr>
</table></td></tr>
</table>

Stage 2 rejection of study treatment (r)	4	8	4	4
Total sample size (n)	**30**	**30**	**30**	**30**
Expansion[d]	NA	NA	NA	30

a. All subjects will have completed at least the Week 24 (Week 16 for synovial sarcoma) assessment, completed the final study visit, or terminated early from the study, whichever is sooner.
b. All subjects will have completed at least the Week 32 assessment, completed the final study visit, or terminated early from the study, whichever is sooner - based on Amendment 4.
c. Within each cohort, the interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 15 subjects are treated and followed for the specified time. In this scenario, the total sample size (Stage 1 + Stage 2) for a cohort would still remain unchanged at 30 subjects.
d. An additional 30 subjects may be enrolled for expanded evaluation of efficacy and safety. Enrollment in the expansion stage may be opened once the Stage 2 rejection criterion has been surpassed. If this occurs prior to the full enrollment of Stage 2, the total cohort sample size (Stage 1 + Stage 2 + expansion) will remain unchanged at 60 subjects.

The Cohort 5 expansion stage was opened in December 2016 after the Stage 2 DCR criterion was surpassed. In May 2017, Epizyme met with the FDA regarding future development plans for tazemetostat. Based on specific recommendations from FDA, with Amendment 5, the primary endpoint for Cohort 5 has been changed to ORR and duration of response in responding subjects has been elevated to the most important secondary endpoint.

Expansion: The additional 30 subjects enrolled in Cohort 5 will allow for increased precision for the point estimates of DCR and ORR. The table below shows the 95% exact binomial confidence interval (CI) for potential point estimates of DCR and/or ORR:

Potential DCR or ORR	20%	30%	40%
Subjects meeting endpoint	12 of 60	18 of 60	24 of 60
95% exact binomial CI	10.8%-32.3%	18.8%-43.2%	27.6%-53.5%

Sample Size Rationale for Cohort 6:

Cohort 6 was added outside of a 2-stage design framework based on clinical data demonstrating encouraging evidence of antitumor activity, and no concerning safety signals in ES subjects in Cohort 5. Preliminary evidence of the immune-priming effect of tazemetostat evaluated by IHC provided the rational for collecting mandatory paired tumor biopsies in this cohort. Twenty (20) paired tumor biopsies will afford sufficient data to quantify the immune priming effects of tazemetostat. Due to the expectation that some subjects will withdraw consent after the post-screening biopsy and other subjects may not be able to provide a post-treatment biopsy, Cohort 6 will enroll up to 40 subjects to ensure that 20 paired tumor biopsies are collected and adequate for analysis.

In January 2020, tazemetostat was approved for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced ES not eligible for complete resection. Under the conditions of the approval, Epizyme agreed with the FDA to enroll an additional 25 subjects in cohort 6 to further evaluate the ORR in subjects

	with metastatic or locally advanced ES. The primary endpoint of Cohort 6 has been changed to ORR and the effects of tazemetostat on tumor immune priming has been changed to an exploratory endpoint. The requirement for mandatory pre- and post- dose tumor biopsies has been made optional in amendment 9. With a sample size of at least 40 subjects, the study has a power of more than 80% to test the hypothesis that the objective response rate would be 20% or higher against the null hypothesis that it would be 5% or lower at one-sided significance level of 0.025. **Sample Size Rationale for Cohort 8:** As with Cohort 6, Cohort 8 was added outside of a 2-stage design framework based on clinical data in ES subjects in Cohort 5 (see rationale above for Cohort 6). Cohort 8 was added to evaluate safety, PK, and efficacy profile of once daily tazemetostat dosing; 16 subjects will be enrolled for evaluation of PK, efficacy, and safety.

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3.1. List of Figures

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4. ABBREVIATIONS

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
ATRT	atypical teratoid rhabdoid tumor
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BM	bone marrow
Brookmeyer	Brookmeyer-Crowley method
CAP	College of American Pathologists
CEC	central ethics committee
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	oral clearance
CLIA	Clinical Laboratory Improvement Amendments
cm	centimeter
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	clinical trial directive
C_{trough}	observed concentration at the end of a dosing interval, immediately before the next dose administration

Abbreviation	Definition
CYP	cytochrome
DCR	disease control rate
DDI	drug-drug interaction
Devine	Devine Formula
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EIAED	enzyme inducing anti-epileptic drug
EMA	European Medicines Agency
EMC	extraskeletal myxoid chondrosarcoma
EMPNST	epithelioid malignant peripheral nerve sheath tumor
ER	efflux ratio
ES	epithelioid sarcoma
EU CT Dir	European Union Clinical Trial Directive
EZH2	enhancer of zeste homologue-2
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FFPE	formalin fixed paraffin- embedded
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FLAIR	fluid-attenuated inversion recovery
FTIH	first-time-in-human
GCP	Good Clinical Practice
GOF	gain of function
H3K27	lysine 27 of histone H3
H3K27me3	H3K27 trimethylation
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus

Abbreviation	Definition
HMT	histone methyltransferase
HR	heart rate
IB	Investigator's Brochure
IBW	ideal body weight
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	international Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
INI1	integrase interactor 1
INR	international normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-Treat
IV	intravenous
Ka	first-order absorption rate constant
kg	kilogram
L	liter
LLN	lower limit of normal
LN	lymph node
LSLV	last subject, last visit
m^2	squared meter
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mm	millimeter
mL	milliliter
MPN	myeloproliferative disorder
msec	millisecond
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRT	malignant rhabdoid tumor
MRTO	malignant rhabdoid tumor of the ovary

Abbreviation	Definition
MSDS	Material Safety Data Sheet
MTD	maximum tolerated dose
MUGA	multi-gated acquisition scan
NA	not applicable
NE	not evaluable
NHL	Non-Hodgkin's lymphoma
NIH	National Institutes of Health
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PCH	partial clinical hold
PD	pharmacodynamic or progressive disease
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PGx	pharmacogenetics
PK	pharmacokinetics
PR	partial response
PRC2	polycomb repressive complex 2
PT	prothrombin time or preferred term
PTT	Partial thromboplastin time
QC	quality control
QD	once daily
QTcF	QT interval corrected by Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RTK	rhabdoid tumor of the kidney
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
RMC	renal medullary carcinoma
RT	radiation therapy
SAE	serious adverse event
SAM	S-adenosyl methionine
SAP	Statistical Analysis Plan

Abbreviation	Definition
SCCOHT	small cell carcinoma of the ovary, hypercalcemic type
SD	stable disease or standard deviation
SET	sun(var)3-9, enhancer-of-zeste and trithorax
SI	International System of Units
SMARCA4	SWItch/Sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
SWI/SNF	SWItch/Sucrose Non-Fermentable
T	temperature
$t_{1/2}$	apparent elimination half-life
T-ALL	T-cell acute lymphoblastic leukemia
TEAE	treatment-emergent adverse event
TESS	treatment-emergent signs and symptoms
T-LBL	T-cell lymphoblastic lymphoma
T-LBL/T-ALL	T-cell lymphoblastic lymphoma/ T-cell acute lymphoblastic leukemia
T_{max}	Time to maximum concentration
TRAE	Treatment-related adverse event
ULN	upper limit of normal
UV	ultraviolet
Vd/F	oral volume of distribution
WBC	white blood cell
WES	whole-exome sequencing
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

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 methyl transferases (HMTs) which all use S-adenosyl methionine (SAM) as a co-factor 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. Enhancer of Zeste homologue 2 (EZH2) 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, 2011).

EZH2 mutation and/or over-expression has been observed in several cancer types, leading to an aberrant H3K27 trimethylation (H3K27me3) state which is oncogenic (Burkhardt, 2009). For instance, somatic EZH2 gain of function (GOF) mutations at three hotspots (Y646, A682, and A692 [NM_001203247]) are found in 10% to 20% of follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). These GOF mutations result in an oncogenic dependency on EZH2 production of abnormally high H3K27me3 levels, and resultant transcriptional reprogramming of the cell (Morin, 2010).

Consequently, inhibition of EZH2 leads to reduction in H3K27me3 and cell death in lymphoma cell lines bearing the mutation. While lymphoma cells with wild-type EZH2 are growth inhibited by EZH2 inhibition, only EZH2 GOF mutation-bearing cells undergo cell death in culture (Beguelin, 2013; Knutson, 2014).

While uncommon, other solid tumors are known to harbor EZH2 GOF mutations which include Ewing's sarcoma (2.7%) and melanoma (< 2%) (Tirode, 2014; Zingg, 2015). Overexpression of EZH2 with a GOF mutation in melanocytes induces high-penetrance melanoma in cooperation with Braf, confirming the oncogenic role of aberrant H3K27 trimethylation in this indication (Souroullas, 2016). EZH2 inactivation or resulted in a reduction in either melanoma growth or metastasis in vivo, suggesting that EZH2 inhibition may be a promising treatment paradigm in the management of advanced melanoma (Zingg, 2015; Souroullas, 2016).

In addition to genetic alterations in EZH2 itself, genetic changes in other proteins can lead to an oncogenic dependency on EZH2 activity, specifically those affecting proteins of the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex. At many gene loci, PRC2 and SWI/SNF antagonize each other and loss of the SWI/SNF component, integrase interactor 1 (INI1), has been demonstrated to generate over-activation of the PRC2 pathway and tumor cell proliferation (Wilson, 2010). Genetic loss of INI1 has been described in many human malignancies, e.g., rhabdoid tumors, epithelioid sarcoma (ES), epithelioid malignant peripheral nerve sheath tumor (EMPNST), extraskeletal myxoid chondrosarcoma (EMC), myoepithelial carcinoma, poorly differentiated chordoma, and renal medullary carcinoma (RMC) (Margol, 2014; Mobley, 2010). Inhibition of EZH2 activity by either knock-down or small molecule inhibition induces tumor cell killing and durable tumor regressions in nonclinical models of

rhabdoid tumors (Alimova, 2013; Knutson, 2013). Thus, EZH2 inhibition represents a viable potential therapeutic strategy for genetically defined INI1-negative tumors.

Malignant rhabdoid tumors (MRTs) arise in the brain, kidney, and other soft tissues. The pathognomonic genetic alteration consists of bi-allelic inactivation of INI1, which can be detected, in nearly all such tumors. The tumor suppressor role of INI1 has been confirmed in murine studies. Mice lacking one copy of INI1 develop tumors consistent with MRT as early as 5 weeks of age (Roberts, 2000). Bi-allelic conditional inactivation of INI1 in the T-cell lineage leads to fully penetrant cancer formation with a median onset of 11 weeks (Wilson, 2010). In humans, rhabdoid tumors in children have been characterized by bi-allelic loss of INI1 in up to 98% of tumors and often present in infancy (Jackson, 2009). These tumors are diagnosed in children even at birth, have rapid onset, are highly resistant to all treatment and are characterized by aberrant chromatin remodeling and associated dependency on EZH2, highlighting the antagonistic relationship of PRC2 and SWI/SNF. In addition, over-expression of EZH2 has been reported in atypical teratoid rhabdoid tumor (ATRT) (central nervous system [CNS] form of MRT) patient samples, and EZH2 inactivation by either ribonucleic acid (RNA) inhibitor or chemical inhibition leads to apoptosis and increased sensitivity to radiation (Alimova, 2013). Tazemetostat induces apoptosis and differentiation of INI1-negative MRT cells in vitro. Tazemetostat dosing of MRT xenograft bearing mice induces durable tumor regressions and tumors did not re-grow after cessation of dosing (Knutson, 2013).

Another rare tumor, small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) has been described to have inactivating mutations in the chromatin remodeling gene *SMARCA4* with loss of SMARCA4 protein, an important component of the SWI/SNF chromatin remodeling complex (Jelinic, 2014; Ramos, 2014; Witkowski, 2014). Recently the morphologic similarity of SCCOHT to MRT and ATRT has been described (Foulkes, 2014). They describe in a majority of tumors sequenced with whole-exome sequencing (WES) and Sanger sequencing, deleterious mutations in *SMARCA4*. Foulkes notes that virtually all MRTs and ATRTs have mutations in this gene as well as the *SMARCB1* gene and are morphologically and molecularly similar to rhabdoid tumors, thus proposes reclassifying SCCOHT as a malignant rhabdoid tumor of the ovary (MRTO).

SMARCA4 loss has also been described in a subset of undifferentiated thoracic sarcomas. These tumors when genetically characterized are related to MRT and SCCOHT with TP53 mutations and SMARCA4 inactivation being the sole recurrent alterations. The 19 cases evaluated had consistent pathological features that were rhabdoid in morphology and homogeneous in presenting clinical features (Le Loarer, 2015).

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 MRT. 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 (Kadoch, 2013). This creates a state of INI deficiency without a mutation or deletion of INI1 itself, and results in aberrant SWI/SNF complex chromatin remodeling activity at various genes. It also has been reported that the SS18-SSX fusion proteins recruit repressive complexes such as PRC2 to

ATF2 target gene loci, abnormally repressing them (Souroullas, 2016). EZH2 inhibition is hypothesized to release this aberrant repression, leading to anti-proliferative effects.

5.2. Clinical Characteristics of Targeted Tumors

MRTs and their CNS counterpart, ATRT, are rare, have historically poor overall survival (OS) and in children and adults have no established standard treatment approaches (Mobley, 2010; Morgenstern, 2010; Sultan, 2010). The historical 5-year OS in children is estimated to be 17-33% (Ginn, 2012). The median age at diagnosis is 6 years; however, patients 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. Though current treatment at 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; Wen, 2010).

MRTO is a highly aggressive and lethal form of ovarian cancer presenting in young women with a mean age at diagnosis of 24 years. For both patients with local and advanced disease, the prognosis is poor. In the small number of case review reports, advanced tumors and local disease have a 6.5% and 30-40% survival respectively (Young, 1994; Reed, 2014). The current standard of care is uncertain due to a lack of prospective studies given the rarity of the disease. Surgery and multi-agent platinum based chemotherapy, often with the addition of radiotherapy, is typically utilized (Harrison, 2006). Despite an aggressive approach, most women will have recurrence of disease during or shortly after completing adjuvant chemotherapy and 65% will die from their disease within two years of diagnosis (Errico, 2014). Undifferentiated thoracic sarcomas with SMARCA4 additionally have a highly aggressive clinical presentation with large masses at time of presentation, young age of onset (median 41 years) with limited response to therapy and median OS of seven months (Le Loarer, 2015).

Other tumors with INI1 deficiency include ES, EMPNST, EMC, myoepithelial carcinomas, poorly differentiated chordomas, and RMC. Current standard of care for these other INI1-negative tumors has not been well established due to their rarity. The incidence of INI1-negativity in patients with ES was recently reported to be 90% with homozygous deletion of the INI1 gene found in 83% of these patients (Sullivan, 2013). ES is a rare soft tissue sarcoma often found in young adults and accounts for < 1% of all soft tissue sarcomas (Jones, 2012). Local recurrence 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. Likely, because of the rarity of the disease, no published prospective studies of patients with this histologic subtype have been identified. Retrospective institutional experiences have been reported. In one such review, the institutional experience of 21 patients with ES treated with chemotherapy from 1990 to 2009 was presented. The median PFS was determined to be 29 weeks, with median overall survival of 51 weeks. Three of the patients achieved a partial response, all of whom were treated in the first line setting; 12 had stable disease as best response; and 5 progressed. It should be emphasized that this review described patients receiving first (N=20), second (N=7) or third (N=3) line chemotherapy; however, the majority were treated in the frontline setting (Jones, 2012). Another similar study reported on 28 patients

with ES at one institution between 1989 and 2012, 12 of whom received treatment with gemcitabine and docetaxel. Median PFS was 8 months overall, and 9 months in those receiving this regimen as first-line treatment (Pink, 2014).

Chordoma is a rare, slow growing sarcoma of the skull base and spine that is typically bulky and advanced at the time of diagnosis. Chordomas predominantly occur in adults with relapse occurring in > 50% of cases resulting in death from local and metastatic disease (Mobley, 2010; Stacchiotti, 2013). The current standard of care continues to be surgery followed by radiotherapy, while systemic chemotherapy is generally regarded as ineffective in advanced chordoma (Lebellec, 2015). Although, prior to metastasis, chordoma is believed to be an indolent disease, a subset of chordomas referred to as poorly differentiated are clinically more aggressive. This clinically aggressive subset of chordomas has been shown to have a characteristic loss of INI1 (Hasselblatt, 2016). Phase 2 prospective studies dedicated to chordoma have been completed looking at single agent activity of lapatinib, imatinib, and sorafenib with best objective response rates (ORR) reported as 0, 1.7, and 3.7% with a PFS of 8.2, 9, and up to 15 months, respectively (Bompas, 2015).

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; Le Loarer, 2015). Finally, RMC is a highly aggressive tumor that often affects younger patients with sickle cell trait or disease and fatality approaches 100% within several weeks to months of diagnosis (Cheng, 2008). These tumors are very rare and there are no reported controlled clinical trials specific to these INI1-negative populations.

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; Errico, 2014). 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.

5.3. Rationale for Tazemetostat Treatment

In INI1-deficient tumors, EZH2 activity is deregulated, inducing aberrant oncogenic gene expression (Wilson, 2010; Alimova, 2013). Tazemetostat has been shown to induce apoptosis and differentiation in INI1-negative MRT cell lines (Knutson, 2013). In xenograft bearing mice, treatment with tazemetostat resulted in dose-dependent regression of MRTs with correlated diminution of intra-tumoral H3K27 methylation and prevention of tumor regrowth after dosing cessation. Data from the ongoing Phase I study E7438-G000-101 demonstrates early but compelling clinical activity in subjects with INI1-negative tumors (unpublished data). To date, of the 6 treated subjects with INI1-negative tumors (MRT and ES), there have been 3 subjects with objective responses (1 complete response [CR] and 2 partial responses [PRs]). With one MRT subject with pathologically confirmed complete remission continuing on treatment through Week

44 on study and 2 subjects with ES remaining on study. An additional subject with MRT has stable disease (SD) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and exhibited a 15% tumor reduction after 8 weeks of treatment. Of two treated subjects with MRTO, one had a confirmed PR at Week 8 and remains on study for 25 weeks and one had SD and remains on study for 25 weeks. Of the 3 subjects with synovial sarcoma treated thus far there have been no responses observed. All 3 subjects with advanced synovial sarcoma experienced progressive disease, although only one was treated at the recommended Phase II dose (RP2D) (unpublished data).

5.4. Tazemetostat

5.4.1. Investigational Product

In June 2020, the US Food and Drug Administration (FDA) granted accelerated approval of Tazverik® (tazemetostat) in the US for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for the treatment of adult patients with R/R FL who have no satisfactory alternative treatment options.

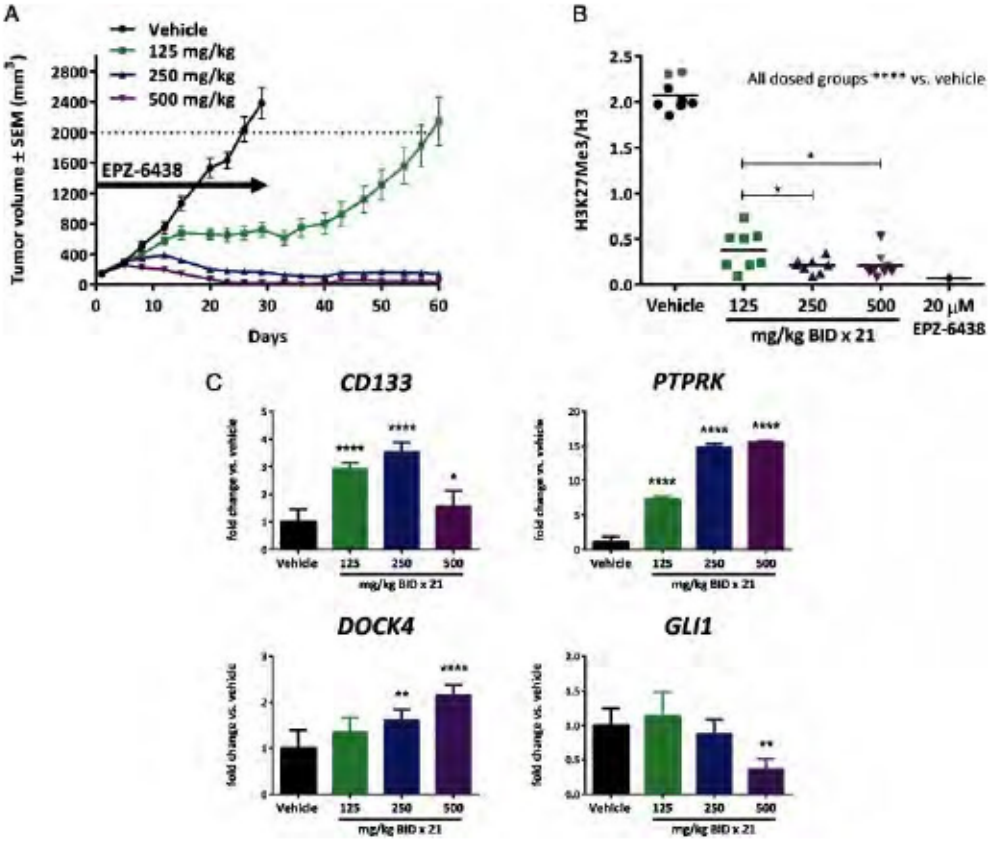
In January 2020, the US FDA granted accelerated approval to Tazverik for adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

In June 2021, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) granted approval of Tazverik for the treatment of patients with relapsed or refractory EZH2 gene mutation-positive follicular lymphoma (limited to use when difficult to treat with standard treatments) to Epizyme's development partner, Eisai Co., Limited.

5.4.2. Nonclinical Pharmacology

Tazemetostat (EPZ-6438) is a selective small molecule inhibitor of the histone-lysine methyltransferase *EZH2* gene (Knutson, 2013). Tazemetostat inhibits both wild-type *EZH2* and mutated *EZH2* residues Y641, A677G and A687 with half maximal inhibitory concentrations (IC_{50}) ranging from 2-38 nmol/L. The compound shows a 35-fold selectivity over the most closely related HMT, EZH1 and greater than a 4500-fold selectivity over other HMTs. It selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective cell killing of cell lines. Tazemetostat specifically inhibits human lymphoma cell lines bearing EZH2 point mutations and INI1 unit deficient (also known as SNF5, SMARCB1, or BAFT47) MRT cell lines with IC_{50} in the nanomolar range. Additionally, tazemetostat administered orally has demonstrated antitumor activity in vivo against several EZH2 mutant human lymphoma xenograft murine models (Knutson, 2014). INI1 mutant MRT xenografts treated for 21-28 days demonstrated near elimination of the tumors with no regrowth observed. The MRT tumors demonstrated strong inhibition of H3K27me3, which correlated with antitumor activity (Figure 1) (Knutson, 2013).

Figure 1 Tazemetostat in INI1 Deleted MRT Xenografts in SCID Mice



Abbreviations BID twice daily, DOCK dedicator of cytokinesis, EPZ-6438 tazemetostat, GLI glioma-associated oncogene, PTPRK protein tyrosine phosphatase receptor type, k.
A) Tumor regressions with BID administration for 28 days;
B) EZH2 target inhibition for mice euthanized at Day 21;
C) Change in gene expression in G401 mice for mice treated for 21 days.

Tazemetostat has shown enhanced antitumor activity when administered in combination with chemotherapy regimens used for the treatment of NHL and sarcomas, with or without doxorubicin, in animal models. Finally, administration of tazemetostat led to dose- and time-dependent decreases in intracellular H3K27 methylation in both tumor and selected non-tumor tissues.

Preliminary data with tazemetostat in 2D model in vitro proliferation assays has demonstrated that all synovial sarcoma cell lines tested (both SS18-SSX1 and SS18-SSX2 fusion positive) are sensitive to EZH2 inhibition. In vivo, dose-dependent tumor growth inhibition was observed with tazemetostat treatment in two patient-derived xenograft (PDX) models, both harboring the SS18-SSX2 fusion, and a cell line xenograft model using the Fuji synovial sarcoma cell line, which also contains the SS18-SSX2 fusion.

Loss of the SWI/SNF component SMARCA4 has been described to be specific to SCCOHT. A panel of ovarian cancer cell lines of different histologies with and without SMARCA4 loss was screened using an EZH2 inhibitor in 2D tissue culture proliferation assays for 14 days. SMARCA4-negative (SCCOHT) cell lines were identified to be the most sensitive in response to

EZH2 inhibition, as demonstrated by decreased proliferation and/or morphology changes, at concentrations that are clinically achievable [Epizyme internal communication].

5.4.3. Pharmacokinetics (PK)

The PK of tazemetostat and desethyl metabolite, ER-897387, have been characterized following single (Day 1) and multiple (Day 15) administration to subjects with advanced solid tumors or B-cell lymphoma (n=36). Doses administered were 100 mg twice daily (BID) as a suspension (n=3) or tablet (n=3) formulation and 200, 400, 800, and 1600 mg BID as a tablet formulation. Tazemetostat was rapidly absorbed with a time to the maximum plasma concentration (t_{max}) of approximately 1-2 hours post-dose. Plasma concentrations declined in a mono-exponential manner with a mean $t_{1/2}$ of approximately 3-5 hours, and quantifiable plasma concentrations of both tazemetostat and its metabolite, ER-897387 were measurable up to 12 hours post-dose. The tazemetostat maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased in a greater than dose-proportional fashion after a single dose and in an approximately a dose-proportional fashion at steady-state. After multiple dosing, there was a dose-dependent decrease in tazemetostat exposure between Days 1 and 15. The accumulation ratio ($R_{ac} = AUC_{D15}/AUC_{D1}$) at the RP2D of 800 mg BID was 0.58. However, drug exposure at steady-state did not change beyond Day 15 as evidenced by the C_{trough} levels from Days 15 to 29. There was negligible change in t_{max} or $t_{1/2}$ on multiple dosing across the dose range. Preliminary results indicate that <5% of the administered dose was excreted in urine as unchanged tazemetostat. The t_{max} of tazemetostat was observed at 1-2 hours post-dose and its elimination paralleled that of tazemetostat ($t_{1/2}$ = 3-5 hours). Metabolite profiling and identification studies are planned to assess tazemetostat metabolism in humans.

The effect of food on the PK of tazemetostat was evaluated in subjects with advanced solid tumors or B -cell lymphoma (n=12) as part of study E7438-G000-101. Administration of tazemetostat with a high-fat meal decreased geometric mean area under the concentration-time curve from zero extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} values approximately 6% and 28%, respectively, relative to administration in the fasted state. However, for both C_{max} and $AUC_{0-\infty}$, all values observed after administration of tazemetostat following a high-fat meal were within the range of values observed after administration in the fasted state. Administration of tazemetostat with a high-fat meal also resulted in a 4-fold increase in median t_{max} relative to administration in the fasted state. The relationship between tazemetostat AUC on Day 15 and inhibition of H3K27 methylation in skin observed in the dose escalation part of Study E7438-G000-101 indicates that target inhibition is related to AUC. The decrease in systemic exposure as measured by $AUC_{0-\infty}$ is not clinically significant, and therefore, tazemetostat can be taken without regards to meals.

The effect of tazemetostat on the PK of midazolam also was investigated as part of Study E7438-G000-101. Subjects with solid tumors received a single oral dose of 2 mg midazolam on Day -1 and Day 15. Tazemetostat 800 mg BID was administered continuously starting on Day 1. Serial blood samples for the analysis of plasma midazolam and metabolites were collected over 24 hours on Day -1 (midazolam alone) and Day 15 (midazolam plus tazemetostat).

A summary of preliminary midazolam PK parameters after administration alone (Day -1) and with tazemetostat 800 mg BID (Day 15) in subjects with solid tumors is presented in Table 1.

Table 1 Summary of Preliminary Midazolam Pharmacokinetic Parameters After Administration Alone (Day -1) or with Tazemetostat 800 mg BID for 15 Days (Day 15) in Study E7438-G000-101 (n=12)

Parameter	Day -1	Day 15[a]	GLSMR (90% CI)
$AUC_{0-\infty}$ ng•h/mL	51.9 (87.2)	31.1 (48.1)	0.60 (0.46, 0.78)
C_{max} ng/mL	16.5 (94.3)	13.0 (48.3)	0.78 (0.57, 1.08)
$t_{1/2}$ h	5.67 (34.3)	4.25 (32.4)	NC

Abbreviations: AUC area under the concentration-time curve NC not calculated

[a] Data presented as geometric mean (%CV)

[b] GLSMR geometric least squares mean ratio

Plasma midazolam $AUC_{0-\infty}$ and C_{max} decreased approximately 40% and 22%, respectively, after administration with tazemetostat 800 mg BID relative to administration of midazolam alone. Geometric mean $t_{1/2}$ for midazolam decreased approximately 25%, after administration of midazolam with tazemetostat 800 mg BID relative to administration of midazolam alone. These results indicate that administration of tazemetostat 800 mg BID resulted in net induction of CYP3A-mediated metabolism in subjects with solid tumors. The decrease in midazolam $AUC_{0-\infty}$ caused by concomitant administration with tazemetostat 800 mg BID was less than 50%. Therefore, tazemetostat 800 mg administered BID is a weak inducer of CYP3A-mediated metabolism.

5.4.4. Clinical Experience

In 2013, the first-time-in-human (FTIH), single-agent, Phase I/II safety, and PK study (E7438-G000-101) of tazemetostat in adult subjects with advanced B-cell lymphomas and solid tumors was initiated in France by Eisai. 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). As of 01 April 2015, 40 subjects have been enrolled and treated at 5 dose levels of 100, 200, 400, 800, and 1600 mg BID. The diagnoses for the 16 subjects with B-cell NHL included follicular lymphoma, diffuse large B-cell lymphoma including one subject with primary mediastinal lymphoma and one marginal zone lymphoma. Subjects with solid tumors included 4 subjects with MRT and 2 subjects with ES. The median age of subjects enrolled is 59 years (range: 19-84 years). The dose escalation portion of E7438-G000-101 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 serious adverse event (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 II study in adults with INI1-negative tumors and the Phase II study in NHL adult subjects in Europe and Australia.

Tazemetostat has shown clear evidence of robust clinical activity in subjects with genetically defined INI1 negative tumors consisting of 3 of 6 subjects showing objective response (1 CR + 2 PRs) within 8 weeks of receiving the first dose of study treatment. A fourth INI1-negative subject has experienced tumor reduction, but did not meet RECIST 1.1 criteria for PR at the first re-staging at 8 weeks. Tazemetostat has also demonstrated activity in subjects with previously treated B-cell lymphomas with objective responses in 7 of 16 subjects with 4 subjects remaining on study treatment for 41 to 68 weeks.

As of 09 September 2016, 85 subjects were enrolled to the ongoing Study EZH-202. The safety profile of subjects in this study was generally consistent with that observed for subjects in the Phase 1 Study E7438-G000-101 as reported above. The IDMC for this study convened on 04 October 2016 to review Cohorts 2 (relapsed/refractory synovial sarcoma) and 5 (ES). Based on the review of safety and efficacy data, the IDMC concluded that futility hurdles had been surpassed in both cohorts and no safety issues were identified.

At the request of the sponsor, the IDMC re-convened on 21 October 2016 to discuss amending the clinical benefit endpoint in Cohort 5. Based on a more recent literature review (Section 5.2) and additional discussions with investigators experienced in treating ES, the clinical significance of subjects who maintain long-term SD was unaddressed in the original endpoint. Therefore, a proposal was set forth to the IDMC to change the primary endpoint from ORR to disease control rate (DCR), defined as subjects who achieve confirmed response (CR+PR) or who have SD lasting at least 32 weeks. This was based upon clinical activity observed as of 04 October 2016 which includes long-term disease control as well as confirmed and unconfirmed ongoing responses. Based upon the initial clinical activity and low toxicity profile observed, the IDMC endorsed expanding Cohort 5 by an additional 30 subjects. The additional subjects will allow for increased precision around the point estimates of DCR and ORR, as well as, provide expanded safety experience in ES. If in the future, similar signals of positive activity are seen in other cohorts, expansion for further evaluation of efficacy and safety may be considered for those cohorts as well.

The Cohort 5 expansion stage was opened in December 2016 after the Stage 2 DCR criterion was surpassed. In May 2017, Epizyme met with the FDA regarding future development plans for tazemetostat. Based on specific recommendations from the FDA, with Amendment 5, the primary endpoint for Cohort 5 has been changed to ORR and duration of response in responding subjects has been elevated to the most important secondary endpoint.

TAZVERIK® (tazemetostat) received accelerated approval for marketing in the US to treat the following:

- Adults and pediatric patients aged 16 years and older with metastatic or locally advanced ES not eligible for complete resection.
- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

In Japan, TAZVERIK has received approval for the treatment of subjects with relapsed or refractory EZH2 gene mutation positive FL (limited to use when difficult to treat with standard treatments) by Epizyme's co-development partner, Eisai.

Under the conditions of the approval, Epizyme agreed with the FDA to enroll an additional 25 subjects in cohort 6 to further evaluate the ORR in subjects with metastatic or locally advanced epithelioid sarcoma. The primary endpoint of cohort 6 has been changed to ORR and the effects of tazemetostat on tumor immune priming has been changed to an exploratory endpoint. Additionally, the mandatory pre- and post-dose tumor biopsies required for Cohort 6 have been made optional.

Enrollment in all cohorts of the study was completed in September of 2021 and a total of 267 subjects were enrolled to receive treatment. Treatment and data collection for study objectives and endpoints is ongoing.

5.4.5. Pharmacodynamics (PD)

In the adult Phase I study the PD of H3K27 methylation following tazemetostat dosing was measured in skin to provide evidence for on-target methylation inhibition in a surrogate tissue. In that study, immunohistochemistry (IHC) analysis of skin biopsies collected pre-dose and after 28 days of tazemetostat treatment revealed a post-dose decrease in H3K27Me3-positive cells across all doses explored (100-1600 mg BID), with a maximum reduction in the percentage of H3K27Me3-positive cells to 50% of baseline. Interestingly differences were observed in the tazemetostat induced reduction in H3K27Me3 levels in different skin layers potentially pointing to different kinetics for H3K27Me3 turnover in the cells that occupy different skin layers.

In this study, pre- and post-treatment tumor biopsies will be evaluated to enable the assessment of tazemetostat 800 mg BID dosing on H3K27Me3 levels in tumor tissue. H3K27Me3 IHC data will provide mechanistic insight into the impact of EZH2 inhibition on H3K27Me3 levels in cell populations within tumor. In addition, these data will be evaluated in the context of tazemetostat exposure data to explore PK-PD relationships.

A robust reduction in H3K27me3 by IHC staining was observed in a limited number of paired pre- and post-dose tumor biopsies collected thus far in Study EZH-202. In addition to monitoring H3K27me3, expression profiles of immune markers PD-L1 and CD8 also were assessed. To date, two of six subjects tested had increased tumor PD-L1 expression while undergoing treatment with tazemetostat. The increased expression of tumor PD-L1 was associated with an increased number of CD8-positive cells infiltrating the tumor stroma. These data are supportive of an observation made in the Phase 1 trial E7438-G000-101 in which biopsies from a subject with ES demonstrated increased PD-L1 expression and evidence of T-cell infiltration. Given the limited number of tumor biopsies collected to date and the variability of time points assessed, it is difficult to draw conclusions regarding the immune-priming effects of tazemetostat. To further evaluate this immune stimulatory effect and to standardize the collection time point of post-dose biopsies, Study EZH-202 has been amended to include mandatory biopsies in Cohort 6 to help guide future combination studies (e.g., immune checkpoint inhibitors). With the implementation of amendment 9, the mandatory pre and post dose biopsies for Cohort 6 have been made optional.

5.4.6. Cohort 8 Dosing Justification: 1600 mg QD

The current recommended dose of tazemetostat as monotherapy is 800 mg BID. This dose is supported primarily by available PK/PD/safety and efficacy data from the dose escalation study E7438-G000-101 (Phase 1 Portion). Briefly, in the dose escalation part, subjects with advanced solid tumors or B-cell lymphomas received oral tazemetostat continuously in 28-day cycles. The starting dose was 100 mg BID, with subsequent dose cohorts evaluated at 200 mg, 400 mg, 800 mg, and 1,600 mg BID. Among subjects with advanced solid tumors, 2 (5%) of the 43 subjects achieved an objective response, including CR in 1 subject with INI1-negative malignancy at the tazemetostat 800 mg BID dose level and 1 PR in a subject with SMARCA4-negative malignancy at the tazemetostat 1600 mg BID dose. Of the 2 responders in the advanced solid tumor subgroup, the DOR was 16.1 weeks for the subject with PR and 112.1+ weeks for the subject with CR; the latter subject was ongoing in response as of the data cutoff date (Study E7438-G000-101).

The predominant enzyme responsible for the metabolism of tazemetostat in humans is CYP3A4. Notably, the effect of tazemetostat on CYP3A4 is complicated, with opposing induction and time-dependent inhibition of the enzyme. The net clinical DDI outcome is an induction of CYP3A4, as indicated by an approximately 40% reduction of midazolam AUC following 800 mg BID dosing for 15 days (Study E7438-G000-101). In-addition, the exposure response efficacy analysis conducted in Cohort 5 of Study EZH-202 showed a separation of DOR based on the time-averaged AUC when binned into two groups ($p=0.03$): time-averaged AUC < 3212 vs time-averaged AUC ≥ 3212. Likewise, DCR and ORR when evaluated graphically versus time averaged AUC showed a visual tendency for higher time averaged AUC for subjects that had DCR and ORR. Taken together, these results support the exploration of a dosing regimen that would allow for achieving a higher AUC while maintaining a comparable safety/tolerability profile to the 800 mg BID dose. The objective of adding a new dosing schedule, 1600 mg tazemetostat QD (Cohort 8), in Amendment 7 is to keep the current total daily dose of tazemetostat the same (i.e., 1600 mg), but administer the dose QD as opposed to BID, as this will allow for achievement of potentially higher AUC at steady-state of approximately 7000 ng*h/mL due to potentially lower inductive effect of the CYP3A4 enzyme.

5.5. Study Rationale

The clinical benefit of tazemetostat has not yet been established in subjects ≥18 years of age with INI1-negative tumors, SMARCA4-negative tumors, solid tumors with EZH2 GOF mutation, or relapsed/refractory synovial sarcoma. This study will characterize the safety, efficacy, and PK in this population. As there is a reasonable expectation based upon nonclinical data and the Phase 1 experience in adults that clinical activity may be observed in adults with INI1-negative tumors, SMARCA4-negative tumors, solid tumors with EZH2 GOF mutation, and synovial sarcoma. As many of the targeted tumors occur in young adults, the lower age limit would enable participation of subjects who are historically under-represented in clinical trials.

5.6. Benefit: Risk Assessments

5.6.1. Animal Toxicology

Nonclinical safety assessments of tazemetostat included in vitro and monkey safety pharmacology studies, genotoxicity studies, and single- and repeat-dose toxicity studies in Sprague-Dawley rats and cynomolgus monkeys of 4- and 13-weeks duration. No notable cardiovascular, central nervous system (CNS), or respiratory risks were identified in nonclinical safety pharmacology assessments. Tazemetostat was not genotoxic in standard in vitro and in vivo assays. The following potential risks were identified for tazemetostat based on nonclinical safety data: T-LBL (rat), increased bone formation in bone and teeth (rat), non-progressive bile duct hyperplasia (monkey), teratogenicity (rat and rabbit), lymphoid depletion (rat and monkey), and phototoxic potential (in vitro). Other effects at high, non-tolerated doses, toxicities included bone marrow effects (hypocellularity, rat), and gastrointestinal toxicity (distention, ulceration, and degeneration, rat).

Steady-state exposures (area under the concentration–time curve from 0 to 24 hours [AUC0-24]) in rats at the lowest dose (100 mg/kg/day) at which no T-LBL occurred in the 13-week adolescent rat study were 2.5- to 7.5-fold greater than that observed in humans at the recommended Phase 2 dose (RP2D; 800 mg BID) from the ongoing Phase 1/2 Study E7438-G000-101. No incidences of abnormal bone formation have been observed in the ongoing clinical study. Female subjects of reproductive age will provide blood and urine samples for pregnancy testing at screening. All subjects must agree to use a reliable birth control method during the study, and for 30 days after the last tazemetostat dose, and additionally will be actively monitored for signs or symptoms of abnormal bone formation.

Additional animal toxicology is provided in the Investigator's Brochure (IB) for tazemetostat.

5.6.2. Photo-Reactive Potential

There are nonclinical data supporting a potential for phototoxicity, which has not been evaluated in humans. Hence, prolonged exposure to sunlight should be avoided during treatment. In addition, subjects should take other measures to avoid ultraviolet (UV) exposure such as wearing sun screen and sun glasses, wearing protective clothing, and avoiding tanning beds. Refer to the tazemetostat IB for details.

5.6.3. CYP3A Metabolism

Tazemetostat is metabolized primarily by CYP3A and is a substrate for P-glycoprotein (P-gp). Therefore, treatment with strong inhibitors or strong inducers of CYP3A within 14 days prior to first dose of tazemetostat and for the duration of study treatment is prohibited. Tazemetostat was also shown to be a time-dependent CYP3A inhibitor and a CYP3A4 inducer (EC_{50} value = 2.6 µmol/L) as well as an inhibitor of P-gp, CYP2D6, and the CYP2C family in vitro. P-gp, CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 substrates should be used with caution. Medications that are substrates for CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 should be avoided if possible.

5.6.4. Anticipated Safety Profile

More than 1105 clinical study subjects have received tazemetostat as monotherapy or in combination with other drugs in Epizyme-sponsored trials. The majority of adverse events observed in these studies are consistent with known adverse reactions of the drugs under investigation and/or comorbidity, are generally mild to moderate in severity, respond to dose modification and resolve without sequelae. The safety profile of tazemetostat is well characterized and stable. The benefit-risk remains positive.

Adverse events of special interest include T-LBL/T-ALL, AML, MDS, and other myeloid malignancies like MPN.

Tazemetostat is in late-stage clinical development and has shown clinical activity in subjects across the tazemetostat program, including objective responses and sustained disease stabilization. Tazemetostat has received accelerated approval in the US for ES and FL.

Tazemetostat is considered to be a clinically active drug that has the potential to benefit both adult and pediatric oncology subjects across different tumor types where there are unmet medical needs.

TAZVERIK® (tazemetostat) has received accelerated approval for marketing in the US to treat the following:

- Adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.
- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

In Japan, TAZVERIK has received approval for the treatment of subjects with relapsed or refractory EZH2 gene mutation positive FL (limited to use when difficult to treat with standard treatments) by Epizyme's co-development partner, Eisai.

Further details of study designs, tazemetostat exposure, and treatment-emergent AEs regardless of causality are outlined in the current IB.

5.6.5. Summary

Treatment with orally administered tazemetostat led to clinically meaningful efficacy in subjects with ES and other INI1 negative tumors. Objective responses were observed in 15% of ES subjects in Cohort 5. Further, the responses were durable with many subjects having disease stabilization for at least 32 weeks.

The safety profile of tazemetostat was favorable across a broad population of subjects with malignancies, including those with ES. Tazemetostat was generally well tolerated with few subjects requiring discontinuation of treatment due to drug-related toxicity allowing for continued treatment. There were no serious, treatment-related events of cytopenias, febrile neutropenia, hepatotoxicity, or cardiac abnormalities.

In conclusion, tazemetostat has led to durable responses and has shown a favorable safety profile in subjects with locally advanced or metastatic ES and other INI1 negative tumors, a population with an unmet need. Therefore, there is an appropriate risk benefit to continue study of tazemetostat in subjects with SWI/SNF deficient tumors.

6. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
Cohorts 1 (rhabdoid tumors), 3 (other INI1-negative tumors or any solid tumor with EZH2 GOF mutation), 4 (RMC), 5 (ES), Cohort 6 (ES with optional tumor biopsy), and 7 (chordoma): To assess the ORR following oral administration of tazemetostat 800 mg BID.	ORR (confirmed CR + PR) for tazemetostat in subjects with INI1-negative tumors using disease-appropriate standardized response criteria (primary CNS tumors: Response Assessment for Neuro-Oncology [RANO] and all others: RECIST 1.1)
Cohort 2 (relapsed/ refractory [R/R] synovial sarcoma): To determine the progression-free survival (PFS) rate following 16 weeks of oral administration of tazemetostat 800 mg BID.	PFS rate after 16 weeks of treatment with tazemetostat. This is the number of subjects with confirmed CR or PR, or stable disease (SD) at the Week 16 assessment.
Cohort 8 (ES treated with tazemetostat 1600 mg once daily [QD]): To assess the safety and tolerability of tazemetostat 1600 mg QD.	AEs and clinical laboratory tests
Secondary:	
To evaluate the duration of response (DOR) in subjects with rhabdoid tumors (Cohort 1), R/R synovial sarcoma (Cohort 2), other INI1-negative tumors or any solid tumor with EZH2 GOF mutation (Cohort 3), RMC (Cohort 4), ES (Cohort 5), ES undergoing optional biopsy (Cohort 6), chordoma (Cohort 7), and ES receiving 1600 mg tazemetostat QD (Cohort 8) and to evaluate the DOR in Cohorts 1, 3, 4, 5, 6, and 7 combined.	DOR, defined as the time from the first documented evidence of CR or PR to the time of first documented disease progression or death due to any cause, whichever comes first, using disease-appropriate standardized response criteria
To assess the disease control rate (DCR) in subjects with ES (Cohort 5) and ES undergoing optional biopsy (Cohort 6) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD.	DCR for tazemetostat (defined as the number of subjects who achieve confirmed response [CR+PR] or who have SD lasting at least 32 weeks)
To assess the ORR in subjects with R/R synovial sarcoma (Cohort 2) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD.	ORR (defined as the number of subjects who achieve confirmed response [CR+PR] per RECIST 1.1)
To determine the PFS and OS at Weeks 24, 32, and 56 and overall in subjects with rhabdoid tumors (Cohort 1), R/R synovial sarcoma (Cohort 2), other	PFS at Weeks 24, 32, 56, and overall for each cohort. PFS is defined as the time from the date of first dose of study treatment to the earlier of the

Objectives	Endpoints
INI1-negative tumors or any solid tumor with EZH2 GOF mutation (Cohort 3), RMC (Cohort 4), ES (Cohort 5), ES undergoing optional biopsy (Cohort 6), and chordoma (Cohort 7) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD.	date of first documented disease progression or date of death due to any cause OS at Weeks 24, 32, 56, and overall for each cohort. OS is defined as the time from the date of the first dose of study treatment to the date of death due to any cause
Exploratory:	
To explore the relationship between plasma PK and tumor pharmacodynamic (PD) markers as permitted by data	Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation and cell proliferation, and their correlation with activity
To assess tumor tissue and blood for somatic mutations, germline variants, messenger ribonucleic acid (mRNA), and/or proteins as candidate markers of response to tazemetostat	Somatic mutation analysis of tumor tissue and blood derived circulating deoxyribonucleic acid (DNA) Germline DNA analysis for INI1 or SMARCA4 variants
Cohort 6 only: To assess the effects of tazemetostat on tumor immune priming	Assessment of pre- and post-dose biopsies for immune priming (e.g. PD-L1 and CD8 IHC)
Cohort 6 only: To investigate the PD effects of tazemetostat in tumor tissue, if a post-dose tumor sample is available	Assessment of pre- and post-dose biopsies for H3K27me3 and for changes in gene expression.

7. STUDY DESIGN

7.1. Overall Experimental Plan

This is a Phase II, multicenter, open-label, single-arm, 2-stage study of tazemetostat 800 mg BID or 1600 mg QD (Cohort 8) administered orally in continuous 28-day cycles. Screening of subjects to determine eligibility for the study will be performed within 21 days of the first planned dose of tazemetostat. As shown in Figure 2, eligible subjects will be enrolled into one of eight cohorts based on tumor type:

Cohorts using tazemetostat 800 mg BID:

- **Cohort 1:** Rhabdoid tumors (MRT, rhabdoid tumors of the kidney [RTK], ATRT, and selected tumors with rhabdoid features, including SCCOHT, also known as MRTO) (closed to enrollment)
- **Cohort 2:** Relapsed or refractory synovial sarcoma with SS18-SSX rearrangement (closed to enrollment)
- **Cohort 3:** Other INI1-negative tumors or any solid tumor with EZH2 GOF mutation (closed to enrollment), including :
  - EMPNST
  - EMC
  - Myoepithelial carcinoma
  - Other INI1-negative malignant tumors with Sponsor approval
  - Any solid tumor with EZH2 GOF mutation including but not limited to Ewing's sarcoma and melanoma
- **Cohort 4:** RMC (closed to enrollment)
- **Cohort 5:** ES (closed to enrollment)
- **Cohort 6:** ES undergoing optional tumor biopsy (closed to enrollment)
- **Cohort 7:** Poorly differentiated chordoma (or other chordoma with Sponsor approval) (closed to enrollment)

Cohorts using tazemetostat 1600 mg QD:

- **Cohort 8:** ES (closed to enrollment)

Note: Changes to Cohorts:

Cohort 3 was initially intended to enroll various INI1-negative tumors, including RMC and ES. Initial screening and enrollment trends indicated that Cohort 3 would be heavily weighted toward RMC and ES tumor types, therefore, losing the potential to evaluate other INI1-negative tumors. Thus, Cohort 4 (RMC) and Cohort 5 (ES) were added as part of Amendment 3. Subjects with RMC and ES who were enrolled in Cohort 3 prior to Amendment 3 were moved to the appropriate cohort based on the specific disease type documented prior to start of treatment.

Amendment 4 allowed the inclusion of subjects with solid tumors and EZH2 GOF mutations into Cohort 3, based upon observed clinical activity in the Phase 1 Study E7438-G000-101 in subjects with EZH2-mutant non-Hodgkin lymphoma (NHL).

Amendment 5 added 2 additional cohorts: Cohort 6 (ES undergoing mandatory biopsy) and Cohort 7 (chordoma). Cohort 6 was added to further explore the immune-priming effects of tazemetostat (see Section 5.4.5). Cohort 7 was added to allow the inclusion of subjects with chordoma, a very rare sarcoma with a large percentage of the poorly differentiated variants having loss of INI1, based on observed clinical activity in the Phase 1 pediatric Study EZH-102 "A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma." Subjects with chordoma who were enrolled in Cohort 3 prior to Amendment 5 were moved to Cohort 7.

Amendment 7 added Cohort 8, which uses a new dosing schedule of tazemetostat 1600 mg QD in ES subjects. It was hypothesized that 1600 mg QD may achieve a higher AUC at steady-state of approximately 7000 ng*h/mL (see dose justification in Section 5.4.6).

Interim Analyses

For each cohort (except Cohorts 6 and 8), a two-stage, Green-Dahlberg design was utilized with a stopping rule to allow for early termination at the end of Stage 1 if there was strong evidence of lack of efficacy. If early stopping criteria were met for a cohort, enrollment was to be stopped. To avoid disruptions in the study, enrollment and treatment of subjects was not to be halted in order to conduct the interim analysis at Stage 1.

For Cohorts 1, 3, 4, 5, and 7, the Stage 1 interim analysis was planned to be performed after the first 15 subjects enrolled had completed at least the Week 24 assessment, completed the final study visit, or terminated early from the study, whichever was sooner. As it was desirable to perform the interim analysis in a timely manner, both confirmed and unconfirmed responses were included. Cohort 4 (RMC) and Cohort 7 (chordoma) were terminated based on the Stage 1 interim analysis. Cohort 1 (rhabdoid tumors), Cohort 3 (INI1-negative/EZH2 GOF mutation), and Cohort 5 (ES) continued into Stage 2, to enroll an additional 15 subjects each. Additionally, Cohort 5 went on to enroll an additional 30 subjects with ES into the Cohort 5 Expansion starting in 2016. In May 2017, Epizyme met with the FDA regarding future development plans for tazemetostat. Based on a specific request from the FDA, with Amendment 5, the primary endpoint for Cohort 5 has been changed back to ORR, and duration of response in responding subjects has been elevated to the most important secondary endpoint.

Given sufficient evidence of antitumor activity and no concerning safety signal observed during the 2-stage design for Cohort 5, Cohort 6 and Cohort 8 were added outside the 2-stage design framework. Cohort 6 (ES undergoing mandatory tumor biopsy) was added to further explore the immune-priming effects of tazemetostat. Cohort 8 (ES) was added to evaluate safety and PK following oral administration of 1600 mg tazemetostat once daily.

In January 2020, tazemetostat was approved for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced ES not eligible for complete resection. Under the conditions of the approval, Epizyme agreed with the FDA to enroll an additional 25 subjects in Cohort 6 to further evaluate the ORR in subjects with metastatic or locally advanced ES. The primary endpoint of Cohort 6 was changed to ORR. The effects of

tazemetostat on tumor immune priming were made an exploratory endpoint and tumor biopsies were made optional for this cohort.

For Cohort 2 (relapsed or refractory synovial sarcoma), the Stage 1 interim analysis was performed after the first 15 subjects enrolled had completed at least the Week 16 assessment, completed the final study visit, or terminated early from the study, whichever was sooner. Cohort 2 continued into Stage 2, to enroll an additional 15 subjects.

Treatment

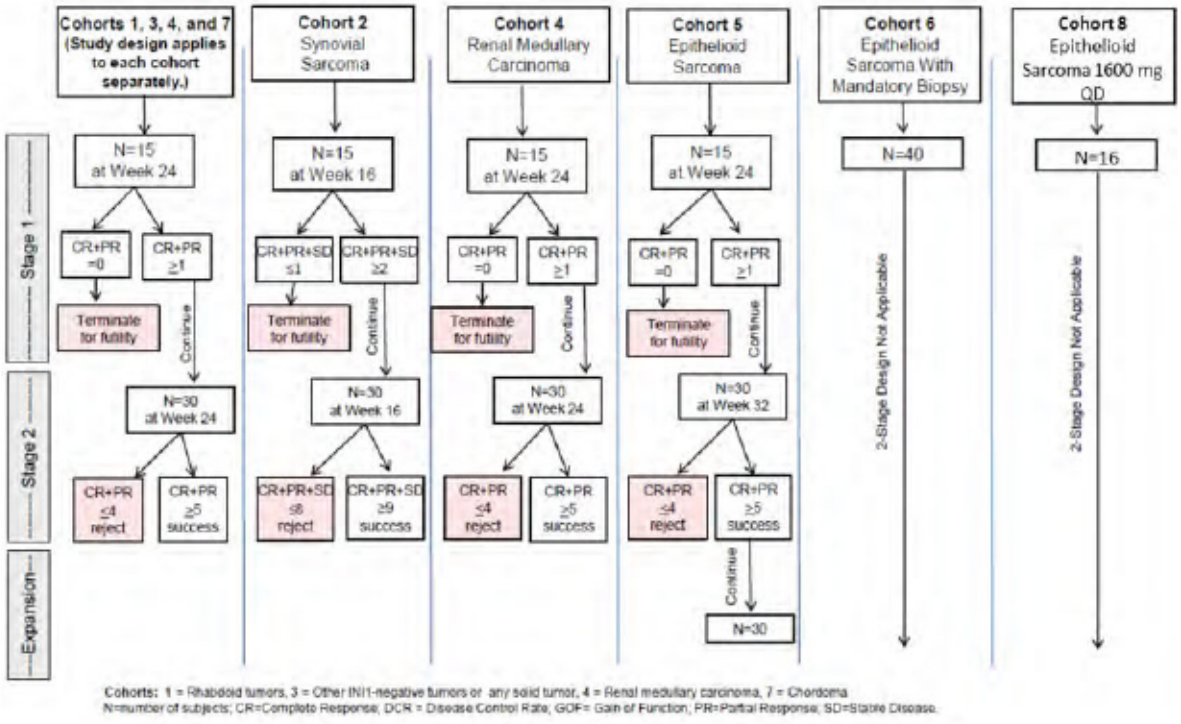
Subjects will receive tazemetostat in continuous 28-day cycles. Subjects may discontinue study treatment at any time due to disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Subjects will have an EOT visit up to 30 days after last dose of treatment in this study or prior to the start of a new anticancer therapy, whichever occurs first. All subjects will be followed for survival. Response is defined as having documented evidence of complete response (CR) or partial response (PR). Response assessment performed every 8 weeks while on treatment and every 8-12 weeks in survival follow-up.

Rollover Study

All subjects who received tazemetostat in this study (EZH-202) and are eligible to continue receiving tazemetostat or to continue survival follow-up, can transfer to a Rollover Study (EZH-501) for continued study drug and/or continued monitoring at the Investigator and Medical Monitor's discretion.

Figure 2 Study Schema



Note: Amendment 9 allowed for the enrollment of an additional 25 subjects in Cohort 6. In addition, the mandatory tumor biopsy was made optional.

7.2. Estimated Study Duration

7.2.1. Study Duration for Participants

The study duration is approximately 24 months for each subject. The duration of screening for each subject will be approximately 21 days. The subject accrual period is planned for approximately 15 months. The duration of treatment will vary for each subject. Subjects will receive tazemetostat in continuous 28-day cycles. Subjects may discontinue study treatment at any time due to disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Subjects will have an EOT visit up to 30 days after last dose of treatment in this study or prior to the start of a new anticancer therapy, whichever occurs first. All subjects will be followed for survival.

7.2.2. End of Study

Primary Completion: This includes time until the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis of the study. The primary completion is expected to occur approximately 6 months after the date the last subject is enrolled to treatment and evaluated for response.

End of Study: This includes time when the last subject is assessed or receives an intervention for evaluation in the study. The end of study will occur when the last subject discontinues the study treatment and has had the opportunity to complete the end of treatment visit or the long-term survival follow-up period, whichever is later. Please review if this language is still applicable.

7.3. Rules for Suspension of Enrollment

The Investigators, Institutional Review Boards (IRB)/Ethics Committees (EC), regulatory agencies and IDMC will be urgently informed and the IDMC convened to review the data and to make recommendations for potential changes in study conduct if one or more subjects develop any of the following AEs deemed to be definitely related to study treatment by the Investigator and/or Medical Monitor, based upon close temporal relationship or other factors:

- Death
- Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
- T-LBL/T-ALL

Should study enrollment be suspended, the study will not be restarted until all parties have agreed to the course of action to be taken and the IRBs/ECs have been notified.

If a case of adult T-LBL/T-ALL occurs, enrollment will be suspended, and the benefit-risk of the drug will be assessed by the Tazemetostat Safety Committee and will be communicated to all Health Authorities and Ethics Committees (Section 14.4.3).

8. SUBJECT POPULATION

8.1. Number of Subjects

It is expected that approximately 130–291 subjects will be enrolled. Each cohort (except Cohorts 6 and 8) will use a two-stage Green-Dahlberg design. See Section 17.2.1 for sample size assumptions. The number of subjects to be enrolled in each stage are provided in the table below:

	Each Cohort Separately: **Cohort 1 (Rhabdoid tumors)** **Cohort 2 (Relapsed/refractory synovial sarcoma)** **Cohort 3 (INI1-negative/EZH2 GOF mutation)** **Cohort 4 (Renal medullary carcinoma)** **Cohort 7 (Chordoma)**	**Cohort 5** **(ES; tazemetostat 800 mg BID)**	**Cohort 6** **(ES undergoing optional biopsy)**	**Cohort 8** **(ES; tazemetostat 1600 mg QD)**
Stage 1	15	15	NA	NA
Stage 2	15	15	NA	NA
Expansion	NA	30	NA	NA
Total	**30**	**60**	**65**	**16** (Note: Cohort 8 was closed prior to reaching this enrollment goal)

Abbreviations: BID twice daily; ES epithelial sarcoma; GOF gain of function; NA not applicable; QD once daily; R/R relapsed/ refractory; RMC renal medullary carcinoma.

8.2. Inclusion Criteria

A subject must meet ALL of the following criteria to be eligible for enrollment in this study:

1. Age (at the time of consent/assent): ≥18 years of age
2. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Appendix 1)

   NOTE: If subject is unable to walk due to paralysis, but is mobile in a wheelchair, subject is considered to be ambulatory for the purpose of assessing their performance status.
3. Has provided signed written informed consent
4. Has a life expectancy of >3 months
5. Has a malignancy:
   - For which there are no standard therapies available (Cohorts 1, 3, 4, & 5)

- That is relapsed or refractory, defined as metastatic or non-resectable, locally advanced disease that has previously been treated with and progressed following approved therapy(ies), if therapy(ies) exists (Cohort 2)
- That has progressed within 6 months prior to study enrollment (Cohort 5 Expansion, Cohort 6, and Cohort 8 only)

6. Has a documented local diagnostic pathology of original biopsy confirmed by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) or other Sponsor-approved laboratory certification
7. **For Cohort 1 (rhabdoid tumors) only:** The following test results must be available by local laboratory:
   - Morphology and immunophenotypic panel consistent with rhabdoid tumors, and
   - Loss of INI1 or SMARCA4 confirmed by IHC, or
   - Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss or mutation when INI1 or SMARCA4 IHC is equivocal or unavailable
8. **For Cohort 2 (subjects with relapsed/refractory synovial sarcoma) only:** The following test results must be available by local laboratory:
   - Morphology consistent with synovial sarcoma, and
   - Cytogenetics or Fluorescence in situ hybridization (FISH) and/or molecular confirmation (e.g., DNA sequencing) of SS18 rearrangement t(X;18)(p11;q11)
9. **For Cohorts 3, 4, 5, 7, and 8 (subjects with INI1-negative tumors or any solid tumor with EZH2 GOF mutation) only:** The following test results must be available by local laboratory:
   - Morphology and immunophenotypic panel consistent with INI1-negative tumors (not applicable for solid tumors with EZH2 GOF mutation), and
   - Loss of INI1 confirmed by IHC, or
   - Molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC is equivocal or unavailable, or
   - Molecular evidence of EZH2 GOF mutation
10. **For Cohort 6 (subjects with ES undergoing optional tumor biopsy) only:**
    - Morphology and immunophenotypic panel consistent with ES (e.g., CD34, EMA, Keratin, and INI1)
    - If providing optional biopsy: Willingness to provide informed consent to undergo pre- and post-dose biopsy
11. Has all prior treatment (i.e., chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per CTCAE, version 4.03 or are clinically stable and not clinically significant, at time of enrollment

12. Prior anti-cancer therapy(ies), if applicable, must be completed according to the criteria below:

Prior Therapy	Time from Last Prior Therapy
Chemotherapy: cytotoxic	At least 14 days since last dose of chemotherapy prior to first dose of tazemetostat
Chemotherapy: nitrosoureas	At least 6 weeks since last dose of nitrosoureas prior to first dose of tazemetostat
Chemotherapy: non-cytotoxic (e.g., small molecule inhibitor)	At least 14 days since last dose of non-cytotoxic chemotherapy prior to first dose of tazemetostat
Monoclonal antibody (ies)	At least 28 days since the last dose of monoclonal antibody prior to first dose of tazemetostat
Immunotherapy (e.g., tumor vaccine)	At least 42 days since last dose of immunotherapy agent(s) prior to first dose of tazemetostat
Radiotherapy (RT)	At least 14 days from last local site RT prior to first dose of tazemetostat At least 21 days from stereotactic radiosurgery prior to first dose of tazemetostat At least 12 weeks from craniospinal, ≥50% radiation of pelvis, or total body irradiation prior to first dose of tazemetostat
High Dose Therapy with autologous or allogeneic hematopoietic cell infusion	At least 60 days from last infusion prior to first dose of tazemetostat
Hematopoietic growth factor in support of anti-cancer therapy	At least 14 days from last dose of hematopoietic growth factor prior to first dose of tazemetostat

13. Has sufficient tumor tissue (slides or blocks) available for central confirmatory testing of IHC and/or cytogenetics/FISH and/or DNA mutation analysis (required for study entry but enrollment based on local results).
14. Has **measurable** disease based on either RECIST 1.1 for solid tumors or RANO for CNS tumors as defined in Section 12.5.5.
15. Has adequate hematologic (bone marrow and coagulation factors), renal and hepatic function as defined by criteria below:

System	Laboratory Value
Hematologic (Bone Marrow Function)	
Hemoglobin[a]	≥9 g/dL
Platelets[b]	≥100 000/mm^3 (≥100 × 10^9/L)
ANC[c]	≥1000/mm^3 (≥1.0 × 10^9/L)
Hematologic (Coagulation Factors)	
INR/PT[d]	<1.5 ULN

System	Laboratory Value
PTT	<1.5 ULN
Renal Function	
Serum creatinine[e]	≤1.5 × ULN
Hepatic Function	
Total[f] bilirubin	<1.5× ULN
AST[g]	<3 × ULN
ALT[g]	<3 × ULN

Abbreviations: ALT alanine aminotransferase; ANC absolute neutrophil count; AST aspartate aminotransferase; CrCl creatinine clearance; LLN lower limit of normal; PT prothrombin time; PTT partial thromboplastin time; ULN upper limit of normal

a May receive transfusion

b Should be evaluated after at least 7 days since last platelet transfusion

c Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days

d INR is the preferred value to be measured. However, if only PT can be performed in the testing laboratory that is acceptable

e If creatinine is not <1.5×ULN, then calculate by Cockcroft-Gault methods or local institutional standard and CrCl must be >50 mL/kg/1.73 m^2 (see Appendix 3)

f If attributed to documented Gilbert's disease, total bilirubin < 2.5 × ULN. Eligibility can be determined by total or conjugated bilirubin.

g If attributed to tumor involvement, AST and ALT <5×ULN

16. Subjects a history of hepatitis (Exclusion Criterion No. 13) must have ALT within the normal range

    NOTE: Laboratory results obtained during screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the Investigator may retest the subject and the subsequent within range screening result may be used to determine the subject's eligibility.

17. **For subjects with CNS tumors only:** Subject must have seizures that are stable, not increasing in frequency or severity and controlled on current anti-seizure medication(s) for a minimum of 21 days prior to the planned first dose of tazemetostat

    NOTE: 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 planned first dose of tazemetostat

18. Has a shortening fraction of >27% or an ejection fraction of ≥50% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan and New York Heart Association (NYHA) Class ≤2 (see Appendix 2)

19. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec

20. **Female subjects of childbearing potential must:**

- Have a negative beta-human chorionic gonadotropin (β-hCG) pregnancy test at time of screening and within 14 days prior to planned first dose of tazemetostat (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing), **and**
- Agree to use effective contraception, as defined in Section 12.6.1, from a minimum of 7 days prior to first dose until 6 months following the last dose of tazemetostat and have a male partner who uses a condom, **or**
- Practice true abstinence, (when this is in line with the preferred and usual lifestyle of the subject, see Section 12.6.1) **or**
- Have a male partner who is vasectomized

21. **Male subjects with a female partner of childbearing potential must:**
    - Be vasectomized, **or**
    - Agree to use condoms as defined in Section 12.6.2, from first dose of tazemetostat until 3 months following the last dose of tazemetostat, **or**
    - Have a female partner who is NOT of childbearing potential

8.3. 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. 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
3. Has known active CNS or any leptomeningeal metastasis of primary extracranial tumor. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging 4 weeks prior to the first dose of study drug and any neurologic symptoms have stabilized), have no evidence of new or enlarging brain metastases, and are on stable or tapering doses of steroids for at least 7 days prior to first dose of study drug.

   NOTE: Subjects with asymptomatic brain metastases found on screening MRI may be entered into the study without prior radiation therapy to the brain if they do not require immediate surgical or radiation therapy in the opinion of the treating Investigator and in the opinion of a radiation therapy or neurosurgical consultant.
4. Has had a prior malignancy other than the malignancies under study

   Exception: Subject who has been disease-free for 5 years, or a subject with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma is eligible.
5. Has had major surgery within 3 weeks prior to enrollment

NOTE: Minor surgery (e.g., minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment.

6. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) pero or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS). Has abnormalities known to be associated with MDS (e.g. del 5q, chr 7 abn) and MPN (e.g. JAK2 V617F) observed in cytogenetic testing and DNA sequencing.

   NOTE: Bone marrow aspirate/biopsy will be conducted following abnormal peripheral blood smear morphology assessment conducted by central laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy.

7. Has a prior history of T-LBL/T-ALL.
8. Is unwilling to exclude grapefruit juice, Seville oranges and grapefruit from the diet and all foods that contain those fruits from time of enrollment to while on study.
9. Has cardiovascular impairment, history of congestive heart failure greater than NYHA Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of tazemetostat; or ventricular cardiac arrhythmia requiring medical treatment
10. Is currently taking any prohibited medication(s) as described in Section 11.3
11. Has an active infection requiring systemic treatment
12. Is immunocompromised (i.e., has a congenital immunodeficiency), including subjects known history of infection with human immunodeficiency virus (HIV)
13. Has known active infection with hepatitis B virus or hepatitis C virus

    NOTE: Subjects with a history of hepatitis B or C with normal ALT and undetectable HBV DNA or HCV RNA are eligible for this study

14. Has had a symptomatic venous thrombosis within 2 weeks prior to study enrollment

    NOTE: Subjects with a history of a deep vein thrombosis >2 weeks prior to study enrollment who are on anticoagulation therapy with low molecular weight heparin are eligible for this study.

15. **For subjects with CNS involvement (primary tumor or metastatic disease):** Have any active bleeding, or new intra-tumoral 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.
16. Has known hypersensitivity to any of the components of tazemetostat or other inhibitor(s) of EZH2
17. Is unable to take oral medications, or has malabsorption syndrome or any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea or vomiting) that might impair the bioavailability of tazemetostat

18. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements.
19. **For female subjects of childbearing potential:** Is pregnant or nursing
20. **For male subjects:** Is unwilling to adhere to contraception criteria from time of enrollment in study to at least 3 months after last dose of tazemetostat.

9. INVESTIGATIONAL PRODUCT

9.1. Description

Tazemetostat (EPZ-6438) is an Epizyme investigational product (IP) and is defined as an Investigational Medicinal Product (IMP) under the European Union Clinical Trials Directive (EU CT Dir). Tazemetostat (trade name: TAZVERIK®) has received accelerated approval for marketing in the US to treat the following:

- Adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.
- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

In Japan, TAZVERIK has received approval for the treatment of subjects with relapsed or refractory EZH2 gene mutation positive FL (limited to use when difficult to treat with standard treatments) by Epizyme's co-development partner, Eisai.

The contents of the package label will be in accordance with all applicable regulatory requirements. The expiry date will be printed on the label.

	Investigational Product
Product name:	Tazemetostat (EPZ-6438)
Formulation description:	200 mg tablet
Dosage form:	Tablet
Physical description:	Red, round, and biconvex film-coated tablets packaged in white high-density polyethylene bottle with a child resistant, tamper-evident polypropylene screw cap
Dose/Route/Schedule/Duration:	800 mg/Oral/ BID/Continuous (Cohorts 1-7) 1600 mg/Oral/QD/Continuous (Cohort 8 Only)

9.2. Preparation, Handling, and Storage of Investigational Product

Preparation: No preparation is needed.

Handling: The occupational hazards and recommended handling procedures are provided in the Material Safety Data Sheet (MSDS). A MSDS describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from the Sponsor upon request.

Storage: Tazemetostat must be stored in a secure area, in compliance with storage requirements listed on the label, with access limited to the Investigator and authorized site staff only.

9.3. Dosage and Administration

Tazemetostat must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Standard institutional procedures for administering an oral agent via by mouth will be followed. An adequate supply will be provided with instructions on home administration.

Tazemetostat will be administered at the RP2D of 800 mg/dose given BID (exception: Cohort 8). Doses must be administered at least 8 hours apart. An adequate supply will be provided with instructions on home administration.

Cohort 8: Tazemetostat will be administered at 1600 mg dose given QD.

Tazemetostat will be administered with or without food.

Vomiting: If the subject vomits within 30 minutes of dosing, anti-emetics should be given and a second fresh dose of study treatment given. All doses given, missed, and vomited, should be recorded.

Rollover Study

All subjects who received tazemetostat in this study (EZH-202) and are eligible to continue receiving tazemetostat or to continue survival follow-up, can transfer to a Rollover Study (EZH-501) for continued study drug and/or continued monitoring at the Investigator and Medical Monitor's discretion.

9.3.1. Missed Doses

Tazemetostat 800 mg doses given BID must be taken at least 8 hours apart. If a dose is missed (e.g., missed morning dose or vomited and did not re-dose within appropriate time) it should not be taken if it is less than 8 hours until the next dose.

For subjects in Cohort 8 who receive tazemetostat 1600 mg QD, dosing should occur at approximately the same time each day. If a dose is missed, it should be taken the following day at the regularly scheduled time.

9.3.2. Procurement of IP

The initial shipment of tazemetostat to a clinical site will occur after all essential regulatory documents (including, but not limited to the receipt of the signed protocol signature page, signed Form Food and Drug Administration (FDA) 1572 or Statement of Investigator, curriculum vitae (CV) of Principal Investigator (PI) and designees, IRB/EC approval letter, and approved informed consent form [ICF]) are collected.

Refer to the Pharmacy Manual for directions on re-supply shipments.

9.4. Accountability

The Investigator/designee will be responsible for taking an inventory of each shipment of tazemetostat received and comparing it with the accompanying shipment form. The Investigator/designee will verify the accuracy of the information on the form, sign, and date it, and acknowledge the shipment receipt according to the instructions provided.

The Investigator/designee must keep accurate written records of all tazemetostat received from the Sponsor. Additionally, the Investigator/designee must keep accurate records of the tazemetostat dispensed to subjects enrolled in this study including the quantity of tablets, lot number, date dispensed, subject initials and identification number, dose administered, balance forward, and the initials of the person dispensing the IP. Based on the entries in the site accountability forms, it must be possible to reconcile IP delivered with that used and returned. All IP must be accounted for and all discrepancies investigated and documented appropriately.

Tazemetostat stock may not be removed from the investigative site where originally shipped without prior knowledge and consent of the Sponsor or its designee. When authorized, all applicable local, state, and national laws must be adhered to for the transfer.

At the end of the study, all unused tazemetostat will be destroyed by the investigative site or sent to a designated contractor for disposal on behalf of the Sponsor, per the instructions at that time. Any IP returned to the Sponsor-designated contractors must be counted and verified by site personnel and the Sponsor or its designee. All certificates of delivery/receipts and/or return forms must be signed prior to shipment. The IP for return must be packed in a tamper-evident manner to ensure integrity is maintained during return. All IP returned must be in accordance with local, state, and national laws and must first be authorized by the Sponsor prior to shipment.

10. STUDY TREATMENT

10.1. Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

10.2. Restrictions During Study Treatment

Subjects will abstain from ingesting Seville oranges and grapefruit or grapefruit juice and foods/beverages that contain those, for 24 hours prior to the first dose of study treatment until the last dose of study treatment.

Subjects should avoid prolonged exposure to sunlight while receiving study treatment. In addition, subjects should take other measures to avoid UV exposure such as wearing sunscreen and sunglasses, wearing protective clothing, and avoiding tanning beds.

10.3. Dose Modification

No modification of dose is required for the following Grade 3 or greater non-hematologic toxicities:

- Transient fatigue or asthenia
- Transient myalgia or arthralgia
- Nausea that resolves to <Grade 2 within 7 days (with or without anti-emetics)
- Vomiting that resolves to <Grade 2 within 48 hours (with or without anti-emetics)
- Diarrhea that resolves to <Grade 2 within 48 hours

10.3.1. Dose Modification due to Treatment-Related Toxicity

Other toxicities that, in the opinion of the Investigator are possible, probably, or definitely related to study treatment, should be managed per Table 2. Toxicities that are felt by the Investigator to be unrelated to tazemetostat but clinically significant should be discussed with the Medical Monitor. In the event of an urgent unrelated toxicity, study treatment should be interrupted as per Table 2. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be discontinued. Dose re-escalation is not permitted.

Table 2 Dose Modifications for Treatment-Related Toxicities

Toxicity	During Therapy	800 mg BID tazemetostat: Dose Adjustment	1600 mg QD tazemetostat: Dose Adjustment[b]
Grade 1			
All occurrences	Continue study treatment	Maintain dose level	Maintain dose level
Grade 2			
All occurrences	Continue study treatment	Maintain dose level	Maintain dose level
Grade 3 (not including neutropenia)			
1st occurrence	Interrupt study treatment until resolved to Grade ≤1 or baseline[b]	Restart at 600 mg BID	Restart at 1200 mg QD
2nd occurrence		Restart at 400 mg BID	Restart at 800 mg QD
3rd occurrence	Discontinue study treatment	Not applicable	
Grade 3 neutropenia (ANC: <1 – 0.5 × 10^9/L)			
1st occurrence	Interrupt study treatment until resolved to ANC ≥1.0 × 10^9/L	Maintain dose level	Maintain dose level
2nd occurrence		Restart at 600 mg BID	Restart at 1200 mg QD
3rd occurrence		Restart at 400 mg BID	Restart at 800 mg QD
4th occurrence	Discontinue study treatment	Not applicable	
Grade 3 Thrombocytopenia			
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID	Restart at 1200 mg QD
2nd occurrence		Restart at 400 mg BID	Restart at 800 mg QD
3rd occurrence	Discontinue tazemetostat	Not applicable	
Grade 4			
All occurrences	Interrupt study treatment until resolved to Grade ≤1 or baseline and discuss with Medical Monitor	Pending discussion with Medical Monitor	Pending discussion with Medical Monitor

Abbreviations: ANC absolute neutrophil count; BID twice daily; QD once daily

[a] Excluding alopecia and nausea, vomiting or diarrhea not receiving adequate treatment.
[b] A delay of tazemetostat for more than 14 days due to any toxicity must be discussed with the Medical Monitor before treatment can be resumed.
[c] Any case of Grade 2 toxicity which the investigator deems an interruption or dose modification is warranted should be discussed with the Medical Monitor
[d] Exclude Grade3 anemia: Subjects are allowed to continue tazemetostat at their current dose level with transfusion per Investigator discretion.

10.4. Continuation of Treatment

In subjects that are potentially benefitting (CR, PR, or SD per RECIST 1.1 or RANO) from tazemetostat treatment and have not incurred unacceptable toxicity, tazemetostat administration

may be continued at the Investigator's discretion with the subject's or his/her legal representative consent.

There may be some instances when subjects are noted to have modest disease progression, for example a slight increase in target lesions but with stable non-target lesions, and in the absence of clinical deterioration are receiving continued clinical benefit in the opinion of the Investigator. In such a situation, the Investigator should contact the Medical Monitor to discuss the assessment of risk: benefit of keeping the subject on study.

Prior to declaring progressive disease, the Investigator should be certain that special circumstances on progression defined by RECIST 1.1 are not met. In these situations of equivocal findings of progression, subjects may continue treatment until the next scheduled disease assessment. If progression is confirmed, the date of the previous assessment will be used as the date of disease progression.

Study treatment may continue if the following parameters are met on Day 1 of each cycle:

- Platelet count must be $\geq 50 \times 10^9$/L
- ANC $\geq 1.0 \times 10^9$/L, and
- Any Grade 3 or higher toxicity must have resolved to Grade 1 or baseline

Study treatment may be interrupted for up to 14 days. Treatment interruptions longer than 14 days need Medical Monitor approval to proceed.

Rollover Study

All subjects who received tazemetostat in this study (EZH-202), and are eligible to continue receiving tazemetostat or to continue survival follow-up, can transfer to a Rollover Study (EZH-501) for continued study drug and/or continued monitoring at the Investigator and Medical Monitor's discretion.

10.5. Duration of Tazemetostat Treatment

Subjects may discontinue study treatment at any time due to disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Subjects will have an EOT visit up to 30 days after last dose of treatment in this study or prior to the start of a new anticancer therapy, whichever occurs first. All subjects will be followed for survival.

10.6. Treatment Compliance

Compliance for doses taken outside of the clinic may be assessed by a count of the tablets returned to the study trial site by the subject and review of doses taken with the subject. This will be recorded in the source documents, which may include the use of a subject medication diary per institutional practice.

10.7. Treatment of Overdose

In the event of an overdose of tazemetostat (defined in Section 14.1.4), the Investigator should contact the Medical Monitor or their designee immediately and closely monitor the subject for AEs/ SAE and laboratory abnormalities.

A subject suspected of overdose should be monitored until tazemetostat can no longer be detected systemically. For reference, five half-lives of tazemetostat would be at minimum 25 hours, longer in subject with delayed clearance. Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor or their designee based on the subject's clinical evaluation.

A plasma sample for PK analysis may be requested on a case-by-case basis. If requested, the plasma sample should be collected at least within 7 days from the date of the last dose of study treatment.

The quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

11. CONCOMITANT MEDICATIONS

Documentation of all concomitant medication administered during study treatment will be recorded in the eCRF at each visit.

Because there is a potential for interaction of tazemetostat with other concomitantly administered drugs through the cytochrome P450 system, over-the-counter medications, or alternative therapies must be recorded in the eCRF. The Investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

11.1. Permitted Medication(s)

- Supportive care measures and symptomatic treatment for any treatment-related toxicity, including short courses of glucocorticoids, if clinically indicated
- Glucocorticoids may be taken by subjects with CNS tumors, under the following conditions:
  - For control of neurological symptoms that may continue at a tapering dose
  - Intermittent use for control of nausea (not to exceed 0.3 mg/kg/dose dexamethasone, maximum of 20 mg) every 12 hours as needed
- Non-enzyme inducing anti-epileptic drugs
- Prophylactic use of standard anti-emetics
- Blood and platelet transfusions, as needed per the judgment of the Investigator

11.2. Medications to be used with Caution

Substrates of P-gp, CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 should be used with caution. Medications that are substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 should be avoided if possible.

NOTE: A listing of CYP inhibitors, inducers, and substrates can be found using the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

A list of medications that are P-gp substrates and a list of medications that are CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 substrates can be found with following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

11.3. Prohibited Medication(s)

- Antineoplastic therapy or other investigational therapy for the treatment of cancer
- Prophylactic use of hematopoietic colony stimulating factors

  NOTE: Therapeutic use of hematopoietic colony stimulating factors is discouraged and should be discussed with the Medical Monitor and should be conducted

according to the 2006 American Society of Clinical Oncology (ASCO) Guideline for use of white blood cell (WBC) growth factors (Smith, 2006).

- Treatment with strong inhibitors or strong inducers of CYP3A4 should not be taken within 14 days prior to first dose of study treatment and for the duration of study.

  NOTE: A listing of CYP inhibitors, inducers, and substrates can be found using the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

- Enzyme inducing anti-epileptic drug(s) (EIAED) including, but not limited to, carbamazepine, phenobarbital, phenytoin, and barbiturates, should not be taken within 14 days prior to the first dose of study treatment and for the duration of study treatment
- All herbal remedies and (including remedies in the form of herbal teas/infusions) are excluded while enrolled in the study.
- Medicinal food supplements such as calcium, folic acid, vitamin D, multi-vitamin, etc., which have been taken under the advice from a physician, should be continued at the same dose and regimen during the study provided there are no contraindication as above. These should be listed as concomitant medications in the CRF.
- Any other supplements or alternative therapies should be discussed with the medical monitor prior to enrollment in the study or prior to initiating them during the study.

11.4. Non-Drug Therapies

Radiation Therapy: Palliative radiation therapy and potential concurrent dose interruptions will be permitted for pain or severe symptom control after discussion with the Medical Monitor. Radiation will be limited to non-target lesions only and documented in the eCRF.

Other Palliative Procedures: Other procedures intended for symptom control and potential concurrent dose interruptions may be permitted after discussion with the Medical Monitor. These procedures will be limited to non-target lesions only and documented in the eCRF.

12. STUDY ASSESSMENTS AND PROCEDURES

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

12.1. Schedule of Assessments and Procedures

Refer to Table 3 for the assessments and procedures to be carried out at screening, during the study, post-treatment, and at follow up.

Table 3 Schedule of Assessments and Procedures

Visit Description / Study Weeks	Screen[a]	Cycle 1		Cycle 2		Cycles 3+	End of Treatment[b]	Survival Follow-up[c,d]
		Day 1	Day 15	Day 1	Day 15	Day 1		
Visit		1	2	3	4	5+		
Study Day Procedures/Assessments[e]	-21 to -1	1	15 (±3 days)	29 (±3 days)	43 (±3 days)	57 (Every 28 Days Thereafter) (±3 days)	Up to 30 days post-treatment	
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics[f]	X							
Medical history/Current medical conditions[g]	X	X	X	X	X	X	X	
Prior and concomitant medications	Throughout the study							
Physical examination - Complete	X	X		X		X (Day 1 of each Cycle)	X	
Physical examination - Symptom directed			X		X			
Weight	X	X		X		X	X	
Height	X							
Vital signs[h]	X	X	X	X	X	X	X	
ECOG performance status	X	X		X		X	X	
12-lead ECGs[i]	X	X	X	X	X	X	X	
ECHO or MUGA scan[j]	X	If clinically indicated					X	

Visit Description / Study Weeks	Screen[a]	Cycle 1		Cycle 2		Cycles 3+	End of Treatment[b]	Survival Follow-up[c,d]
		Day 1	Day 15	Day 1	Day 15	Day 1		
Visit		1	2	3	4	5+		
Study Day **Procedures/Assessments[e]**	-21 to -1	1	15 (±3 days)	29 (±3 days)	43 (±3 days)	57 (Every 28 Days Thereafter) (±3 days)	Up to 30 days post-treatment	
Pregnancy test[k]	X	X		X		X	X	
Hematology[l]	X	X	X	X	X	X	X	
Blood chemistry[l]	X	X	X	X	X	X	X	
Hepatitis titers for subjects with history of hepatitis (per Exclusion Criterion No. 11)[l]	X	X		X		X	X	
Coagulation profile[m]	X	If clinically indicated					X	
Urinalysis	X	X		X		X	X	
PGx blood sample[n]	X							
Circulating DNA blood sample[o]	X	X At the time of tumor assessment from Cycle 3 on						
Archival tissue for confirmation[p]	X							
Optional tumor biopsy (Cohort 6 only)[q]	X	X C2D1 (± 7 days)			X (optional - at disease progression)			
Tumor biopsy for H3K27 PD[r]						X (any time after Cycle 2)		
Tumor biopsy at disease progression[s]	At disease progression							
Tumor assessments: CT and/or MRI[t,u]	X	X (Tumor assessments every other cycle beginning at start of Cycle 3, Cycle 5, Cycle 7 etc.)						

Visit Description / Study Weeks	Screen[a]	Cycle 1		Cycle 2		Cycles 3+	End of Treatment[b]	Survival Follow-up[c,d]
		Day 1	Day 15	Day 1	Day 15	Day 1		
Visit		1	2	3	4	5+		
Study Day **Procedures/Assessments[e]**	-21 to -1	1	15 (±3 days)	29 (±3 days)	43 (±3 days)	57 (Every 28 Days Thereafter) (±3 days)	Up to 30 days post-treatment	
Optional chest ultrasound[v]	X	An optional chest ultrasound may be performed every 8 weeks from start of dosing						
CT or MRI of the brain	X	If clinically indicated						
AEs/SAEs	Throughout the study							
Tazemetostat administration		800 mg tazemetostat BID or 1600 mg tazemetostat QD (Cohort 8 only) in continuous 28-day cycles						
Overall survival								X

Abbreviations:: AE adverse event, β-hCG beta-human chorionic gonadotropin, BP blood pressure, ^{18}FDG-PET positron emission tomography with fluorodeoxyglucose, C2D1 Cycle 2 Day 1; CR complete response, CT computed tomography, DNA deoxyribonucleic acid, ECG electrocardiograms, ECHO echocardiogram, h hour, HR heart rate, MRI magnetic resonance imaging, MUGA multi-gated acquisition, PGx pharmacogenomics, , PD pharmacodynamic, RR respiratory rate, SAE serious adverse event, T temperature

[a] **Screening:** Screening Period extends from Day -21 to Day -1.

[b] **End of Treatment:** An EOT visit will be conducted up to 30 days (±3 days) after last dose of tazemetostat or prior to the start of a new treatment or therapy at the end of study or if the subject's participation is terminated early. The EOT assessments will be required and, in the event of a continuing AE, the subject will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely.

[c] **Follow-Up for Progression-Free Survival:** Subjects may receive tazemetostat. Subjects who discontinue study treatment for reasons other than disease progression will continue to have disease assessments when possible, every 8-12 weeks until disease progression or death.

[d] **Follow-Up for Overall Survival:** Subjects who permanently discontinue study treatment will be followed (by phone, email, or clinic visit) for survival every 16 weeks until death, withdrawal of consent, or loss to follow-up. Survival follow-up will continue for 2 years for each subject or until 80% of subjects enrolled have died. All anticancer therapies will be collected (the Sponsor may choose to stop the collection of therapies after the first anticancer treatment). Additionally, AESI and subsequent anti-cancer therapy information will be collected throughout survival follow up.

[e] Pre-study procedures and tumor assessment must be performed within 21 days before first dose of study treatment.

[f] **Demographics:** Year of birth, gender, ethnicity and race (as allowed) must be recorded.

[g] **Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions, full history of the course of the subject's malignancy including primary diagnosis, stage and date, and information on prior antitumor therapies including response to prior therapies must be recorded at Screening.

[h] **Vital Signs:** Blood pressure (BP), heart rate (HR), and temperature (T) must be measured after the subject has been sitting for five minutes at screening and at regular intervals during treatment.

[i] **ECG:** 12-lead ECG must be performed at each visit prior to dosing. On Days 1 and 15, an additional ECG should be performed at the 1-hour post-dose time. A single ECG will be recorded unless there is an abnormality such as prolonged QTc(F) ≥ 480 msec, new arrhythmia, or other clinically significant finding. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. See Section 12.2 for window timing allowances.

[j] **ECHO:** An ECHO must be performed at screening as part of the screening cardiac assessment for study entry. If an ECHO cannot be performed, a MUGA scan is acceptable for assessment of cardiac function, but is not required.

[k] **Pregnancy Test:** A serum or urine pregnancy test must be performed at Screening for all females who are of childbearing potential. A urine pregnancy test should be performed before the first dose of study treatment if the negative screening pregnancy test is >72 hours prior to dosing. For subsequent testing, either a urine or serum pregnancy test is to be performed every 4 weeks (monthly) after first dose of study treatment. Positive urine tests should be confirmed with serum testing.

[l] **Laboratory Tests:** Chemistries include: alkaline phosphatase, ALT, AST, bilirubin (conjugated bilirubin when possible or total bilirubin), electrolytes (including sodium, potassium, chloride and bicarbonate when possible), Blood urea/blood urea nitrogen, creatinine, albumin, calcium, magnesium, glucose, phosphorus, total protein, and triglycerides. A complete peripheral blood smear morphology assessment needs to be collected along with normal hematology testing. If the morphology results are abnormal, a bone marrow aspirate/biopsy will be required for cytogenetic testing and DNA sequencing to closely monitor subjects for abnormalities associated with MDS/AML/MPN. Bone marrow aspirate/biopsy will be conducted following an abnormal peripheral blood smear morphology assessment conducted by the central laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy. See Section 12.5.14 for further details. Creatinine clearance only required if serum creatinine greater than age and sex ULN. Creatinine clearance by Cockcroft-Gault formula (Appendix 3) or institutional standard. For subjects with a history of hepatitis per Exclusion Criterion No. 11, hepatitis titers should be drawn if ALT exceeds the ULN at any time during treatment with tazemetostat.

[m] **Coagulation Profile:** Coagulations tests include: prothrombin time (PT), partial thromboplastin time (PTT), and INR.

[n] **PGx:** A single 6 mL blood sample will be collected at Screening. Do not collect samples for PGx from subjects enrolled after Amendment 7.

[o] **Circulating DNA:** 20 mL circulating tumor DNA blood samples to be obtained at Screening and at time of each disease assessment including at time of disease progression.

[p] **Tumor Tissue:** Archival tissue (block or slides) will be requested for central confirmation of pathology, IHC, and additional molecular testing, e.g. detection of somatic mutations and/or candidate biomarkers of response. If archived tumor material is not available tumor biopsy obtained during Screening is also acceptable.

[q] **Optional Tumor Biopsy for Tazemetostat:** An optional tumor biopsy is requested at screening and C2D1 (± 7 days) to assess the immune priming effect of tazemetostat

[r] **Tumor Biopsy for Tazemetostat PD:** An optional tumor biopsy to assess H3K27 is requested from all subjects, when medically feasible, any time after 15 days of continuous dosing. This may coincide with the Week 8 tumor assessment.

[s] **Tumor Biopsy at Disease Progression:** An optional Tumor biopsy is requested, where medically feasible, at disease progression in all subjects.

[t] Disease Assessment: Tumor assessments by disease-appropriate standard criteria (RECIST 1.1 or RANO) using CT, MRI of known sites of disease as clinically indicated. For subjects with bone disease or CNS disease at baseline, a bone or brain scan, respectively, is required every 8 weeks or sooner, if clinically indicated. Tumor assessments must be performed at Screening and every other odd numbered cycle beginning at Cycle 3 Day 1 (±3 days) from start of dosing (every 8 weeks and irrespective of treatment delays) or sooner, if clinically indicated.

[u] **Disease Assessment:** 18FDG-PET scan should be performed as clinically indicated at the Investigator's discretion, and is not a required tumor assessment.

[v] **Optional Chest Ultrasound:** An optional chest ultrasound may be performed every 8 weeks at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL.

12.2. Timing Window Allowances for ECGs

ECG	
Timepoint	**Tolerance Window**
pre-dose	-4 hours to 0 hour
1-hour post-dose	-15 minutes/ +15 minutes

12.3. Consent

A child is a person who has not attained the legal age for consent to treatments or procedures involved in research, under local and/or state law.

Assent means a child's affirmative agreement to participate in research.

The National Institutes of Health (NIH) includes individuals up to the age of 21 as minors (children); however, some local and/or state laws may have different ages or age ranges (i.e., subjects aged 15 to 21 years) considered as adults for the purposes of medical decision-making.

The local IRB/EC will determine if consent and/or assent must be obtained from/for each subject. The IRB/EC should apply local and/or state law(s) related to the age at which an individual is considered a minor (child) or an adult for medical decision-making.

When a child cannot legally give consent, informed consent must be obtained from one or both of their (biological or adoptive) parent(s) (parental consent) or the legally appointed guardian(s). Permission from parent(s) or guardian(s) must be obtained prior to enrolling a child in a research study.

When, in the judgment of the IRB/EC, the child is capable of providing assent the IRB/EC may determine that assent is required. Adequate provisions should be made for soliciting the assent of the child, and whether and how assent is obtained must be documented.

Emancipated Minors: Local and/or state laws will determine the age of emancipation. Parental consent is not necessary if the minor (child) is emancipated.

Married Minors: Local and/or state laws will determine if a married minor is considered to be at the age of majority upon their being married and thus parental consent is not necessary. Proof of marriage is required.

12.4. Screening Assessments

A signed, written informed consent (and assent, if applicable) must be obtained prior to any study-specific assessments or procedures being performed.

All screening assessments, including tumor assessment, must be performed within 21 days of enrollment.

Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, chemistries, imaging studies) and obtained prior to consent may be used for screening provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

12.5. Study Assessments

For study assessments not included in sections below (e.g., vital signs, performance status, ECHO), refer to the Schedule of Assessments and Procedures in Section 12.1 for details.

12.5.1. Physical Examinations

12.5.2. Comprehensive Physical Examination

A comprehensive physical examination of all body systems must be performed at screening, Day 1 of each Cycle thereafter during treatment by a qualified licensed individual. A review of body systems will include the following:

- General appearance
- Skin
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Neurological examination with sensory testing and seizure status, if applicable
- Musculoskeletal
- Genitourinary (required only if clinically indicated)

Weight is required to be measured at screening, on Day 1 of each cycle, and at the End of Treatment visit.

Height measurement is required at screening only.

Any abnormalities or changes in intensity noted during the review of body systems should be documented in the source document and reported appropriately in the eCRF. If a new clinically significant finding (e.g., not noted at screening) occurs from the initial tazemetostat administration until the end of the study, an AE must be documented. In addition, resolution of any abnormal findings during the study will be noted in source document and the eCRF if clinically significant.

These assessments will be completed as indicated in the Schedule of Assessments and Procedures, refer to Section 12.1.

12.5.3. Symptom-Directed Physical Examination

A symptom-directed physical examination must be performed when a complete physical examination is not required (on Day 15 of Cycles 1 and 2) by a qualified licensed individual. This will consist of a focused review of systems and physical examination addressing any new symptoms, AEs, or complaints.

These assessments will be completed as indicated in the Schedule of Assessments and Procedures (Section 12.1).

12.5.4. Electrocardiograms (ECGs)

The ECGs will be performed as indicated in the Schedule of Assessments and Procedures (Section 12.1). Machine read ECGs should be reviewed by the Investigator at the time of assessment. A single ECG will be recorded unless there is an abnormality, such as prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 msec, new arrhythmia, or other clinically significant finding. If a clinically significant abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart.

If cardiotoxicity is suspected, the Investigator may conduct additional testing per institutional standard of care (e.g., cardiac biomarkers including B-type natriuretic peptide and cardiac troponin I or cardiac troponin T).

12.5.5. Disease Assessment

Disease assessment will be performed as indicated in the Schedule of Assessments and Procedures (Section 12.1) and as described in Appendix 5 and Appendix 6.

12.5.6. Optional Chest Ultrasound

An optional chest ultrasound may be performed every 8 weeks along with other radiological assessments per the protocol.

12.5.7. Pharmacokinetics

Note: Annual PK assessments are no longer required to be collected for subjects as of Protocol Amendment 10 (July 2021). Annual PK samples collected from subjects enrolled under previous versions of the protocol will be analyzed as planned. However, new annual PK samples should not be collected after July 2021, regardless of the protocol version the subject initially enrolled under.

Cohort 8 Only:

Blood samples for PK analyses are no longer required to be collected from subjects as of a Memo to File dated 14 February 2020. Samples previously collected from subjects will be analyzed as planned.

Refer to Laboratory Manual and see Table 3 for additional details.

12.5.8. Pharmacogenomics (PGx)

A single whole blood sample is collected during the screening phase to provide DNA for analysis of genes involved in drug disposition (i.e., absorption, distribution, metabolism, and excretion [ADME]). This will support investigation of whether subject genotype, specifically of ADME genes, is related to the PK of tazemetostat. **Note as of Amendment 7**, subjects enrolled will not be tested for PGx; sufficient PK PGx data have been collected to determine the role of genetic variability on the disposition of tazemetostat.

A laboratory manual detailing the PGx sample collection, preparation, storage, and shipping process will be provided.

12.5.9. Tumor Sampling

12.5.10. Archive Tumor or Biopsy at Screening

An archival tumor block or biopsy is required at screening from all subjects enrolled in the study. As available, the diagnostic pathology block or tumor tissue obtained at the time of the subject's initial diagnosis and/or at the time of subsequent procedures is acceptable. The Sponsor or its designee will return all blocks to the originating site on completion of the associated analyses. If a tumor block is not available, 10-20 unstained, paraffin-embedded, tumor-tissue containing slides may be provided. Please see laboratory manual for details.

If archive tumor material is not available, tumor biopsy obtained during screening also is acceptable. Please see laboratory manual for details.

Independent central confirmation will **not** be required for study entry. Central confirmation of diagnosis with appropriate IHC, karyotyping, and DNA sequencing as appropriate will be performed on the tumor block or 10-20 unstained slides.

In addition to central confirmation, full genetic characterization of the SMARCB1 or SMARCA4 locus will be performed for those subjects determined to have loss of protein expression in their tumor. These studies need high quality DNA from either frozen or formalin fixed paraffin-embedded (FFPE) tumor tissue. Therefore, either 1 µg of isolated DNA, or five 20 µM thick sections (scrolls) cut from the FFPE blocks are requested. This material is optional and is in addition to the tumor tissue provided for central confirmation. Tumor tissue may be analyzed for DNA, mRNA and/or proteins potentially associated for response to tazemetostat up to and including whole genome sequencing.

A laboratory manual detailing the tumor sample collection, preparation, storage, and shipping process will be provided.

12.5.11. Optional Tumor Biopsies Taken on Study (Cohorts 1 through 5, 7, and 8)

An optional tumor biopsy for PD analysis is to be requested from all subjects, when medically feasible, at any time following 15 days of continuous dosing. This may coincide with the Week 8 tumor assessment.

An additional tumor biopsy is to be requested from all subjects, when medically feasible, at disease progression to enable assessment of adaptive mechanisms of resistance.

A laboratory manual detailing the tumor sample collection, preparation, storage, and shipping process will be provided.

12.5.12. Optional Tumor Biopsies Taken on Study (Cohort 6 Only)

Optional tumor biopsies will be collected pre-dose and at the Cycle 2 Day 1 visit (± 7 days) to assess the effects of tazemetostat on immune priming. The biopsy should only be taken when medically safe and technically feasible.

In addition to the two optional biopsies, an additional optional third tumor biopsy is to be requested at disease progression from all subject enrolled in Cohort 6. The third tumor biopsy will be examined to further assess the tumor for immune priming and enable the assessment of adaptive mechanisms of resistance.

A laboratory manual detailing the tumor sample collection, preparation, storage, and shipping process will be provided.

12.5.13. Circulating Tumor DNA

Blood samples are collected at screening and at each response assessment to provide circulating tumor DNA that can be used for identification of candidate biomarkers of response to tazemetostat.

A laboratory manual detailing the circulating tumor DNA sample collection, preparation, storage, and shipping process will be provided.

12.5.14. Clinical Laboratory Assessments

All clinical laboratory assays will be performed at local laboratories according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. (See Appendix 4 for peripheral blood drawn guidelines).

Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated until confirmed, explained, or resolved. Laboratory value changes starting from the initial tazemetostat exposure will be recorded in the eCRF as an AE if clinically significant.

Hematology: Hemoglobin, hematocrit, WBC, differential blood count with ANC, platelet count, and complete peripheral blood smear morphology assessment as conducted by the local laboratory are performed at screening and at regular intervals.

Note: If the peripheral blood smear morphology assessments show abnormal results, a bone marrow aspirate/biopsy will be required for cytogenetic testing and DNA sequencing. The cytogenetic testing and DNA sequencing will be conducted by the central laboratory.

Coagulation Profile: This will include: partial thromboplastin (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).

Serum Chemistry: Serum chemistries are performed at Screening and at regular intervals.

- Chemistries (liver function) include alkaline phosphatase, ALT, AST, and bilirubin (conjugated bilirubin when possible or total bilirubin)
- Chemistries (renal function) include blood urea nitrogen, creatinine, electrolytes (including bicarbonate when possible)
- Chemistries (metabolism) include albumin, calcium, magnesium, glucose, phosphorus, total protein, and triglycerides

Urinalysis: Urinalysis testing to include at minimum glucose, blood, protein, and pH, and is to be performed at screening, on Day 1 of each cycle, and at the End of Treatment visit.

Creatinine Clearance: Only required if serum creatinine is >1.5 upper limit of normal (ULN). Creatinine clearance should be calculated by Cockcroft-Gault formula (Appendix 3) or by institutional standard and must be ≥50 mL/min/1.73 m^2.

Bone Marrow Aspirate/Biopsy: At screening, a peripheral blood smear will be collected along with normal hematology testing and assessed for abnormal morphology. If results are abnormal then the subject will be required to undergo a bone marrow aspirate/biopsy conducted by the central laboratory. If morphology is abnormal, then cytogenetic testing will be conducted to closely monitor subjects with cytogenetic testing and DNA sequencing for abnormalities known to be associated with MDS (e.g. del 5q, chr 7 abn) and MPN (e.g. JAK2 V617F). If the results are abnormal (per the central laboratory) and are associated with myeloid malignancies, the subject will be excluded from the study.

During the study, additional tests including complete peripheral blood smear morphology assessment along with normal hematology testing will be included. If the morphology assessment shows abnormal results a bone marrow aspirate/biopsy will be required for cytogenetic testing and DNA sequencing as conducted by the central laboratory. If cytogenetic testing and DNA sequencing shows abnormal results, then tazemetostat will be held and after discussion with the Investigator, dose will be modified or drug will be discontinued.

12.5.15. Survival Follow-Up

Subjects who permanently discontinue study treatment will be followed (by phone, email or clinic visit) for survival every 16 weeks until death, full withdrawal of consent, lost to follow-up, or until the subject has been followed for 2 years from start of first dose of study treatment.. AESI and subsequent anti-cancer therapy information will be collected throughout the survival follow up.

12.5.16. Subsequent Therapy After Discontinuation of Study Treatment

Once a subject has permanently discontinued study treatment, every effort should be made to have the subject complete the End of Treatment visit prior to initiating any subsequent anti-cancer therapy (approved or investigational). Post-study anti-cancer therapy will not be provided as part of this study. The subject may receive subsequent anti-cancer therapy at the discretion of the treating physician. The subsequent anti-cancer therapy should be documented on the eCRF.

12.5.17. Evaluation of Response to Subsequent Anti-Cancer Therapy

To identify a potential epigenetic priming effect of tazemetostat, subjects who are withdrawn from this study due to disease progression and who go on to receive subsequent therapy should be followed for response whenever possible. Data to be recorded on the subsequent regimen should include agents received, best response, and duration of response.

Refer to the Schedule of Assessment and Procedures (Section 12.1) for additional details.

12.5.18. Pregnancy

There has been no experience to date of the use of tazemetostat during pregnancy or lactation. In an ongoing embryofetal development study, evidence of increased skeletal developmental abnormalities in fetuses from the pregnant rats relative to fetuses from control rats was observed. Consequently, there is a potential risk for teratogenicity, and precautions must be taken to avoid any pregnancy that could potentially be conceived during exposure to tazemetostat by EITHER male OR female subjects.

12.5.19. Definition of Childbearing Potential: Female Subjects

A female subject is considered of childbearing potential if she:

- Is anatomically and physiologically capable of becoming pregnant, and
- Will be or could possibly be sexually active with a male while undergoing study treatment with the possibility of posing harm to a fetus

A female subject is considered to be of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) if she:

- Is post-menopausal (at least 12 months consecutive amenorrheic)
- Is surgically sterilized (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) with surgery at least 1 month before the first dose of study treatment
- Has a documented congenital or acquired disorder that is incompatible with pregnancy

12.5.20. Definition of Childbearing Potential: Male Subjects

A male subject is considered of childbearing potential if he:

- Is anatomically and physiologically capable of causing a pregnancy in a female partner, and
- Will be or could possibly be sexually active with a female (who is or may become pregnant) while undergoing study treatment with the possibility of posing harm to a fetus

A male subject is considered to be of non-childbearing potential if he:

- Has a documented successful vasectomy (with confirmed azoospermia)

12.5.21. Pregnancy Testing

All female subjects of childbearing potential must have a negative pregnancy test (urine or serum) at screening and within 14 days of the first dose of study treatment. A separate assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study treatment.

Subsequent pregnancy tests performed every 4 weeks after first dose of study treatment may be either urine or serum.

Positive urine tests are to be confirmed by serum testing.

12.6. Prevention

12.6.1. Female Subjects

Females of childbearing potential must agree to use a highly effective method of contraception that results in a failure rate of < 1% per year when used consistently and correctly, starting at screening, during study treatment, and for 6 months after the final dose of study treatment, and have a male partner who uses a condom when using hormonal contraceptives.

Acceptable highly effective contraception includes:

- Placement of an intrauterine device
- Established hormonal contraceptive methods: oral, injectable, or implant.

NOTE: Female subjects who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to the first dose of study treatment and must continue to use the same contraceptive during study treatment and for 6 months after discontinuation of study treatment.

Due to the potential of enzyme induction with tazemetostat, female subjects who use hormonal contraceptives should use an additional barrier method of birth control while on study treatment and for 6 months after discontinuation of study treatment.

Female subjects exempt from this requirement are subjects who practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception), or have a male partner who is vasectomized. If currently abstinent, the subject must agree to use a highly effective method of contraception as described above if they become sexually active during study treatment, and for 6 months after discontinuation of study treatment.

12.6.2. Male Subjects

Male subjects must agree to use condoms with their female partner of childbearing potential from first dose of tazemetostat until 3 months after the final dose of tazemetostat. Males should refrain from sperm donation for 3 months after the final dose of tazemetostat.

12.6.3. Reporting of Pregnancy

Pregnancy will not be considered an SAE. Any report of pregnancy recorded for any female subject or a female partner of a male subject should be reported. To ensure subject safety, each pregnancy must be reported to the Sponsor or its designee within 2 weeks of learning of its occurrence using a clinical trial Pregnancy Report Form. A Pregnancy Report Form should be completed and submitted by email and/or fax to the Sponsor or its designee.

The pregnant female subject must be withdrawn from the study. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the Investigator to obtain all pregnancy information.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study treatment, must be promptly reported to the Sponsor.

The Investigator also must attempt to collect and report to the Sponsor or its designee pregnancy information on any female partner of male study subjects who become pregnant while the subject is enrolled in the study.

13. WITHDRAWAL AND REPLACEMENT OF SUBJECTS

13.1. Withdrawal of Subjects from Treatment/Procedures

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to future medical care by the physician or institution.

Subjects (or legally authorized representatives) can decline to continue receiving tazemetostat and/or other protocol-required procedures at any time during the study but can continue participation in the study (e.g., for follow-up information). If this occurs the Investigator is to discuss with the subject appropriate processes for discontinuation and the options for procedures that may continue such as collection of data, including endpoints and AEs. The Investigator must document the agreement in the procedures that the subject will continue with and the level of follow-up that is agreed to by the subject (e.g., in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records.)

Reasons for removal from protocol-required treatment or procedures might include the following:

- Disease progression
- Subject request to end study treatment and/or procedures
- Safety concern (e.g. AE, failure to follow contraception or pregnancy, excluded medication required)

13.2. Withdrawal of Subjects from Study

Withdrawal of full consent for a study means that the subjects does not wish to receive further protocol-required treatment, procedures and does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent (e.g., death records). The Investigator must document this agreement regarding withdrawal of full consent as well as discuss appropriate procedures for withdrawal from the study.

Reasons for removal of a subject from the study might include the following:

- Death
- Decision by Sponsor to terminate the study
- Subject request to withdraw from study
- Lost to follow-up

13.3. Replacement of Subjects

Subjects will not be replaced in this study.

14. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

14.1. Definitions

14.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product (IP), whether or not related to the IP.

Worsening of a pre-treatment event, after initiation of tazemetostat, must be recorded as a new AE. For example, if a subject experiences mild intermittent dyspepsia prior to dosing tazemetostat, but the dyspepsia becomes severe and more frequent after the first dose of tazemetostat, a new AE of severe worsening dyspepsia (with the appropriate date of onset) should be recorded in the eCRF.

"Lack of efficacy" or "failure of an expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

14.1.2. Adverse Events Associated with Tumor Biopsies

For subjects undergoing biopsies, site personnel will record the occurrence and nature of each subject's pre-existing condition(s) prior to obtaining a biopsy. If a pre-existing condition worsens (increases in severity or frequency) after the biopsy, the worsened condition is to be considered as an AE. The Investigator will report any AEs associated with the biopsy, including any treatment(s) (e.g., antibiotics for infection). Additionally, the Investigators will determine the relationship of each AE to the study procedure of obtaining a biopsy, seriousness and intensity, and whether study drug had been administered (i.e., did AE occur during pre-dose biopsy).

14.1.3. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life threatening

NOTE: The term 'life threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.
f. Medically significant: important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions (in subjects without pre-existing seizure disorder).

14.1.4. Special Situations

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

- **Overdose:** An overdose is defined, regardless of any associated AEs or sequelae, as:
  - On a per dose basis, any amount of the orally administered drug(s) that is over the protocol-specified dose assigned to a given subject.
  - On a schedule or frequency basis, anything taken more frequently than the protocol-required schedule or frequency.
- **Misuse:** Intentional and inappropriate use of study drug not in accordance with the protocol
- **Abuse:** Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

- **Medication error:** Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All instances of special situations must be reported on the dosing administration eCRF. AEs associated with these occurrences are to be captured on the AE eCRF.

All instances of special situations are to be reported using the SAE form, regardless of presence or absence of an associated AE. Refer to Section 14.12 for detailed instructions on how to handle the reporting of special situations.

In the event of a special situation, the Investigator should immediately contact the Medical Monitor or their designee and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

14.2. Laboratory Abnormalities

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention or accompanied by clinical symptoms. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the Laboratory section of the clinical study report (CSR). If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (e.g., anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded on concomitant medications).

The Investigator should decide, based upon the AE criteria and the clinical condition of the subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

If, at the end of the treatment phase with the study drug, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (i.e., concomitant disease) is found for the pathological laboratory values.

14.3. Other Safety Assessment Abnormalities

Other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline and events in the medical and scientific judgment of the Investigator are considered to be clinically significant, are to be recorded as an AE or SAE, in accordance with the definitions provided in Section 14.1.1 and Section 14.1.3, respectively.

Any other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay is also to be recorded as an AE or SAE.

14.3.1. Disease-Related Events

Events that meet the criteria for seriousness but are thought to be associated with progression of the disease under study should not be reported as SAEs unless they are untoward for that subject and/or disease under investigation.

NOTE: Disease progression should not be reported as an SAE term.

14.4. Adverse Events of Special Interest (AESIs)

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., regulators) might also be warranted (Council for International Organizations of Medical Sciences, 2005).

The following AESIs have been identified, requiring mitigation steps and monitoring to minimize the risk for the occurrence of these events.

14.4.1. T-Lymphoblastic Lymphoma/T-Acute Lymphoblastic Leukemia

Lymphoblastic lymphomas are considered thymus derived malignancies that have not yet completed T-cell maturations. Approximately 90% of lymphoblastic lymphomas are the T-cell phenotype and typically occur in young adults and adolescents, accounting for 29% of pediatric and 2% of adult NHL with a median age at diagnosis of 25 years (Lones, 2007; Lai, 2013; Cortelazzo, 2017). T-LBL is morphologically and immunophenotypically indistinct from T-ALL, with both diseases arising from precursor lymphoid cells of the T-cell lineage (Portell, 2012; Patel, 2014). Despite the similarities of the two diseases, significant yet unknown characteristics lead to differences in clinical presentations (Burkhardt, 2009). Initial clinical manifestation of both adult and pediatric T-LBL includes a mediastinal mass or lymphadenopathy with <25% bone marrow blasts. Adult T-LBL patients tend to have less thymic disease and greater lymph node disease and bone marrow involvement (Baleydier, 2008; Swerdlow, 2008; Campo, 2011). In contrast, T-ALL cases predominantly present with bone marrow and peripheral blood disease, and >25% bone marrow blasts (Swerdlow, 2008; Campo, 2011).

On 06 April 2018, a sentinel event of T-LBL was observed in a pediatric subject on study EZH-102. This event was reported to regulatory authorities as a 7-day suspected unexpected serious adverse reaction (SUSAR) on 13 April 2018 (Case number 2018USEPZ64380299).

Following this report, Epizyme conducted a comprehensive evaluation, including:

- Review of literature and available preclinical/clinical data to better understand the event of T-LBL.
- Review of the literature and available preclinical/clinical data to better understand the risk of MDS/AML and myeloid malignancies, and other solid tumor malignancies.
- Assessment of safety, PK at various doses tested, and benefit-risk across tumor types in adults and children.
- Consultation with well recognized external experts in T-cell lymphoma and pediatric/adult oncology.

Heightened surveillance was implemented along with inclusion/exclusion and dose modification criteria to monitor and identify early signs and symptoms (per local practice/standard of care) of

T-LBL/T-ALL so that tazemetostat may be discontinued in the subject and treatment can be initiated for these malignancies. Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric subjects.

As of the date of this protocol, two events of T-LBL have occurred in approximately 160 pediatric subjects. Total exposure to tazemetostat includes more than 1105 subjects (adults and pediatrics) in clinical trials and over 2,280 subjects from both clinical and post-marketing sources.

The risk of T-LBL/T-ALL in adults is not known; however, the incidence of treatment-related T-LBL/T-ALL in adults is expected to be uncommon. To date, there have been no events of T-LBL/T-ALL in adult patients.

If an adult case of T-LBL/T-ALL occurs in the study, enrollment in the study will be suspended. The benefit-risk of the drug will be assessed ad hoc by the Epizyme Quarterly Safety Review (QSR) Committee and the External Safety Committee (ESC), and the resulting benefit-risk assessment will be communicated to all Health Authorities and Ethics Committees as applicable.

14.4.2. MDS/AML/MPN

As per the current tazemetostat IB, less than 1% of myeloid malignancies have been reported in an estimated cumulative exposure of more than 2,280 subjects from both clinical and post-marketing sources. All myeloid events were reported in adult clinical trial subjects. Brief textual summaries on each myeloid malignancy are provided in the current tazemetostat IB.

In the event of suspicion of these malignancies or related concerns, please contact the Sponsor's or Designee Medical Monitor for evaluation. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any AML, MDS, and other myeloid malignancies like MPN. If a case of AML, MDS, or another myeloid malignancy like MPN occurs in the study, tazemetostat treatment will be discontinued for the subject.

14.4.3. Tazemetostat Quarterly Safety Review and External Safety Committee (ESC)

Monitoring of secondary primary malignancies is a pharmacovigilance function. All potential safety signals and AESIs will be fully evaluated in Quarterly Safety Review (QSR) meetings and in the External Safety Committee (ESC). Monitoring for potential safety signals, AESI and other safety concerns will also be evaluated during SRC.

The QSR is composed of internal Epizyme subject matter experts. It is a cross-functional workgroup whose mission is to provide internal review of aggregate safety data from Epizyme global clinical and safety databases. The core committee is composed of the Epizyme Chief Medical Officer (CMO), Medical Monitor(s), Head of Nonclinical Safety, Vice President (VP) Pharmacovigilance, VP Clinical Operations, and VP Regulatory Affairs.

The primary objective of the QSR is to provide a routine, systematic, internal review of new and aggregate safety information, and to escalate newly identified concerns or issues to executive management and regulatory authorities, as applicable.

The QSR also serves in the review and adjudication of urgent safety findings identified during the course of Epizyme clinical trials and as the escalation path, as applicable.

The ESC is composed of independent oncology medical consultants; one of which serves as Chair. The ESC meets quarterly to review new data, or ad hoc.

The purpose of the ESC is to provide independent review of clinical data for the purposes of identifying and evaluating secondary malignancy safety signals from Epizyme sponsored clinical trials. The ESC also monitors the data of those study subjects who have experienced the tazemetostat AESIs, namely T-LBL/T-ALL, MDS, AML, and other myeloproliferative malignancies such as MPN.

Outcomes from ESC meetings may include, but are not limited to, the identification of new AESI and/or potential risk factors, the need for additional non-clinical studies or data analyses, proposals for risk mitigation measures and confirmation or revision of the tazemetostat benefit-risk. The ESC will make recommendations in the event of an AESI safety concern. Epizyme will implement recommendations which may include suspension of enrollment, protocol amendment and communication to health authorities.

14.4.4. Dose Modification for Occurrence of AESI

If a case of adult T-LBL/T-ALL occurs in this study, the subject will be permanently discontinued from the study. Enrollment of new subjects and dosing of subjects on study will be paused while the QSR/ESC assesses the case; new enrollment and continued dosing will resume pending a decision by the QSR/ESC and communication with health authorities.

If a case of MDS/AML or other myeloid malignancies like MPN occurs in the study, tazemetostat treatment will be discontinued for the subject and the QSR will assess the case, followed by review of the ESC.

Recommendations for next steps in the event of any AESI will be communicated by the Epizyme Chief Medical Officer.

14.4.5. Safety Signal Events Under Evaluation: B-cell Acute Lymphoblastic Leukemia (B-ALL)

A 73-year-old female subject experienced an SAE of B-ALL while enrolled in Study EZH-501. The subject was diagnosed with Grade 2 follicular lymphoma (FL) in Oct 2016 following an initial diagnosis of diffuse large B-cell lymphoma (DLBCL) on 14 Aug 2006.

The subject was enrolled in the FL EZH2 mutant-type cohort of the phase 2 E7438-G000-101 study and began treatment with tazemetostat 800 mg BID on 04 Jan 2017.

Prior to enrollment in the E7438-G000-101 study, the subject had received 2 prior systemic therapeutic regimens as follows: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (22 Sep 2006 to 21 Mar 2007) with the addition of methotrexate and dexamethasone 04 Oct 2006 to 18 Jan 2007. Under an investigational protocol (ROMULUS), the subject received treatment with MabThera (rituximab) with pinatuzumab vedotin (11 Jun 2013 to 17 Sep 2013 and 15 Oct 2013 to 17 Dec 2013).

On the E7438-G000-101 study, the subject received tazemetostat for 26 cycles and achieved an objective PR at week 16 that was maintained through week 104.

The subject was subsequently enrolled onto the EZH-501 maintenance study and received the first dose on 21 Jan 2019.

Molecular characterization of the B-ALL clone found in the bone marrow biopsy from November 2020 was conducted for comparison to the primary FL tumor sample isolated in the October 2016 lymph node biopsy. The molecular analysis of the B-ALL and FL clones indicates that they are not related, and that the B-ALL clone is not derived from the FL clone through a clonal evolution mechanism. Based upon medical review of the biology, nonclinical data, and literature with regard to this sentinel case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure.

There have been no events of B-ALL or B-cell lymphoblastic lymphoma (B-LBL) observed in any nonclinical safety studies performed at Epizyme with EZH2 inhibition. Additionally, no events of B-ALL or B-LBL occurred in preclinical efficacy studies using mouse models with an intact B cell compartment. On the contrary, EZH2 inhibition with tazemetostat in vitro in adult and pediatric B-ALL cell lines did not enhance proliferation and in fact caused modest decreases in proliferation in a subset of cell lines.

Based upon medical review of the biology, nonclinical data, and literature of this case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure. Refer to the tazemetostat IB for case detail. However, Epizyme will continue to monitor subject safety with regard to secondary malignancy and all hematological secondary malignancies will be assessed by the tazemetostat ESC and QSR (Section 14.4.3).

14.5. Other Potential Identified Risks

For this study, other potential identified risks will include:

- Events considered related to abnormal bone formation and confirmed by radiologic scan
- AEs associated with treatment overdose, misuse, abuse, or medication error;
- And any treatment-emergent significant laboratory abnormality.

These risks are to be captured using the SAE procedures but are to be considered as SAEs only if they met one of the above criteria. All adverse events/risks are to be reported on the eCRF whether or not they meet the criteria for an SAE.

14.6. Grading and Severity

The severity of all AEs and SAEs, including appropriate laboratory values, will be graded utilizing the CTCAE v4.03. The link to the CTCAE Version 4.03 is:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guideline:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[a]
Grade 3:	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Abbreviations: ADL Activities of Daily Living; AE adverse event

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event (as in 'mild', 'moderate', or 'severe'); both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in Section 14.1.3 which are based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

14.7. Relationship Categorization

A qualified Investigator must make the determination of relationship to tazemetostat for each AE or SAE. The Investigator should decide whether, in his or her medical judgment there is a reasonable possibility that the event may have been caused by tazemetostat.

14.7.1. Assessing Relationship to Study Treatment

The following should be considered when assessing the relationship of an AE to study treatment:

- Temporal relationship of the onset of the event to the first dose of tazemetostat
- The course of the event, considering especially the effect of discontinuation of study treatment or the reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

The relationship of an AE to study treatment is to be classified as follows:

Not Related: A causal relationship between tazemetostat and the AE is not a reasonable possibility.

Related: A causal relationship between tazemetostat and the AE is a reasonable possibility (includes probably, possibly, and definitely related).

If the causal relationship between an AE/SAE and tazemetostat is related, that determination will be used for purposes of expedited regulatory reporting.

14.8. Outcome Categorization

Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved, or death.

All treatment-related AEs/SAEs will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal), or until an outcome is reached, stabilization occurs (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, regardless of whether the subject is still participating in the study. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

14.9. Timeframe for Reporting AEs and SAEs

AEs: AEs will be collected from the time the first dose of study treatment is administered until the earlier of either 30 days after the discontinuation of study treatment or until the initiation of subsequent anti-cancer therapy.

AEs Related to Biopsy: AEs will be collected from the time of screening biopsy until either 30 days after the discontinuation of study treatment or until the initiation of subsequent anti-cancer therapy (whichever is earlier).

SAEs: SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment must be recorded from the time a subject provides consent to participate in the study up to and including any follow-up contact. All SAEs will be reported to the Sponsor within 24 hours.

After Discontinuation of Study Treatment: The Investigator will monitor all ongoing AEs/SAEs until resolution or stabilization of the event or until the subject is lost to follow-up or has withdrawn consent. For a period of 30 days after the last dose of study treatment or until the initiation of subsequent anti-cancer therapy, whichever is earlier, the Investigator will report any AE that they consider to be possibly related to study treatment.

Note that any incidence of secondary malignancy, even if occurring more than 30 days after the last dose of study drug, will be reported to the Sponsor as in Section 14.4.

14.10. Reporting of SAEs

All SAEs will be reported within 24 hours of the Investigator becoming aware of the event. The Investigator must promptly notify the Sponsor or its designee of all SAEs in order that the legal obligations and ethical responsibilities of the Sponsor or its designee are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IP under clinical investigation. The Sponsor and its

designee will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and Investigators.

Any AE that is both unexpected (not consistent with the applicable product information) and also meets the definition of a serious adverse event/reaction would be considered a suspected unexpected serious adverse reaction ("SUSAR"). SUSARs are prepared for expedited reporting according to local regulatory requirements and are forwarded to Investigators as necessary. The Sponsor is legally obligated to report the event to the regulatory authorities within 7 days for fatal or life-threatening SUSARs or 15 days for all others.

An Investigator who receives an Investigator safety report describing a SUSAR or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the IB and will notify the IRB/EC, if appropriate according to local requirements.

14.11. Reporting of AESIs

AESIs are to be captured using the SAE procedures, but are to be considered as SAEs only if they meet one of the above criteria. All AESIs are to be reported whether or not they meet the criteria for an SAE.

All potential and identified AESIs must be discussed with the Medical Monitor.

14.12. Reporting of Special Situations

Report the special situation(s) of overdose, misuse, abuse, and/or medication error (described in Section 14.1.4) using one of the following sets of instructions according to whether the special situation occurred without any associated AEs, with an associated non-serious AE, or with an associated SAE:

Special situation(s) without associated AE(s):

- Report to Epizyme using a paper Special Situations Form following the procedures for reporting SAE (Section 14.10).

Special situation(s) with an associated non-serious AE:

- Enter the non-serious event on the AE eCRF and mark the SAE field, "no". SAE related narrative fields should not be completed.
- Report to Epizyme using a paper Special Situations Form following the procedures for reporting SAE (Section 14.10).

Special situation(s) with an associated SAE:

- Complete the AE eCRF per protocol for the associated SAE term ONLY (Special situations are not AE terms in and of themselves); complete eCRF SAE fields.
- Report to Epizyme using both a paper Special Situations Form and a paper Serious Adverse Event Form following the procedures for reporting SAE (Section 14.10).

14.13. Reporting to Regulatory Authorities, IRB/EC and Central Ethics Committees (CECs)

The Sponsor or its designee is responsible for notifying the investigational sites of all expedited SAEs. The Sponsor or designee shall also notify the CEC of new serious, related, and unexpected AE(s) or significant risks to subjects, per country requirements.

The Investigator will notify the IRB/EC of serious, related, and unexpected AE(s) or significant risks to subjects, per local country requirements. The Investigator must keep copies of all AE information, including correspondence with the Sponsor or local IRB/ECs on file.

It is the responsibility of the Principal Investigator to notify the IRB/EC of all SAEs that occur at his/her site. Investigators will be notified of all suspected, unexpected SAEs (7/15-Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying their IRB/EC of these additional SAEs.

All studies that are conducted within any European country will comply with the European CTD 2005/28/EC and CTD 2001/20/EC. All SUSARs will be reported as required to the Competent Authorities of all involved European member states.

MEDICAL MONITOR CONTACT INFORMATION

	Name	Address	Phone/Mobile/Fax	Email
North America/ Australia Medical Monitor	PPD	Medpace Inc. 5375 Medpace Way Cincinnati, OH 45227	P: PPD	PPD
EU Medical Monitor	PPD		P: PPD M: PPD	PPD

SAE REPORTING HOTLINE INFORMATION

	Phone	Fax	Email
For North American and Australian Clinical Sites only	PPD Ext. PPD or PPD Ext. PPD	PPD or PPD	PPD
For EU Clinical Sites only	PPD	PPD	PPD

15. CORRELATIVE ASSESSMENTS

15.1. Biomarkers of Response Assessment

Correlations of trends in subjects' clinical response to the molecular characteristics of their tumor (e.g., diagnostic molecular lesions, somatic mutations) may provide evidence of the biological basis for response to tazemetostat. Such investigations are emerging as an effective strategy to inform future clinical development.

Tumor Tissue Sample(s): Tumor tissue will be assessed to centrally confirm molecular data required for enrollment and identify candidate biomarkers of response to tazemetostat via methods, which may include characterization of subjects' tumor heterogeneity using both protein and nucleic acid based methodologies up to and including whole genome sequencing of tumor RNA/DNA. Local pathology results are acceptable for enrollment and eligibility determination.

Blood samples: Blood samples will be collected at screening and at each response assessment to provide circulating tumor DNA that can be used for identification of candidate biomarkers of response to tazemetostat.

15.2. Assessment of Relapse/Resistance to Tazemetostat

Subjects who initially respond to tazemetostat could subsequently either relapse or become resistant to tazemetostat through as yet unidentified mechanisms such as drug-induced de-novo mutation.

Tumor Biopsy: A subsequent tumor biopsy, if medically feasible, at disease progression will be requested to enable assessment of adaptive mechanisms of resistance. Tumor characterization by DNA, RNA, or protein may be performed to define molecular changes observed in relapsed tumors.

15.3. Future Use of Tissue Samples

Not all of the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Following the conclusion of the study, the samples may be used for additional research. These samples will be held for a maximum of 15 years. This research will help to understand disease subtypes, drug response and toxicity, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done according to the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 2006) and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMEA/CHMP/PGxWP/201914/2006). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the Sponsor will destroy the samples as described in this FDA guidance. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

16. DATA MANAGEMENT

Data from eCRFs and other external data will be entered into an Electronic Data Capture (EDC) clinical database. These data will be electronically verified through the use of real-time checks processed during data entry, and through programmed edit checks as specified in the data management plan. Discrepancies in the data will be brought to the attention of the clinical team and investigational site personnel, if necessary, in the form of an electronic data query. Resolutions to these issues will be reflected in the database and an audit trial within the system will track all queries and changes made to the data. Quality control audit(s) will be performed.

16.1. Coding

Concomitant medications will be assigned a code using the version of the World Health Organization (WHO) dictionary (version June 2015 or higher) drug codes specified in the data management plan (version June 2015 or higher). Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A listing of concomitant medications by drug and drug class will be included in the CSR for this protocol.

AEs will be classified into standardized terminology from the verbatim description (Investigator term) according to the version of the MedDRA coding dictionary (version 18.0, or higher) specified in the data management plan. AEs will be presented by Preferred Term (PT) nested within System Organ Class (SOC). Verbatim description and PT and SOC MedDRA-level terms for all AEs will be contained in the data listings of the CSR for this study.

17. STATISTICAL METHODS

17.1. Hypotheses

Cohort 1 (Rhabdoid Tumors), Cohort 3 (Other INI1-Negative Tumors or any Solid Tumor with EZH2 GOF Mutation), Cohort 4 (Renal Medullary Carcinoma), and Cohort 7 (Chordoma)

For Cohorts 1, 3, 4, and 7, the null hypothesis is that the ORR (percentage of subjects achieving either a confirmed CR or PR), as assessed at the Stage 2 analysis, is not clinically meaningful (<5%). The alternative hypothesis is that the ORR is clinically meaningful (>20%) and, therefore, the study treatment warrants further development. At the Stage 2 analysis, 30 subjects will be enrolled in each cohort, and the analysis and decision rules specified here are based on 30 subjects. The decision rule at the Stage 2 analysis will differ slightly if there are more than 30 subjects. For the Stage 2 analysis with 30 subjects, at least 5 confirmed CRs plus PRs are needed for the cohort to declare a success i.e., to have demonstrated sufficient clinical activity.

Cohort 2 (Relapsed or Refractory Synovial Sarcoma)

For Cohort 2, the null hypothesis is that PFS rate after 16 weeks of treatment (percentage of subjects with a CR, PR or SD at the Week 16 tumor assessment), as assessed at the Stage 2 analysis, is not clinically meaningful (≤15%). The alternative hypothesis is that the PFS rate at 16 weeks is clinically meaningful (≥35%) and, therefore, the study treatment warrants further development. At the Stage 2 analysis, 30 subjects will be enrolled in Cohort 2, and the analysis and decision rules specified here are based on 30 subjects. The decision rule at the Stage 2 analysis will differ slightly if there are more than 30 subjects. For the Stage 2 analysis with 30 subjects, at least 9 CR+PR+SDs are needed for the cohort to declare a success i.e., to have demonstrated sufficient clinical activity.

Cohort 5 (ES with Tazemetostat 800 mg BID)

For Cohort 5, the null hypothesis is that the DCR (percentage of subjects who achieve either a confirmed CR or PR or who have SD lasting at least 32 weeks), as assessed at the Stage 2 analysis, is not clinically meaningful (<5%). The alternative hypothesis is that the DCR is clinically meaningful (>20%) and, therefore, the study treatment warrants further development. At the Stage 2 analysis, 30 subjects will be enrolled in each cohort, and the analysis and decision rules specified here are based on 30 subjects. The decision rule at the Stage 2 analysis will differ slightly if there are more than 30 subjects. For the Stage 2 analysis with 30 subjects, at least 5 confirmed CRs plus PRs or SDs lasting at least 32 weeks are needed for the cohort to declare a success i.e., to have demonstrated sufficient clinical activity. If the Stage 2 futility criterion is surpassed, enrollment in Cohort 5 may be expanded to include 30 additional subjects.

Cohort 6 (ES Undergoing Optional Tumor Biopsy)

For Cohort 6, the null hypothesis is that the ORR (percentage of subjects who achieve either a confirmed CR or PR), as assessed at the final analysis, is not clinically meaningful (≤5%). The alternative hypothesis is that the ORR is clinically meaningful (≥20%).

Cohort 8 (ES with Tazemetostat 1600 mg QD)

For secondary endpoints of Cohort 8 (duration of response (DOR), DCR, and ORR; potentially PFS and OS, if sufficient data and analysis warranted) statistical analysis will be performed and analyzed as for Cohort 5.

17.2. Study Design Considerations

17.2.1. Determination of Sample Size

Each cohort (exception: Cohorts 6 and 8) will be evaluated separately using a Green-Dahlberg two-stage design, to allow early termination of the cohort due to the lack of efficacy. The sample size of each cohort is calculated on the primary endpoint. Within each cohort, the hypothesis will be tested using a one-sided test with α=0.05 and the type II error rate will be controlled at 0.2. The numbers of subjects to be enrolled in each stage of the Green-Dahlberg two-stage design for each cohort are listed in the table below.

	Each Cohort Separately: Cohort 1[a] (Rhabdoid tumors) Cohort 3[a] (Other INI1-negative tumors or any solid tumor with EZH2 GOF mutation) Cohort 4[a] (RMC) Cohort 7[a] (Chordoma)	**Cohort 2[a] (R/R synovial sarcoma)**	**Initial Design: Cohort 5[a] (ES)**	**Amended Design: Cohort 5[b] (ES)**
Stage 1: Null hypothesis	CR + PR ≤5%	CR + PR + SD at Week 16 ≤15%	CR + PR ≤5%	DCR ≤5%
Stage 1: Alternative hypothesis	CR + PR ≥20%	CR + PR + SD at Week 16 ≥35%	CR + PR ≥20%	DCR ≥20%
Stage 1 sample size (n1)[c]	15	15	15	
Stage 1 rejection of study treatment (r1)[d]	0	1	0	
Stage 2 sample size (n2)	15	15	15	15
Stage 2 rejection of study treatment (r)	4	8	4	4
Total sample size (n)	30	30	30	30

Abbreviations: BID twice daily; CR complete response; ES epithelial sarcoma; GOF gain of function; NA not applicable; PR partial response; QD once daily; R/R relapsed/ refractory; RMC renal medullary carcinoma; SD stable disease.

[a] All subjects will have completed at least the Week 24 (Week 16 for synovial sarcoma) assessment, completed the final study visit, or terminated early from the study, whichever is sooner

[b] All subjects will have completed at least the Week 32 assessment, completed the final study visit, or terminated early from the study, whichever is sooner- based on Amendment 4.
[c] Within each cohort, the interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 15 subjects are treated and followed for the specified time. In this scenario, the total sample size (Stage 1 + Stage 2) for a cohort would still remain unchanged at 30 subjects.
[d] An additional 30 subjects may be enrolled for expanded evaluation of efficacy and safety. Enrollment in the expansion stage may be opened once the Stage 2 rejection criterion has been surpassed. If this occurs prior to the full enrollment of Stage 2, the total cohort sample size (Stage 1 + Stage 2 + expansion) will remain unchanged at 60 subjects.

A cohort may be stopped for futility at the end of Stage 1 based on the results for the first 15 treated subjects. To avoid disruptions in the study, enrollment and treatment of subjects will not be halted in order to conduct the interim analysis. If every cohort completes enrollment of Stage 2 a total of 150 subjects will be enrolled in the entire study.

For Cohorts 1, 3, 4, and 5:

- The probability of early stopping under the null hypotheses is 0.463.
- The probability of early stopping under the alternative hypotheses is 0.035.

For Cohort 2:

- The probability of early stopping under the null hypotheses is 0.319.
- The probability of early stopping under the alternative hypotheses is 0.014.

The expanded sample size for Cohort 5:

An additional 30 subjects may be enrolled for expanded evaluation of efficacy and safety. Enrollment in the expansion stage may be opened once the Stage 2 rejection criterion has been surpassed. If this occurs prior to the full enrollment of Stage 2, the total cohort sample size (Stage 1 + Stage 2 + expansion) will remain unchanged at 60 subjects. The additional 30 subjects will allow for increased precision for the point estimates of DCR and ORR. The table below shows the 95% exact binomial CI for potential point estimates of DCR and/or ORR:

Potential DCR or ORR	**20%**	**30%**	**40%**
Subjects meeting endpoint	12 of 60	18 of 60	24 of 60
95% exact binomial CI	10.8%-32.3%	18.8%-43.2%	27.6%-53.5%

The Cohort 5 expansion stage was opened in Dec. 2016 after the Stage 2 DCR criterion was surpassed. In May 2017, Epizyme met with the FDA regarding future development plans for tazemetostat. Based on a specific request from the FDA, with Amendment 5, the primary endpoint for Cohort 5 has been changed to ORR and duration of response in responding subjects has been elevated to the most important secondary endpoint.

Cohort 6 (ES undergoing optional tumor biopsy) was added outside of a 2-stage design framework based on clinical data demonstrating encouraging evidence of antitumor activity, and no concerning safety signals in ES subjects in Cohort 5. Preliminary evidence of the immune priming effect of tazemetostat evaluated by IHC provided the rational for collecting mandatory paired tumor biopsies in this cohort. Twenty (20) paired tumor biopsies will afford sufficient data to quantify the immune priming effects of tazemetostat. Due to the expectation that some

subjects will withdraw consent after the post-screening biopsy and other subjects may not be able to provide for a post-treatment biopsy, Cohort 6 will enroll up to 40 subjects to ensure that 20 paired tumor biopsies are collected and adequate for analysis.

In January 2020, tazemetostat was approved for the treatment of adults and pediatric subjects aged 16 years and older with metastatic or locally advanced ES not eligible for complete resection. Under the conditions of the approval, Epizyme agreed with the FDA to enroll an additional 25 subjects in cohort 6 to further evaluate the ORR in subjects with metastatic or locally advanced ES. The primary endpoint of cohort 6 has been changed to ORR and the effects of tazemetostat on tumor immune priming has been changed to an exploratory endpoint. Additionally, the requirement for pre- and post- dose tumor biopsies for Cohort 6 has been made optional.

With a sample size of at least 40 subjects, the study has a power of more than 80% to test the hypothesis that the objective response rate would be 20% or higher against the null hypothesis that it would be 5% or lower at one-sided significance level of 0.025.

Cohort 8: As with Cohort 6, Cohort 8 was added outside of a 2-stage design framework based on clinical data in ES subjects in Cohort 5 (see rationale above for Cohort 6). Cohort 8 was added to evaluate safety, PK, and efficacy profile of once daily tazemetostat dosing;16 subjects will be enrolled for evaluation of PK, efficacy, and safety.

17.2.2. Sample Size Re-Estimation

The sample size will not be re-estimated during this study.

17.3. Data Analysis Considerations

17.3.1. Analysis Populations

The Enrolled population will consist of all subjects who sign informed consent and were entered into the electronic case report form for the study. The Enrolled set will be used for summaries of subject disposition and protocol deviations.

The **Intent-to-Treat (ITT)** population will consist of all subjects who receive at least one dose of tazemetostat. The ITT population set will be used for summaries and analysis of the efficacy endpoints.

The **Safety** population will consist of all subjects in the ITT population who have at least one post-dose safety observation recorded. The Safety population will be used for summaries and analysis of the safety and tolerability.

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

Pharmacodynamic (PD) Population will include all subjects in the ITT population who have sufficient samples collected to allow estimation of the PD parameters. The PD population will be used for summaries and graphs of PD data.

17.3.2. Interim Analyses

Except for Cohorts 6 and 8, an interim analysis for futility will be performed for each cohort separately. The decision rules for each cohort at the end of Stage 1 are listed in the table below.

	For Each Cohort Separately **Cohort 1 (Rhabdoid Tumors)** **Cohort 3 (INI1-Negative/EZH2 GOF Mutation)** **Cohort 4 (RMC)** **Cohort 5 (ES)** **Cohort 7 (Chordoma)**	**Cohort 2** **(R/R Synovial Sarcoma)**
Null hypothesis	CR+PR ≤5%	CR+PR+SD at Week 16 ≤15%
Alternative hypothesis	CR+PR ≥20%	CR+PR+SD at Week 16 ≥35%
Stage 1 sample size (n1)	15	15
Stage 1 rejection of study treatment (r1)	0	1

Abbreviations: BID twice daily; CR complete response; ES epithelial sarcoma; GOF gain of function; PR partial response; R/R relapsed/ refractory; RMC renal medullary carcinoma; SD stable disease.

For Cohorts 1, 3, 4, 5, and 7, separately, the end of Stage 1 occurs when the first 15 subjects have completed at least the Week 24 assessment, completed the final study visit or terminated early from the study, whichever is sooner. As it is desirable to perform the interim analysis in a timely manner, both confirmed and unconfirmed responses will be included. To avoid disruptions in the study, enrollment and treatment of subjects will not be halted in order to conduct the interim analysis. For Cohorts 1, 3, 4, 5, and 7, separately, at the end of Stage 1:

- If there are zero CRs + PRs, the tazemetostat treatment will be rejected and enrollment in the cohort will be terminated for futility.
- If there are one or more CRs + PRs, cohort enrollment will continue to its maximum sample size of 30 subjects.

For Cohort 2 (relapsed/refractory synovial sarcoma), the end of Stage 1 occurs when the first 15 subjects have completed at least the Week 16 assessment, completed the final study visit or terminated early from the study, whichever is sooner. For Cohort 2 at the end of Stage 1:

- If there is at most one CR+ PR+ SD at the Week 16 assessment, the tazemetostat treatment will be rejected and enrollment in Cohort 2 will be terminated for futility.
- If there are two or more CR+ PR+ SD at the Week 16 assessment, Cohort 2 enrollment will continue to its maximum sample size.

Within each cohort, the interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 15 subjects are treated and followed for the specified time. In this scenario, the total sample size (Stage 1 + Stage 2) for a cohort would still remain unchanged at 30 subjects.

If enrollment in any cohort is terminated for futility, the final reporting for that cohort will be based on all subject data in the database.

17.3.3. Key Elements of the Analysis Plan

Complete details of the analysis plan will be provided in the Statistical Analysis Plan (SAP). Any deviations from, or additions to, the original analysis plan in this protocol will be documented in the SAP and the CSR.

Since it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to provide valuable information, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of treatment duration.

Since the duration of study treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary among subjects. All available time-to-event data will be analyzed using appropriate statistical methods. Subjects with shorter treatment and follow-up will not be considered to have missing data. Consequently, there will be no imputation for missing time-to-event data.

Demographics and baseline characteristics will be summarized by cohort and overall.

17.4. Efficacy Analyses

17.4.1. Final Analysis of Primary Endpoint by Cohort

Within Cohorts 1, 3, 4, and 7 separately, the data cut-off for the analysis at the end of Stage 2 will occur after all enrolled subjects have completed at least the Week 24 assessment, completed the final study visit or terminated early from the study. Within each cohort, ORR is defined as the percentage of subjects achieving a confirmed CR or PR from the start of treatment until disease progression or the start of subsequent anti-cancer therapy, as per RANO criteria for primary brain tumors or RECIST 1.1 criteria for all other solid tumors (Appendix 5). Subjects with a best response of unknown/non-evaluable response will be treated as non-responders, i.e., they will be included in the denominator when calculating the percentage. An exact 95% confidence interval (CI) for ORR will be provided.

Within Cohort 2, the data cut-off for the analysis at the end of Stage 2 will occur after all enrolled subjects have completed at least the Week 16 assessment, completed the final study visit or terminated early from the study. The progression-free rate at Week 16 is defined as the percentage of subjects with a response of CR, PR, or SD at the Week 16 assessment, as per RECIST 1.1 criteria. Subjects with non-evaluable or missing response will be treated as not progression-free; i.e., they will be included in the denominator when calculating the progression-free rate. As a specific example, subjects with disease progression or death prior to the Week 16 assessment will be included in the denominator. In addition to the PFS rate at Week 16, an exact 95% CI for this rate will be provided.

Within Cohort 5, the data cut-off for the analysis at the end of Stage 2 will occur after all enrolled subjects have completed at least the Week 32 assessment, completed the final study visit, or terminated early from the study. DCR is defined as the percentage of subjects who

achieve a confirmed response (CR or PR, as per RECIST 1.1 criteria) or who have SD lasting at least 32 weeks from the start of treatment until disease progression or the start of subsequent anti-cancer therapy. For subjects with a confirmed response, the onset and duration of the response may be of any length as long as the response is confirmed per RECIST 1.1. An unconfirmed response (CR or PR) will be considered SD at that time point. Subjects with a best response of unknown/non-evaluable response will be treated as non-disease control, i.e., they will be included in the denominator when calculating the percentage. Subjects with a time point response of unknown/non-evaluable response on or before Week 32 will still be classified as having disease control as long as there is a response of CR, PR, or SD on or after Week 32.

For Cohort 5, the futility criterion was surpassed on 04-Oct. 2016. The IDMC endorsed continuing enrollment to Stage 2 completion. On 21-Oct. 2016, the IDMC endorsed a change in the primary endpoint for Cohort 5 from ORR to DCR (which includes subjects who achieve a confirmed response [CR+PR] or who maintain SD for at least 32 weeks). In Dec. 2016, after the Stage 2 DCR criterion was surpassed, enrollment was opened in the extension stage. In May 2017, Epizyme met with the FDA regarding future development plans for tazemetostat. Based on a specific request by FDA, with Amendment 5, the primary endpoint for Cohort 5 has been changed to ORR and duration of response in responding subjects has been elevated to the most important secondary endpoint. The timing of the final analysis will be after all enrolled subjects have completed at least the Week 24 assessment, completed the final study visit or terminated early from the study. An exact 95% CI for ORR and DCR will be provided for subjects enrolled through Stage 2. In addition, a 95% CI for ORR and DCR will be provided for the entire cohort (i.e., including the subjects enrolled as part of the expansion). Also, a 95% CI for ORR and DCR will be provided for the entire Cohort 5 and Cohort 6.

For Cohort 8, the data cut-off for the final analysis will occur after all enrolled subjects have completed at least the Cycle 2 Day 1 assessment, completed the final study visit or terminated early from the study.

For primary endpoint (ORR) and secondary endpoints of Cohort 6 (DOR, DCR, and ORR; potentially PFS and OS, if sufficient data and analysis warranted) statistical analysis will be performed and analyzed as for Cohort 5.

17.4.2. Analysis of Secondary Efficacy Endpoints

Within each cohort, the data cut-off for the Week 32 and Week 56 analyses will occur after all subjects have completed at least the Week 32 and Week 56 assessments respectively, completed the final study visit, or terminated early from the study, whichever is sooner. The overall analysis of all five cohorts combined will occur after all cohorts have reached their individual data cut-offs.

DOR, for the subset of subjects with confirmed CR or PR response, is defined as the time from the first documented evidence of CR or PR to the time of first documented disease progression or death due to any cause, whichever comes first, using disease-appropriate standardized response criteria. Within each cohort and for Cohorts 1, 3, 4, 5, 6, and 7 combined, the duration of response will be calculated for each subject with a confirmed CR or PR. If sample size permits, the median duration of response will be calculated from the Kaplan-Meier estimates. First and third quartiles will also be calculated along with associated 95% CIs if there are a sufficient

number of responders who subsequently progress or die due to any cause. A listing of duration of response will be provided.

DCR is defined as the percentage of subjects who achieve a confirmed response (CR or PR, as per RECIST 1.1 criteria) or who have SD lasting at least 32 weeks from the start of treatment until disease progression or the start of subsequent anti-cancer therapy. For subjects with a confirmed response, the onset and duration of the response may be of any length as long as the response is confirmed per RECIST 1.1. An unconfirmed response (CR or PR) will be considered SD at that time point. Subjects with a best response of unknown/non-evaluable response will be treated as non-disease control, i.e., they will be included in the denominator when calculating the percentage. Subjects with a time point response of unknown/non-evaluable response on or before Week 32 will still be classified as having disease control as long as there is a response of CR, PR, or SD on or after Week 32.

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 anti-cancer 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 anti-cancer 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.

OS is defined as the interval of time between the date of the first dose of study drug and the date of death due to any cause. For subjects who do not die, the time of death will be censored at the date of last contact. Death due to any cause will be included.

Within each cohort, PFS and OS will be calculated using the Kaplan-Meier method. PFS and OS at 24, 32, and 56 weeks and overall along with the associated 95% CIs will be provided. If there are a sufficient number of PFS events (i.e., progressions or deaths), median PFS, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982). If there are a sufficient number of deaths, median OS, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method. Figures and listings of PFS and OS will also be provided.

Within each cohort and for Cohorts 1, 3, 4, 5, 6, and 7 combined, the ORR and an exact 95% CI will be provided.

17.5. Safety Analyses

17.5.1. Extent of Exposure

The data on exposure to tazemetostat will be listed by cohort. Details pertaining to dose interruption or dose modification will also be listed. Duration of exposure and percentage of treatment compliance will be summarized by cohort and overall.

17.5.2. Adverse Events

The data listings of AEs in the CSR will contain the verbatim description, PT and SOC MedDRA-level terms.

Treatment-emergent AEs (TEAEs) are defined by applying treatment-emergent signs and symptoms (TESS) philosophy. AEs will be regarded as TEAEs if one of the following conditions is met:

- Emerge after the time of first dose administration, having been absent prior to the first dose.
- Re-emerge, having been present but stopped prior to the time of first dose administration.
- Worsen in severity after the time of first dose administration relative to the pre-treatment state, when the AE is continuous.

An AE with partial or completely missing start date and/or time will always be assumed as TEAE, unless it can be determined to be "prior to administration" from the incomplete start date/time or resolution date/time (e.g., month, year is before first administration date, or resolution date is before first administration date).

Other than biopsy-related AEs, only TEAEs will be summarized. Summaries of TEAEs will consist of the number and percentage of subjects reporting the AE by SOC and by PT. TEAEs which occur more than once for a subject will be counted only once in the subject frequencies. TEAEs with different CTCAE grades for a subject will be counted at the worst (highest) grade for the same SOC (likewise for PT). TEAEs with different drug relationship for a subject will be counted at strongest relationship for the same SOC (likewise for PT). TEAEs with missing relationship to study treatment will be counted as "related". TEAEs with missing CTCAE grade will be counted as Grade 3 ("severe").

Summaries of AEs by study cohort and overall will be produced to present the number and percentage of subjects with:

- Any TEAE
- Any treatment-related TEAE
- Any TEAE with CTCAE Grade 3 or higher
- Any TEAE leading to study treatment discontinuation
- Any Serious TEAEs
- Any TEAE of special interest

- Any biopsy-related AE

Listings will be provided for the following:

- AEs
- TEAEs leading to study treatment discontinuation
- Serious TEAEs
- Fatal TEAEs
- TEAEs of special interest
- Biopsy-related AEs

17.5.3. Clinical Laboratory Evaluation

All clinical laboratory parameters will be standardized according to the International System of Units (SI) prior to summarization. Separate listings and summary tables (by cohort and overall) will be produced for each laboratory test group (complete blood counts, serum chemistries (liver, renal [with creatinine clearance, if creatinine is abnormal] and metabolism), coagulation profile, and urinalysis).

Shifts from baseline in CTCAE grades for each parameter will be summarized by cohort and overall. The summary will include the worst-case shift from baseline during the post-baseline period, which will include both planned (scheduled) and unscheduled visits after the first dose of study drug. Subjects with laboratory data outside the normal range will be flagged as "L" (Low) or "H" (High) in the data listing.

17.5.4. Other Safety Measures

The results of scheduled assessments of physical examination, vital signs, ECG, ECHO, and ECOG performance status will be summarized by study part and overall. Summaries will include data from scheduled visits. Shifts from baseline will be summarized where appropriate. All data will be listed.

17.6. Pharmacokinetic Analyses

Plasma concentrations of tazemetostat and its metabolite 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. Population estimates of CL/F, Vd/F, and Ka for tazemetostat will be calculated with a non-linear mixed-effects model using NONMEM 7 software. The effect of subject characteristics such as age, weight, body surface area, and gender on the PK parameters may be investigated. The PK data from this study may be combined with data from other studies to determine the final population PK model. The final population PK model will be described in a separate report.

17.7. Exploratory Analysis

As data warrant, exploratory analysis may be performed on each exploratory endpoint listed below. In addition, exploratory analyses may be performed to examine the relationship between exposure to tazemetostat and clinical and safety endpoints (including tumor size or change in tumor size from baseline). The results of these exploratory analyses may be reported separately from the clinical study report (CSR).

- Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation and cell proliferation, and their correlation with activity
- Somatic mutation analysis of tumor tissue and blood
- Germline DNA analysis for INI1 or SMARCA4 variants
- **For Cohort 6:** Assessment of pre- and post-dose biopsies for immune priming (e.g., PD-L1 and CD8 IHC)
- **For Cohort 6:** Assessment of pre- and post-dose biopsies for H3K27me3 and for changes in gene expression.

17.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of:

- Safety data at each predetermined (or ad hoc, if needed) and make recommendations to the Sponsor to continue, modify or terminate any of the cohorts or the study
- Cohort efficacy data at the defined stages to determine if futility has been reached or the cohort should proceed to subsequent stage

A recommendation of study hold, 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.

The schedule of any planned interim analysis and the analysis plan for IDMC review is described in a separate charter.

18. STUDY CONDUCT CONSIDERATIONS

18.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers.

18.2. Regulatory and Ethical Considerations

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Tripartite Guideline E6 (R1): GCP: Consolidated Guideline, and for US Investigators, 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the Investigator, sub-Investigator(s), and essential study staff will be provided to the Sponsor or its designee before starting the study.

If the subject has a primary physician the Investigator should, with the subject's or his/her legal representative's consent, inform them of the subject's participation in the study.

18.2.1. Institutional Review Board (IRB)/ Ethics Committee (EC)

It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or its designate), relevant supporting information and all types of subject recruitment information to the IRB/EC for review. All must be approved prior to site initiation. Prior to implementing changes in the study, the Sponsor and the IRB/EC must also approve any revised ICFs and/or protocol amendments.

On the IRB/EC approval letter, the study reference, the date of review, and actions taken should be clearly stated.

Clinical supplies of tazemetostat will not be released to the site and recruitment of subjects will not begin until the IRB/EC written approval has been received by the Sponsor or its designee.

The Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol and/or ICF. The Investigator must also keep the IRB/EC informed of any serious and significant AEs.

18.2.2. Informed Consent Process

It is the responsibility of the Investigator to obtain written informed consent from each subject before any protocol-specific assessments and/or procedures are performed. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative is requested to sign the ICF after the subject has received and read the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the ICF (subject information sheet and the ICF, as applicable) must be given to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the subject's local language. Signed ICFs must remain in each subject's study file and must be available for verification by Study Monitors at any time.

Each Investigator will provide the Sponsor or its designee with a copy of the IRB/EC approved ICF(s), and a copy of the IRB/EC written approval, prior to the start of the study. Additionally, if the IRB/EC requires modification of the sample subject information and the model ICF provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

The Sponsor reserves the right to delay initiation of the study at a site where the ICF(s) do not meet the standards of applicable regulations and ICH GCP.

18.3. Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the Sponsor and/or their designee(s), participating Investigators, and any staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The Study Monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital), and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

18.4. Study Monitoring

Monitoring of the study will be performed by the Sponsor or its designee(s). At the monitoring visits, the progress of the study will be discussed with the Investigator, or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Subject source data must be available for review. The Investigator and his/her staff are expected to cooperate with the Study Monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

The Study Monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

Telephone contact will be made with the Investigator as necessary during the data collection period and during the data and report writing periods.

18.5. Protocol Deviations

No deviation may be made from the protocol unless an amendment has been agreed to in writing by both the Investigator and the Sponsor and approved by the IRB/EC. Investigative sites will contact the Medical Monitor to request clarifications regarding any aspect of the clinical study or eligibility of subjects.

When an emergency occurs that requires a deviation from the protocol for an individual subject, the deviation will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor or their representative(s), immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the protocol deviation was affected) is to continue in the study. The source documentation will completely describe the protocol deviation and state the reasons for such deviation. In addition, the IRB/EC will be notified in writing of such protocol deviation.

18.6. Protocol Amendment

All amendments to the protocol must be documented in writing, reviewed, and approved by the Investigator and the Sponsor, and submitted to the IRB/EC for approval prior to initiation, except in cases where required for subject safety. If the protocol amendment substantially alters the study design or potential risk to the subject, a new written ICF for continued participation in the study must be obtained from each subject or his/her legal representative.

18.7. Suspension or Termination of Study

Should conditions requiring further clarification arise before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

The Sponsor has the right to terminate this study and remove all study material from the site at any time. Examples of where this might occur include, but are not limited to:

- When it becomes apparent that subject enrollment is unsatisfactory with respect to quality and/or quantity or data recording is inaccurate and/or incomplete on a chronic basis.
- When the incidence and/or severity of AEs in this study indicates a potential health hazard caused by treatment with tazemetostat.

19. ADMINISTRATIVE PROCEDURES

19.1. Recording and Access to Study Records

The circumstances of completion or termination of the study notwithstanding, the Investigator (if regionally required, the heads of the medical institutions) has the responsibility to retain all study records, including but not limited to the protocol, copies of eCRFs, the IB, regulatory agency required documents (e.g., Form FDA 1572/ Statement of Investigator, financial disclosures, etc.), ICFs, and IRB/IEC correspondence. To enable evaluations and/or inspections from regulatory authorities or Sponsor, the Investigator agrees to maintain records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records must be retained by the Investigator according to ICH GCP and/ or applicable local regulatory regulations, whichever is longest, as specified in the Clinical Study Agreement. It is requested that at the completion of the required retention period or, should the Investigator withdraw from the responsibility of maintaining study record (e.g., retire, relocate, etc.), the Investigator (or if regionally required, the heads of the medical institutions) will prospectively notify the Sponsor. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator at the institution or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

19.2. Case Report Forms

Electronic case report forms (eCRF) will be used for data collection for this study.

The Investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into eCRFs, which have been designed to capture all observations and other data pertinent to the clinical investigation. The eCRFs should be completed by the Investigator or delegate as stated on the Delegation of Authority Log. Overwriting of information or use of liquid correcting fluid is not allowed in the source document.

Each investigative site will be visited as frequently as documented in the monitoring plan by the Sponsor or their designee to review the eCRFs for completeness and accuracy. The Sponsor or their designee will highlight any discrepancies found between source documents and the completed eCRFs and ensure that appropriate site personnel address the discrepancies. When a discrepancy results in corrected eCRF data, the correction will be reviewed again against the correct source documentation. Uniform procedures will be discussed at the Site Initiation Visit.

The eCRFs must be reviewed and electronically signed and dated by the Investigator once all data have been entered and all queries resolved. Queries may be raised if the data are unclear or contradictory. The Investigator must address all queries.

19.3. Quality Assurance and Quality Control (QC)

A site monitoring plan will be developed to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the Sponsor's, ICH/GCP, and other applicable regulatory guidelines.

The Investigator will permit authorized the Sponsor or its designee(s), and the respective regulatory authorities, to inspect facilities and records relevant to this study if needed.

Initial site training will be provided by the Sponsor or its designee. Training for new site staff will be provided by previously trained study nurses, study coordinators, or other qualified staff under the supervision of the Primary Investigator. Additional training will be provided by the Sponsor or its designee as needed.

The designated Data Management Team will implement QC procedures beginning with the data entry system and generate data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

19.4. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the Sponsor or its designee's Standard Operating Procedures, protocols and working practice documents, and the requirements of ICH/GCP guidelines. Compliance will be achieved through a combination of study-specific audits of investigative sites and audits at regular intervals of the Sponsor or its designee's systems for data handling, analysis, and reporting.

19.5. Confidentiality

Data collected during this study may be used to support the development, registration, or marketing of tazemetostat. After a subject or his/her legal representative have consented to take part in the study their medical records and the data collected during the study will be reviewed by the Sponsor and/or its designee. These records and data may be reviewed by the following: independent auditors who validate the data on behalf of the Sponsor: third parties with whom the Sponsor may develop, register, or market tazemetostat; national or local regulatory authorities and the IRB/EC(s) which gave its/their approval for this study to proceed.

Although subjects will be known by a unique identifier number, their year of birth will also be collected and used to assist the Sponsor and/or its designee to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct subject.

19.6. Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study will be available for inspection upon request by representatives of the US FDA as well as other national and local regulatory authorities, the Sponsor and/or its designee, interested commercial parties, and the IRB/EC for each study site.

19.7. Provision of Study Results and Publication

A summary of the study results will be made publicly available within 12 months of reaching the end of the study, defined as the date of the LSLV. A full CSR will be made publicly available no later than 18 months after the end of the study.

If a manuscript is published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, in advance of submission. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and the Sponsor.

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