SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma

Protocol Number: EZH-102

Approved By:

Responsible Sponsor Medical Officer:

Signature: PPD _____ **Date:** PPD

Epizyme, Inc.

Responsible Sponsor Medical Monitor:

Signature: PPD _____ **Date:** _____

Epizyme, Inc.

Original: 13 July 2015
Amendment 1.0: 24 August 2015
Amendment 2.0: 02 October 2015
Amendment 3.0: 11 May 2016
Amendment 4.0: 27 July 2016
Amendment 5.0: 20 July 2017
Amendment 6.0: 28 September 2018
Amendment 7.0: 17 December 2018
Amendment 8.0: 20 February 2020

INVESTIGATOR AGREEMENT PAGE

Protocol Title: A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma

Protocol Number: EZH-102

By Signature Below, I agree to comply with the contents of this protocol and to conduct this study in compliance with Good Clinical Practices (GCP) and all applicable requirements.
I acknowledge that I am responsible for the overall study conduct and that I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information and training throughout the conduct of the study.

I have read and agree to the following Confidentiality Statement:

Confidentiality Statement: This protocol and any related documents from Epizyme, Inc., contain privileged information that is confidential and may not be disclosed unless such disclosure is required by federal laws or regulations. In any event, persons to whom the information is disclosed must be informed that it is privileged and/or confidential and may not be further disclosed by them. Information from this study may not be reproduced in any form without the written permission of Epizyme, Inc.

Principal Investigator:

Name: _____

Title: _____

Signature: _____ **Date:** _____

Name/Address of Institution: _____

_____

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma
Compound Name (Number):	Tazemetostat (EPZ-6438)
Protocol Number:	EZH-102
IND Number:	CCI
EudraCT Number:	2015-002468-18
Sponsor:	Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA
Sponsor Medical Monitor:	PPD Epizyme, Inc.
North America Medical Monitor:	PPD
SAE Hotline for North American/Australian Sites Only:	
EU Medical Monitor:	
SAE Hotline for EU Sites Only:	

This protocol has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by an Institutional Review Board or Ethics Committee and the performance of all aspects of the study, including the methods used to obtain informed consent, must also be in accordance with the principles enunciated in the declaration, ICH E6 (R1) guidelines of Good Clinical Practice, US FDA CFR Part 50 Protection of Human Subjects and 21 CFR Part 56 Institutional Review Boards, and all applicable regulatory authority requirements.

TABLE OF CONTENTS

CCI

CCI

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism, and Excretion
ADR	Adverse Drug Reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
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
AUC_{D1}	Area under the concentration-time curve on Day 1
AUC_{D15}	Area under the concentration-time curve on Day 15
$AUC_{(0-t)}$	Area under the concentration-time curve from time 0 to last measurable concentration
$AUC_{(0-12)}$	Area under the concentration-time curve from time 0 to 12 hours post-dose
AUCss	Area under the concentration-time curve at steady-state
AUC_{ss}	AUC at steady-state
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BM	Bone marrow
BSA	Body surface area
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
CSF	Cerebrospinal fluid
CSR	Clinical study report
CSRC	Clinical Safety Review Committee
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Clinical Trial Directive
C_{trough}	Trough plasma concentration
CYP	Cytochrome
DLBCL	diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
ECI	Events of clinical interest
EDC	Electronic Data Capture
EIAED	Enzyme inducing anti-epileptic drug
EMA	European Medicines Agency
EMC	Extraskeletal myxoid chondrosarcoma

Abbreviation	Definition
EMPNST	Epithelioid malignant peripheral nerve sheath tumor
ES	Epithelioid sarcoma
ESC	External Safety Committee
EU CT Dir	European Union Clinical Trial Directive
EZH2	Enhancer of zeste homolog-2
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FISH	Fluorescence in situ hybridization
FL	follicular lymphoma
FLAIR	fluid-attenuated inversion recovery
FTIH	First-time-in-human
GCP	Good Clinical Practice
GI	Gastrointestinal
H3K27	Lysine 27 of histone H3
H3K27me3	H3K27 trimethylation
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
HMT	Histone methyltransferase
hr	Hour
HR	Heart rate
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	international normalized ratio
ITT	Intent-to-Treat
IMP	Investigational Medicinal Product
INI1	Integrase interactor 1
IP	Investigational product
IRB	Institutional Review Board
Ka	First-order absorption rate constant
kg	Kilogram
L	Liter
LLN	Lower limit of normal
LN	Lymph node
LNH	Low, normal, high
LSLV	Last subject, last visit
LV	left ventricular
m^2	Squared meter
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	Millimeter
mL	Milliliter
MPN	Myeloproliferative neoplasms
msec	Millisecond
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRT	Malignant rhabdoid tumor
MRTO	Malignant rhabdoid tumor of the ovary
MTD	Maximum tolerated dose

Abbreviation	Definition
MUGA	Multigated acquisition scan
NA	Not applicable
NE	Not evaluable
NHL	Non-Hodgkin's lymphoma
OAEs	Other Adverse Event
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PBM	Peripheral blood monocytes
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
PTT	Partial thromboplastin time
QC	Quality control
QTc	Corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
QSR	Quarterly Safety Review committee
R_{ac}	Accumulation ratio
RANO	Response Assessment in Neuro-Oncology
RTK	Rhabdoid tumor of the kidney
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
RMC	Renal medullary carcinoma
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCCOHT	Small cell carcinoma of the ovary, hypercalcemic type
SD	Stable disease or standard deviation
SI	International System of Units
SMARCA2	SWItch/Sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2
SMARCA4	SMARC), subfamily A, member 4
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
SWI/SNF	SWItch/Sucrose Non-Fermentable
T	Temperature
$t_{1/2}$	Elimination half-life
T-ALL	T-cell acute lymphoblastic leukemia
TBV	total blood volume
TEAE	Treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TESS	Treatment-emergent signs and symptoms
TID	Three times daily
CCI [redacted]	[redacted]
T_{max}	Time to maximum concentration

Abbreviation	Definition
ULN	Upper limit of normal
UV	Ultraviolet
Vd/F	Oral volume of distribution
WBC	White blood cell
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title of the Study:	A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma
Protocol Number:	EZH-102
Investigational Product:	Tazemetostat (EPZ-6438)
Phase of Development:	1
Number of Sites:	20-30 sites
Study Period:	Dose Escalation: First subject first visit 4Q2015 Dose Expansion: Last subject last visit projected 2Q2022
Objectives:	**Primary Objectives:** **Dose Escalation:** • To determine the maximum tolerated dose (MTD) or the recommended Phase 2 dose (RP2D) of tazemetostat when administered as an oral suspension twice daily (BID) in pediatric subjects with relapsed/refractory rhabdoid tumors, integrase interactor 1 (INI1) negative tumors or synovial sarcoma **Dose Expansion:** • To evaluate the antitumor activity of tazemetostat as assessed by overall response rate (ORR) in pediatric subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1**-closed to enrollment)**, non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4**-closed to enrollment**) using disease-appropriate standardized response criteria **Secondary Objectives:** **Dose Escalation:** • To evaluate the preliminary antitumor activity of tazemetostat as assessed by ORR using disease-appropriate standardized response criteria **Dose Expansion:** • To determine the progression-free survival (PFS) and overall survival (OS) at 24 and 56 weeks and overall in pediatric subjects with relapsed/refractory ATRT (Cohort 1**- closed to enrollment**), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4**- closed to enrollment**) using disease-appropriate standardized response criteria **All Subjects:** • To assess the safety and tolerability of tazemetostat administered as an oral suspension BID and tablet 3 times daily (TID) • To assess the pharmacokinetics (PK) of tazemetostat after administration as suspension or tablets in pediatric subjects • To evaluate the duration of response in subjects achieving a complete response (CR) or partial response (PR) according to disease-appropriate standardized response criteria

Exploratory Objective (All Subjects):

- CCI
-
-

Study Design:

This is a Phase 1, open-label, dose escalation and dose expansion study with BID (suspension) and TID (tablet) oral doses of tazemetostat. Subjects will be screened for eligibility within 14 days of the planned first dose of tazemetostat. Response assessment will be evaluated after 8 weeks of treatment and subsequently every 8 weeks

Tazemetostat will be given continuously, assuming subject (and/or parent/guardian) and Investigator consent/assent, until disease progression or unacceptable toxicity. Subjects may receive tazemetostat for a maximum of 2 years (Section 6.5.3).

Subjects will be dosed in continuous 28-day cycles (Note: If treatment with study drug is discontinued prior to completing 2 years, subjects will be followed for a maximum duration of 2 years from start of study drug dosing.)

The study has two parts: Dose Escalation and Dose Expansion.

Dose Escalation for subjects with the following relapsed/refractory malignancies:

- Rhabdoid tumors:
  - Atypical teratoid rhabdoid tumor (ATRT)
  - Malignant rhabdoid tumor (MRT)
  - Rhabdoid tumor of kidney (RTK)
  - Selected tumors with rhabdoid features
- INI1-negative tumors:
  - Epithelioid sarcoma
  - Epithelioid malignant peripheral nerve sheath tumor
  - Extraskeletal myxoid chondrosarcoma
  - Myoepithelial carcinoma
  - Renal medullary carcinoma
  - Other INI1-negative malignant tumors (e.g., de-differentiated chordoma) with Sponsor approval
- Synovial Sarcoma with SS18-SSX rearrangement

Dose Expansion at the MTD or the RP2D:

- Cohort 1 – ATRT (closed to enrollment)
- Cohort 2 –MRT/RTK/selected tumors with rhabdoid features
- Cohort 3 – INI-negative tumors as follows:

- Epithelioid sarcoma
- Epithelioid malignant peripheral nerve sheath tumor
- Extraskeletal myxoid chondrosarcoma
- Myoepithelial carcinoma
- Renal medullary carcinoma
- Chordoma (poorly differentiated or de-differentiated)
- Other INI1-negative malignant tumors with Sponsor approval

- Cohort 4 - One of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (closed to enrollment)

Number of Subjects (planned):

Dose Escalation: Approximately 48 subjects with relapsed/refractory selected solid tumors and CNS tumors will be enrolled using a "Rolling 6" dose escalation design (subjects who discontinue in absence of a dose-limiting toxicity [DLT] prior to the completing of the DLT evaluation period may be replaced).

Dose Expansion: Approximately 72 subjects will be enrolled into the dose expansion into the following cohorts:

- Cohort 1 – approximately 20 subjects with ATRT
- Cohort 2 – approximately 20 subjects with MRT/RTK/selected tumors with rhabdoid features
- Cohort 3 – approximately 20 subjects with INI-negative tumors as follows:
  - Epithelioid sarcoma
  - Epithelioid malignant peripheral nerve sheath tumor
  - Extraskeletal myxoid chondrosarcoma
  - Myoepithelial carcinoma
  - Renal medullary carcinoma
  - Chordoma (poorly differentiated or de-differentiated)
  - Other INI1-negative malignant tumors with Sponsor approval
- Cohort 4 – up to 12 subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Closed to enrollment after sufficient PK data were collected).

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

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

1. Age (at the time of consent/assent): ≥6 months to <18 years of age
   - Cohort 4 only: ≥10 years to <18 years
2. Performance Status:
   - If <12 years of age: Lansky Performance Status >50% (see Appendix 1)
   - If ≥12 years of age: Karnofsky Performance Status >50% (see Appendix 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/assent
4. Has a life expectancy of >3 months

5. Has relapsed or refractory disease and no standard treatment options as determined by locally or regionally available standards of care and treating physician's discretion
6. Is ineligible or inappropriate for other treatment regimens known to have effective potential
7. 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
8. 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
9. Prior therapy(ies), if applicable, must be completed according to the criteria below:

Prior Therapy	Time from Last Prior Therapy
Other investigational agent (any medicinal product that is not approved in the country of treatment for any indication, adult or pediatric)	At least 30 days or five half-lives, whichever is longer, since last dose of an investigational agent prior to the first dose of tazemetostat
Chemotherapy: cytotoxic	At least -14 days since last dose of chemotherapy prior to the first dose of tazemetostat
Chemotherapy: nitrosoureas	At least 6 weeks since last dose of nitrosoureas prior to the 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 the first dose of tazemetostat
Monoclonal antibody (ies)	At least 28 days since last dose of any monoclonal antibody prior to the first dose of tazemetostat
Immunotherapy (e.g., tumor vaccine)	At least 6 weeks 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
Hematopoietic growth factor	At least 14 days from last dose of hematopoietic growth factor prior to the first dose of tazemetostat

Hematopoietic cell transplantation (allogeneic or autologous)	At least 60 days from infusion of hematopoietic cells prior to the first dose of tazemetostat

10. Has adequate hematologic (bone marrow and coagulation factors), renal and hepatic function as defined by criteria below:

System	Laboratory Value	
Hematologic (BM Function)		
Hemoglobin[a]	≥8 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		
Calculated Creatinine Clearance[e]	≥50 mL/min/1.73 m^2	
OR		
Serum creatinine based on age/gender		
AGE	**Male**	**Female**
6 months to 1 year	0.6 mg/dL (53 µmol/L)	0.5 mg/dL (44 µmol/L)
1 to <2 years	0.6 mg/dL (53 µmol/L)	0.6 mg/dL (53 µmol/L)
2 to <6 years	0.8 mg/dL (71 µmol/L)	0.8 mg/dL (71 µmol/L)
6 to <10 years	1 mg/dL (88 µmol/L)	1 mg/dL (88 µmol/L)
10 to <13 years	1.2 mg/dL (106 µmol/L)	1.2 mg/dL (106 µmol/L)
13 to <16 years	1.5 mg/dL (133 µmol/L)	1.4 mg/dL (124 µmol/L)
≥16 years	1.7 mg/dL (150 µmol/L)	1.4 mg/dL (124 µmol/L)

Hepatic Function	
Total bilirubin[f]	<1.5 × ULN for age
ALT or AST[g]	<3 × ULN

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BM, bone marrow; INR, international normalized ratio; 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 but if only PT can be performed in the testing laboratory that is acceptable
e. Creatinine clearance by 24-hour urine or radioisotope glomerular filtration rate
f. Eligibility can be determined by either total or conjugated bilirubin
g. If attributed to tumor involvement, AST and ALT <5xULN

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.

11. **For subjects with CNS involvement:** Subjects must have:

    - Deficits that are stable for a minimum of 14 days prior to first dose of study drug, or
    - Seizures that are stable, not increasing in frequency or severity and controlled on current anti-seizure medication(s) for a minimum of 7 days prior to first dose of study drug, or
    - Treated brain metastases without evidence of progression (new or enlarging brain metastases by imaging 4 weeks prior to the first dose of study drug) and are on stable or tapering doses of steroids for at least 7 days prior to first dose of study drug.

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

12. Has a left ventricular (LV) fractional shortening of >27% or an LV ejection fraction of ≥50% by echocardiogram or multigated acquisition scan and New York Heart Association Class ≤2

13. Has a QT interval corrected by Fridericia's formula (QTcF) ≤450 msec

14. Is able to swallow and retain orally administered medication and does not have any uncontrolled gastrointestinal (GI) condition such as nausea, vomiting or diarrhea, or any clinically significant GI abnormalities that may alter absorption such as malabsorption syndromes, hereditary fructose intolerance, glucose-galactose malabsorption, sucrose-isomaltase insufficiency, or major resection of the stomach and/or bowels.

    NOTE: Nasogastric and gastrostomy tube administration of the oral suspension formulation of study drug is permitted.

15. Has sufficient tumor tissue (slides or blocks) available for central confirmatory testing of immunohistochemistry and/or cytogenetics/fluorescence in situ

hybridization (FISH) and/or deoxyribonucleic acid (DNA) mutation analysis (required for study entry but enrollment based on local results).

16. Is willing and able to comply with all aspects of the protocol as judged by Investigator
17. **For female subjects of childbearing potential:** Subject must:
    - Have a negative beta-human chorionic gonadotropin (β-hCG) pregnancy test at time of Screening and within 72 hours 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 non-hormonal contraception, as defined in Section 8.5.11 from start of Screening until 6 months following the last dose of study treatment 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 8.5.11, **or**
    - Have a male partner who is vasectomized with confirmed azoospermia
18. **For male subjects with a female partner of childbearing potential:** Subject must:
    - Be vasectomized or
    - Agree to use condoms as defined in Section 8.5.11 from the first dose of tazemetostat until 3 months following the last dose of tazemetostat, or
    - Have a female partner who is NOT of childbearing potential
19. **For subjects enrolling at sites in France only:** Is either affiliated with or a beneficiary of a social security category

For Dose Escalation Only:

To be eligible for enrollment in dose escalation, a subject must meet ALL of the following criteria in addition to the inclusion criteria listed above for all subjects:

1. Has **evaluable** disease as defined as lesions that can be accurately measured at least in one dimension by radiographic examination or physical examination or other lesions such as bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis or hepatosplenomegaly from disease.
2. Has one of the following histologically confirmed tumors:
    - Rhabdoid tumor:
        - Atypical teratoid rhabdoid tumor (ATRT) (Closed to enrollment)
        - Malignant rhabdoid tumor (MRT)
        - Rhabdoid tumor of the kidney (RTK)
        - Selected tumors with rhabdoid features

- INI1-negative tumor:
  - Epithelioid sarcoma (ES)
  - Epithelioid malignant peripheral nerve sheath tumor (EMPNST)
  - Extraskeletal myxoid chondrosarcoma (EMC)
  - Myoepithelial carcinoma
  - Renal medullary carcinoma (RMC)
  - Other INI1-negative malignant tumors (e.g., de-differentiated chordoma) NOTE: Requires prior Sponsor approval
- Synovial sarcoma with SS18-SSX rearrangement (closed to enrollment)

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

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

For Dose Expansion Only:

To be eligible for enrollment in Dose Expansion, a subject must meet ALL of the following criteria in addition to the inclusion criteria for ALL subjects listed above:

1. Has measurable disease as defined in Section 8.5.3.
2. Has one of the following histologically confirmed tumors:
    - Cohort 1 **(enrollment closed):**
        - Atypical teratoid rhabdoid tumor (ATRT)
    - Cohort 2:
        - Malignant rhabdoid tumor (MRT)
        - Rhabdoid tumor of the kidney (RTK)
        - Selected tumors with rhabdoid features
    - Cohort 3 (INI1-negative tumors):
        - Epithelioid sarcoma (ES)
        - Epithelioid malignant peripheral nerve sheath tumor
        - Extraskeletal myxoid chondrosarcoma (EMC)
        - Myoepithelial carcinoma
        - Renal medullary carcinoma
        - Chordoma (poorly differentiated or de-differentiated)
        - Other INI1-negative malignant tumors NOTE: Requires prior Sponsor approval
    - Cohort 4 **(enrollment closed):**
        - One of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement

    NOTE: Evidence of diagnostic pathology of original biopsy confirmed by a CLIA/CAP or other Sponsor-approved certified laboratory must be available.
3. For subjects with ATRT/MRT/RTK only – have the following test results available:
    - Morphology and immunophenotypic panel consistent with rhabdoid tumor, and
    - Loss of INI1 or SMARCA4 confirmed by IHC, or
    - Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss or mutation when INI1 or SMARCA4 IHC is equivocal or unavailable
4. For subjects with INI1-negative tumors only – have the following test results available:
    - Morphology and immunophenotypic panel consistent with INI1-negative tumors, and
    - Loss of INI1 confirmed by IHC, or
    - Molecular confirmation of tumor bi-allelic INI1 loss/mutation when INI1 IHC is equivocal or unavailable
5. For subjects with synovial sarcoma with SS18-SSX rearrangement (in Cohort 4 only. **Cohort 4 is closed to enrollment**) - have the following test results available:
    - Morphology consistent with synovial sarcoma, and
    - Cytogenetics or FISH and/or molecular confirmation (e.g., deoxyribonucleic acid [DNA] sequencing) of SS18 rearrangement t(X;18)(p11;q11)
6. **For subjects to be enrolled in Cohort 4 (Cohort 4 is closed to enrollment):** Able to swallow and retain orally administered tablets

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 homolog-2 (EZH2)
2. Is being actively treated for another concurrent malignancy or is less than 5 years from completion of treatment for another malignancy
3. Has participated in another interventional clinical study and received investigational drug within 30 days or five half-lives, whichever is longer, prior to the planned first dose of tazemetostat
4. Has had major surgery within 2 weeks prior to enrollment

   NOTE: Minor surgery (e.g., minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 2 weeks prior to enrollment.
5. Has 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 at Screening. Cytogenetic testing and DNA sequencing will be conducted by a central laboratory following an abnormal result of bone marrow aspirate/biopsy.
6. Has a prior history of CCI /T-ALL.
7. Has clinically active heart disease including prolonged QTcF (>450 msec).
8. Is currently taking any prohibited medication(s) as described in Section 7.3.
9. 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.
10. Has an active infection requiring systemic treatment.
11. Is immunocompromised (i.e., congenital immunodeficiency), including subjects with a known history of infection with human immunodeficiency virus (HIV).
12. Has known history of chronic infection with hepatitis B virus (hepatitis B surface antigen positive) or hepatitis C virus (detectable HCV RNA).
13. Has had a symptomatic venous thrombosis within 14 days prior to study enrollment.

    NOTE: Subjects with a history of a deep vein thrombosis 14 days prior to study enrollment who are on anticoagulation therapy with low molecular weight heparin are eligible for this study.
14. **For subjects with CNS involvement (primary tumor or metastatic disease):** Have any active bleeding, or new intratumoral hemorrhage of more than punctate size on Screening MRI obtained within 14 days of starting study drug, or known bleeding diathesis or treatment with anti-platelet or anti-thrombotic agents.
15. Has known hypersensitivity to any of the components of tazemetostat or other inhibitor(s) of EZH2, or hypersensitivity to Ora-sweet or methylparaben.

16. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements.

17. **For female subjects of childbearing potential**: Is pregnant or nursing

    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:

Oral Suspension: Subjects will receive tazemetostat as an oral agent BID.

The starting dose for the dose escalation will be 240 mg/m^2/dose given BID for a total daily dose of 480 mg/m^2/day. Dose escalation will be performed using a "Rolling 6" design. The starting dose is derived from physiologically based PK modeling of observed PK data in adult subjects.

Dose Expansion: For patients with no CNS involvement, the dose will be 520 mg/m^2 given BID. For ATRT and tumors with CNS involvement the dose will be 1200 mg/m^2 given BID.

Tablet Formulation: Subjects in Cohort 4 will receive orally administered tazemetostat tablets 800 mg/m^2 TID (2400 mg/m^2/day) CCI [redacted]

Treatment may continue, assuming subject and/or parent/guardian and Investigator consent, until disease progression or unacceptable toxicity. Tazemetostat will be administered for a maximum of 2 years.

Criteria for Evaluation:

Primary Endpoints:

Dose Escalation:

- Incidence and severity of treatment-emergent AEs (TEAEs) qualifying as protocol-defined DLTs, and establishment of the protocol-defined RP2D and/or MTD.

Dose Expansion:

- Overall response rate (CR + PR) to tazemetostat in pediatric subjects with relapsed or refractory ATRT (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria.

Secondary Endpoints:

Dose Escalation:

- Overall response rate (CR+PR) to tazemetostat in pediatric subjects with relapsed or refractory CNS and solid tumors, using disease-appropriate standardized response criteria

Dose Expansion:

- PFS and OS at 24 and 56 weeks and overall following receipt of tazemetostat for subjects with relapsed/refractory ATRT (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria

All Parts and Cohorts:

- Safety and tolerability parameters including TEAEs, clinical laboratory evaluations, and other safety measures
- PK parameters including C_{max}, T_{max}, $t_{1/2}$, $AUC_{(0-t)}$, $AUC_{(0-12)}$, CL/F, Vd/F, Ka (if data permit)
- Response duration, for the subset of subjects with a confirmed CR or PR, defined as the time from the first documented evidence of CR or PR to time of first documented disease progression or death due to any cause, using disease-appropriate standardized response criteria

Exploratory Endpoints:

- CCI
- [redacted]

Statistical Methods:

The number of pediatric subjects for the dose escalation part of the study will be determined based in part on the number of dose escalations required to determine the protocol-defined MTD and/or RP2D.

The sample size for dose expansion (Cohorts 1 to 3) is based on the hypothesized improvement in ORR over historical rates. An ORR no higher than 5% would have no clinical benefit over existing therapies; an ORR of 20% is considered of clinical interest. For each Dose Expansion cohort separately, using a one-sided test and targeting a Type I error rate of 10% and a Type II error rate of 20% requires a total of 20 pediatric subjects to be enrolled per cohort for Cohorts 1 to 3. Up to twelve (12) subjects will be enrolled in dose expansion Cohort 4. Though chosen outside of specific statistical considerations, this number will be adequate to evaluate the PK of tazemetostat when administered in tablet formulation in pediatric subjects. Approximately 72 subjects will be enrolled across the 4 Dose Expansion cohorts.

Primary Endpoints

Dose Escalation:

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

Dose Expansion:

The 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 new anticancer therapy. The 80% confidence interval for ORR in each cohort and overall will be calculated.

1 INTRODUCTION

1.1 Background

Post-translational modifications of histones, the core proteins of chromatin, play an important role in controlling the fidelity of cellular gene transcriptional programs. One of the critical transcription-controlling histone modifications is methylation of specific lysine and arginine residues, catalyzed by histone methyl transferases (HMTs; Copeland, 2013). Alterations in a number of HMTs or associated regulatory proteins have been identified in several human cancers and have been shown to be oncogenic. Enhancer of Zeste homolog 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). This chromatin modification leads to repression of certain important target gene sets such as tumor suppressors, differentiation markers, cell cycle regulators, and apoptotic machinery (Knutson, 2013). Mutations in or dysregulation of EZH2 can lead to aberrant H3K27me3, a state that has been observed in several cancer types. For instance, somatic gain of function mutations within EZH2, found within subsets of non-Hodgkin lymphoma (NHL), result in an oncogenic dependency on EZH2 production of abnormally high H3K27me3 levels, and resultant transcriptional reprogramming of the cell (Chase, 2011).

In addition to oncogenic alterations in EZH2 itself, aberrant functions of 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 increased activation of the PRC2 pathway and resultant 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, and renal medullary carcinoma (RMC) (Margol, 2014). 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; Stacchiotti, 2019). 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, an oncogenic dependency on 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 coinactivating mutations in two SWI/SNF complex protein members; SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily A, member 4 [SMARCA4], and SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily A, member 2 [SMARCA2]. (Jelinic, 2014; Ramos, 2014; Witkowski, 2014). In SCCOHT, SMARCA4 activity is lost via genomic mutations, whereas SMARCA2 mRNA is lost in the absence of any coding mutations (Ramos, 2014; Witkowski, 2014; Jelinic, 2016). The morphologic and molecular similarity of SCCOHT to MRT and ATRT has been described (Foulkes, 2014) , with the proposed reclassification of SCCOHT as a malignant rhabdoid tumor of the ovary (MRTO).

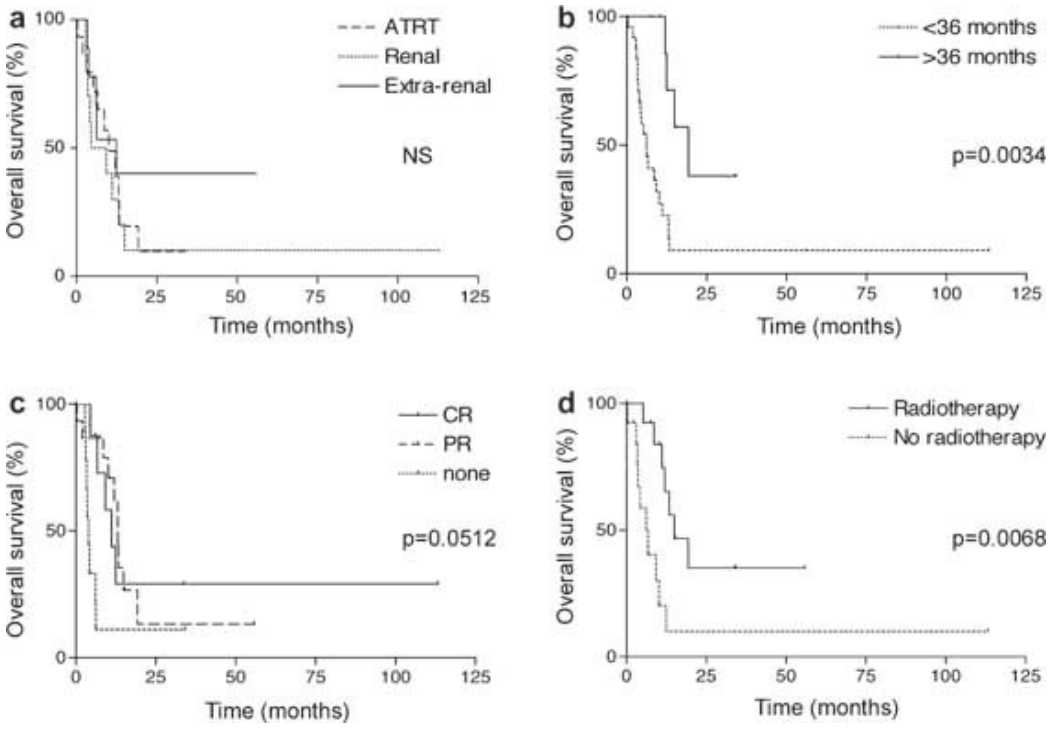
SMARCA4 loss has also been described in a subset of undifferentiated thoracic sarcomas. These tumors when genetically characterized are related to MRT and SCCOHT with TP53 mutations and SMARCA4 inactivation being the sole recurrent alterations. The 19 cases evaluated had consistent pathological features 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 and other INI-negative tumors that have bi-allelic loss of INI1. Tumors harbor characteristic translocations of chromosome X and 18, resulting in 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.

1.2 Clinical Characteristics of Targeted Tumors

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

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



Abbreviations: ATRT= atypical teratoid tumor, CR= complete response, PR= partial response.

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; Wetmore, 2015).

MRTO is a highly aggressive and lethal form of ovarian cancer presenting in young women with a mean age at diagnosis of 24 years, however females as young as 9 years have been diagnosed. 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 2 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 7 months (Le Loarer, 2015).

Other tumors with INI1 deficiency include ES, EMPNST, EMC, RMC, and myoepithelial carcinomas. Current standard of care for other rare 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 for 83% of these patients Sullivan, 2013. ES is an unusual tumor of young adults with a local recurrence rate of 35% and often requires radical excisions and amputations with local radiation as the tumor has a predilection for extremities with nodal metastasis (Chbani, 2009). At time of recurrence there is no standard of care. Epithelioid malignant peripheral nerve sheath tumor (EMPNST) is another rare soft tissue sarcoma that is treated with surgery at time of diagnosis and demonstrates variable response to chemotherapy (Minagawa, 2011). Again, due to the rarity and aggressive nature of the tumors at time of recurrence, there are only anecdotal reports of long-term treatment success. EMC is another soft tissue sarcoma of intermediate malignant potential and case reports discuss treatment with wide local resection (Kawaguchi, 2003). Myoepithelial carcinoma is yet another soft tissue tumor with an aggressive course with median survival of 9 months (Mahdi, 2014). Finally, RMC is a highly aggressive 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). As these tumors are very rare, 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). 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.

1.3 Rationale for Tazemetostat Treatment

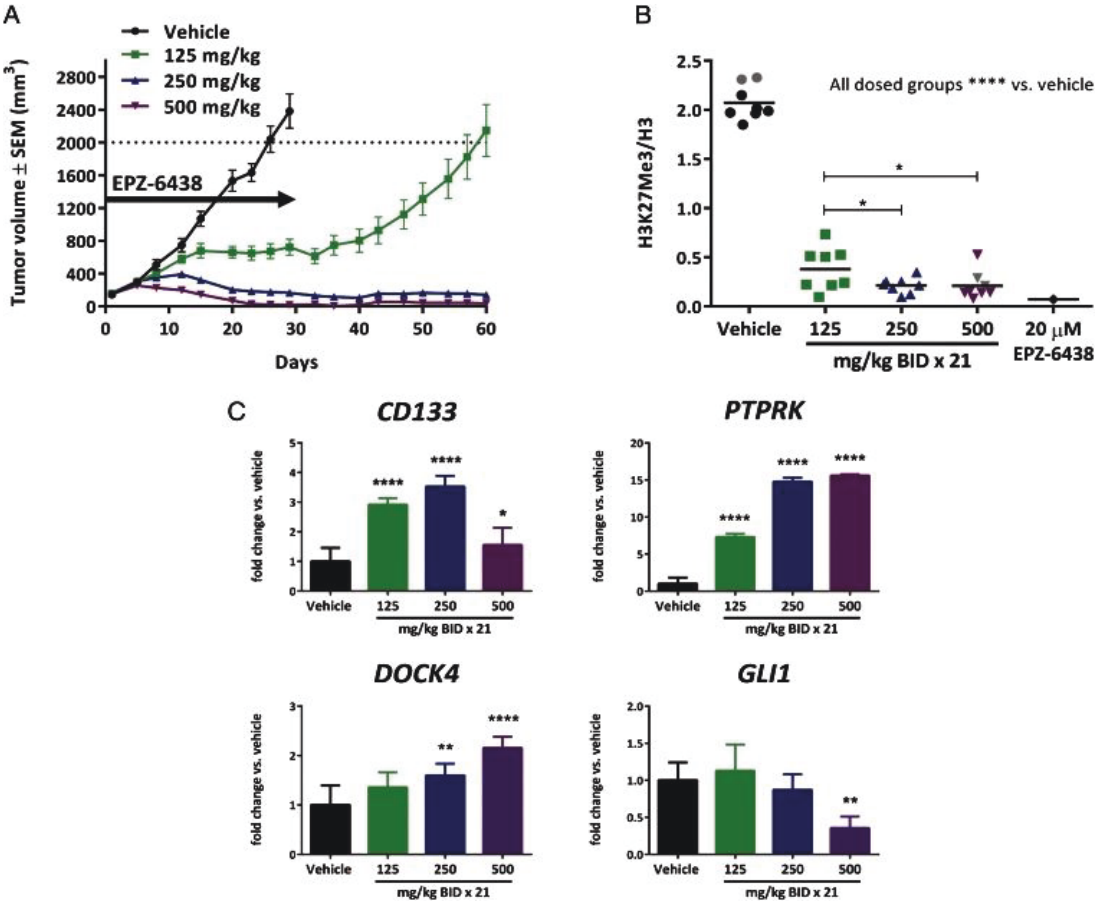
In INI1-negative tumors, EZH2 activity is deregulated, inducing aberrant oncogenic gene expression (Wilson, 2010; Alimova, 2013). Tazemetostat has been shown to induce apoptosis and differentiation in INI1-negative MRT cell lines (Knutson, 2013). In xenograft-bearing mice, treatment with tazemetostat 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 1 study E7438-G000-101 demonstrates early but compelling clinical activity in subjects with INI1-negative tumors [unpublished data]. To date, of the six treated subjects with INI1-negative tumors (MRT and ES), there have been three subjects with objective responses (1 CR and 2 PRs). With one MRT subject with pathologically confirmed complete remission continuing on treatment through Week 44 on study and two 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 three subjects with advanced synovial sarcoma experienced progressive disease, although only one was treated at the recommended Phase 2 dose (RP2D) [unpublished data].

1.4 Tazemetostat

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 *EZH2* mutated at 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-deficient (also known as SNF5, SMARCB1, or BAF47) 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 2) (Knutson, 2013).

Figure 2 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, with or without doxorubicin, in animal models (Knutson, 2014) and in sarcomas in combination with doxorubicin (Kawano, 2016). Finally, administration of tazemetostat led to dose- and time-dependent decreases in intracellular H3K27 methylation in both tumor and selected non-tumor tissues (Knutson, 2014).

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 components SMARCA2 and SMARCA4 within ovarian cancers appears to be specific to SCCOHT. A panel of ovarian cancer cell lines of different histologies with and

without SMARCA2 and 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. The effects of EZH2 inhibition on SMARCA4-negative ovarian cancer cells are context specific, since other cell types with SMARCA4 deletion, such as lung carcinoma cell lines, do not exhibit anti-proliferative affects with EZH2 inhibitor treatment [Epizyme internal communication] (Chan-Penebre, 2017).

1.4.1 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 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 and a mean $t_{1/2}$ of approximately 3 to 5 hours. Quantifiable plasma concentrations of both tazemetostat and its metabolite, ER-897387 were measurable up to 12 hours post-dose. Tazemetostat area under the concentration-time curve (AUC) increased in a greater than dose-proportional fashion after a single dose and at steady-state. Tazemetostat maximum plasma concentration (C_{max}) 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. 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 AUC from zero extrapolated to infinity (AUC0-∞) and Cmax values approximately 18% and 28%, respectively, relative to 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 AUC0-∞ is not clinically significant, and therefore, tazemetostat can be taken without regards to meals.

PK assessments (including cerebrospinal fluid, when possible) will help characterize the PK and exposures to tazemetostat and its metabolite in the pediatric subject population.

1.4.2 Clinical Experience

As of 24 May 2019, a total of 822 clinical study subjects had received tazemetostat as monotherapy, or in combination with prednisolone in 1 cohort of 1 study, across six phase 1 and phase 2 studies, as well as an extension study.

Tazemetostat is under investigation in clinical trials for the treatment of:

- non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).
- mesothelioma.
- integrase interactor 1 (INI1) or switch/sucrose nonfermentable (SWI/SNF)-related, matrix-associated, actin-dependent regulator of chromatin (SMARC), subfamily A, member 4 (SMARCA4)-deficient tumors in both adult and pediatric populations (including synovial sarcoma, rhabdoid tumors, renal medullary carcinoma, epithelioid sarcoma [ES], other INI1- or SMARCA4 deficient tumors).

Among the 822 adult and pediatric subjects treated, the majority 790 (96%) of subjects experienced at least 1 TEAE, with 552 (67%) subjects reporting TEAEs considered treatment related. Of subjects with TEAEs, 52% had TEAEs of grade 3 or 4 severity. Treatment related grade 3 or 4 TEAEs were infrequently reported among subjects with TEAEs (18%).

Forty-three percent (353/822) of all adult and pediatric subjects who received tazemetostat in phase 1 and 2 studies, experienced a treatment-emergent SAE. Treatment-related SAEs were reported in 66 (8%) of subjects. Half of all pediatric subjects (50%) experienced a TESAE, and 9 pediatric subjects (10%) experienced a TESAE that was assessed as treatment related.

A total of 135/822 (16%) adult and pediatric subjects died during treatment or within 30 days after the last dose of tazemetostat, compared with 25 (28%) subjects who died in pediatric study EZH-102 as of 24 May 2019; the vast majority (95%) of these 135 deaths were attributed to either progressive disease or the disease under study (60 and 69, respectively, for a total of 129/135 deaths). In addition, 2 deaths of adult lymphoma patients, one that was due to intestinal obstruction and one with an unknown cause, were assessed as possibly treatment related by the Investigator.

Adverse events of special interest have been identified: CCI /T-ALL, MDS, AML, and other myeloid malignancies like MPN. As of 24 May 2019, there have been AESIs of myeloid malignancies reported in 5 of the 725 subjects in the adult lymphoma population treated with tazemetostat, including 2 cases of MDS (both possibly related), 2 cases of AML (both unrelated), and 1 case of MDS that later transformed to AML (possibly related). However, all 5 cases were heavily confounded by prior treatments. The degree of risk of myeloid malignancies remains uncertain based on paradoxical preclinical literature data, and the risk may be no greater than that expected in this subject population in general. There has been 1 AESI of CCI reported in a

pediatric subject. Refer to Section 10.4 of this protocol and to the current IB for further descriptions of AESIs.

As tazemetostat is a bromide salt, bromide levels were measured in a phase 1 study of tazemetostat in adults (Study E7438-G000-101) and in pediatric subjects (Study EZH-102). As of 24 May 2019, bromide elevation was reported in 3 (3.3%) of 90 pediatric subjects, all of which were considered to be related to tazemetostat treatment. See Section 1.6.2 for additional information. These elevated blood bromide levels were not associated with symptoms of bromide toxicity.

Treatment-emergent AEs are summarized in the Section 1.6.5 (anticipated safety profile) of this protocol and in the current IB.

Thus far, tazemetostat has shown clinical activity in subjects across the tazemetostat program, including objective responses and sustained disease stabilization in the indications shown below.

Table 1 Preliminary Efficacy Results for Tazemetostat Across Studies (ITT Populations)

Population Indication(s)	Study Number	N	ORR (%) (95% CI)	BOR of SD (%)
Adult population				
Synovial sarcoma (SS)	CCI	33	0	36.4
Malignant mesothelioma	EZH-203 (part 2)	61	3.3 (0.4-12.1)	62.3
Epithelioid sarcoma (ES)	CCI (Cohort 5)	62	15 (6.9-25.8)	56
Follicular lymphoma – mutant	E7438-G000-101 ph 2	45	73 (58.1-85.4)	22
Follicular lymphoma – wild type	E7438-G000-101 ph 2	54	33 (21.1-47.5)	30
DLBCL	E7438-G000-101 ph 2	234	16.2 (11.8-21.6)	20.5
Pediatric population				
ES (INI1-)	EZH-102	8	25 (3.2-65.1)	50
Various INI1-solid tumors combined (ATRT, MRT, other INI1-, ES, RTK, RMC, SS, chordoma, rhab, ME carcinoma)	EZH-102	85	13 (6.6-22.0)	20

Abbreviations: ATRT = atypical teratoid rhabdoid tumor; BOR = best overall response; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ES = epithelioid sarcoma; INI1- = integrase interactor 1 negative; ITT = intent to treat; ME = myoepithelial; MRT = malignant rhabdoid tumor; N = number of subjects treated as of efficacy data cut; NE = not estimable; ORR = objective response rate (CR+PR); OS = overall survival; ph = phase; PFS = progression-free survival; rhab = selected tumors with rhabdoid features; RMC = renal medullary carcinoma; RTK = rhabdoid tumor of the kidney; SD = stable disease (≥32 weeks); SS = synovial sarcoma.

Note: Response analyses are based on investigators' assessment.

Note: Summary statistics were calculated with Kaplan-Meier analysis and CIs using the Brookmeyer and Crowley method. Exact binomial CI is presented.

Note: Data cut dates are 08 June 2019 for E7438-G000-101 phase 2; 10 February 2019 (ORR, SD) and 17 September 2018 (PFS, OS) for EZH-102; 17 September 2018 (Cohort 5) and 31 July 2019 (other cohorts) for CCI; 01 August 2019 for EZH-203.

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. Clinical experience is further detailed in the current tazemetostat IB.

1.4.3 Pharmacodynamics

The pharmacodynamics (PD) of H3K27 methylation in the pediatric population has not previously been studied, however the inhibition of H3K27me3 has been demonstrated to be necessary for tazemetostat efficacy in nonclinical models. Preliminary PD data from peripheral blood monocytes (PBMs) demonstrated a relationship between Cycle 1, Day 15 tazemetostat exposure and H3K27me3 levels, with consistent and significant post-dose reductions in H3K27me3 observed at the 900 and 1200 mg/m^2 doses.

1.5 Rationale

1.5.1 Study Rationale

The clinical benefit of tazemetostat has not yet been established for pediatric subjects. This study will identify an RP2D for tazemetostat in pediatric subjects and characterize the safety profile and PK in this population. As there is a reasonable expectation based on nonclinical data and the Phase 1 experience in adults that clinical activity may be observed in children with INI1- and SMARCA4-negative tumors and synovial sarcoma, subjects will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.5.2 Dose Rationale

1.5.2.1 Starting Dose for Escalation

Physiologically based PK modeling of the existing adult exposure data obtained in the FTIH study E7438-G000-101 informed the selection of the starting dose for this pediatric study. Systemic exposure data in adults together with in vitro data on the absorption, distribution, metabolism, and elimination (ADME) of tazemetostat were used to build a PK model that accurately described the time-concentration data from adults. This model was then transformed accounting for known age and developmental changes in physiological parameters, such as organ size and blood flows, as well as biochemical factors, e.g., the maturation of drug metabolizing enzyme expression and activity, to derive a series of age-based pediatric models for the PK of tazemetostat.

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

Preliminary PK parameters from the 240 mg/m^2 BID and 300 mg/m^2 BID dose cohorts in Study EZH-102 were determined and are displayed in Table 2, which follows.

Table 2. Preliminary Geometric Mean (CV%) PK Parameters from Subjects 1 to 18 Years of Age in the 240 mg/m^2 BID Through 1200 mg/m^2 BID Dose Cohorts in Study EZH-102

Dose mg/m^2 BID	Cycle 1 Day	n	Cmax ng/mL	Tmax[a] h	$AUC_{(0-8)}$[b] ng•h/mL	$AUC_{(0-24)}$[c] ng•h/mL
240	1	8	538 (72.7)	1 (1 – 4)	1360 (50.3)	NC
	15	7	324 (95.4)	2 (1 – 4)	935 (74.1)	2020 (74.9)
300	1	6	444 (50.5)	1 (1 – 2)	1330 (96.9)	NC
	15	5	357 (91.7)	1 (1 – 2)	1100 (101)	2370 (103)
400	1	6	711 (108)	1.5 (1 – 4)	2120 (69.0)	NC
	15	6	563 (211)	1 (1 – 4)	1680 (141)	3610 (134)
520	1	7	1900 (73.3)	2 (1 – 4)	7300 (85.8)	NC
	15	6	2130 (20.8)	1 (1 – 2)	5870 (34.4)	12,500 (35.1)
700	1	6	1830 (101)	1.5 (1 – 4)	6650 (104)	NC
	15	6	1150 (63.9)	1 (1 – 4)	3660 (52.1)	8140 (65.6)
900	1	6	4380 (35.8)	1.5 (1 – 2)	14,300 (33.7)	NC
	15	5	2380 (52.0)	2 (2 – 4)	9810 (33.3)	21,000 (32.6)
1200	1	6	1950 (61.4)	2 (2 – 8)	6640 (85.2)	NC
	15	6	3860 (31.6)	2 (1 – 2)	13,900 (38.2)	29,700 (43.9)

Abbreviations: BID= twice daily, C_{max}= maximum plasma concentration, T_{max}= Time to maximum concentration, AUC=Area under the concentration-time curve.

[a]Median (range) T_{max}
[b]Last PK blood sample collection time point = 8 h
[c]$AUC_{(0-24)}$ on Day 15 calculated as $AUC_{(0-12)} \times 2$
NC = not calculated

In children 1 to 18 years of age, the mean $AUC_{(0-24)}$ and C_{max} on Day 15 did not increase in a dose-proportional fashion at each dose level. There was an apparent trend for mean $AUC_{(0-24)}$ and C_{max} on Day 15 to increase in a greater than dose-proportional fashion when the tazemetostat dose increased from 240 mg/m^2 BID to 1200 mg/m^2 BID. The mean $AUC_{(0-24)}$ after administration of tazemetostat 1200 mg/m^2 BID is greater than the $AUC_{(0-24)}$ observed from the 50 mg/kg day dose group in which thymic lymphoma was observed in a single female rat in the 18-week toxicity study conducted in juvenile rats (18,500 ng•h/mL). However, the mean $AUC_{(0-24)}$ after administration of tazemetostat 1200 mg/m^2 BID is approximately 4-fold less than the $AUC_{(0-24)}$ from male rats in the 150/300 mg/kg day dose group (125,000 ng•h/mL) in which the incidence of thymic lymphoma appeared to increase to 4 of 21 animals in the 18-week toxicity study conducted in juvenile rats. (For more information on the results from the 13-week see Section 1.6.1.)

1.5.2.2 Determination of the Recommended Phase 2 Dose (RP2D) for Expansion

The Clinical Safety Review Committee (CSRC) convened on 06-Jul-2017 to review safety and PK from subjects at the 1200 mg/m^2 dose level. The mean $AUC_{(0-24)}$ after administration of tazemetostat 1200 mg/m^2 BID was 29,700 ng•h/mL was approximately 2-fold greater than the mean $AUC_{(0-24)}$ after administration of the highest dose evaluated dose (1600 mg BID) in adult subjects in Study E7438-G000-101 (15,400 ng•h/mL). No DLTs were observed at 1200 mg/m^2 dose level. Although the Rolling 6 statistical design supported the escalation to the next dose

level of 1600 mg/m^2, elevated chloride levels were observed in 3/6 evaluable subjects in the 1200 mg/m^2 dose level, and at previous dose levels as well. As tazemetostat is formulated as a hydrobromide salt, it was considered that the hyperchloremia could be an artifact of elevations in serum bromide. Thus, bromide levels were evaluated in two of five subjects on active treatment and were found to be elevated, though without any associated clinical signs or symptoms of neurologic toxicity associated with bromism. The CSRC reviewed data demonstrating a PK:PD relationship between Cycle 1 Day 15 tazemetostat exposure and H3K27me3 levels in PBMs consistent and significant post-dose reductions in H3K27me3 at the 900 and 1200 mg/m^2 doses. Given the occurrence of elevated bromide levels, as well as the PD data, a decision was made by the CSRC to proceed to the dose expansion phase of the protocol with the putative RP2D determined to be 1200 mg/m^2 BID dose level with the understanding that bromide levels as well as clinical signs and symptoms of bromide toxicity would be closely monitored in all newly and currently enrolled subjects receiving tazemetostat with guidelines for immediate dose reduction as indicated.

In this pediatric clinical study, subjects in dose escalation cohorts received BID oral treatment every day. For new patients with ATRT or any INI1-negative tumors with CNS involvement, the starting dose will remain 1200 mg/m^2 BID. For new patients that are non-ATRT, the starting dose will be 520 mg/m^2 BID (See Section 5.3). However, Cohorts 1 and 4 are now closed to enrollment.

As older subjects may prefer to take tazemetostat administered as tablets rather than as an oral suspension, the exposure of tazemetostat administered as tablets in subjects aged 10 years and older was explored in Cohort 4. However, Cohort 4 is now closed to enrollment. The bioavailability of tazemetostat administered as tablets is not expected to be greater than that of tazemetostat when administered as a suspension. Therefore, the safety profile of tazemetostat is expected to be similar when equal doses of tablets and suspension are administered. Due to concerns about tablet burden, subjects in Cohort 4 received tazemetostat 800 mg/m^2 TID (2400 mg/m^2/day equivalent to 1200 mg/m^2 BID).

Tazemetostat may be administered, assuming subject and/or parent/guardian and Investigator consent, until disease progression (treatment failure) or unacceptable toxicity occurs.

1.6 Benefit: Risk Assessments

1.6.1 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. CCI [redacted]

CCI

CCI These studies were conducted in rats that, at initiation of dosing, were approximately 8 weeks old (adolescent rats; standard for support of dosing in adult patients) or 7 days old (juvenile rats; to support dosing of pediatric patients). CCI was not observed in 4-week studies in adolescent or juvenile rats. A brief summary of data from the 13-week studies is provided below in Table 3.

Table 3 Key Findings in 13-Week Rat Studies With Tazemetostat

Study Number	Age of rats at start of study	Tazemetostat doses mg/kg/day	CCI
K14009	~8 week old adolescent rats	100 300 600	
WIL-154506	Post-natal day 7 juvenile rats	50, 100 150/300[1] 150/600	

[1] Rats in the 2 highest dose groups were dosed at 150 mg/kg/day from post-natal day (PND) 7 to PND 21 and escalated to 300 or 600 mg/kg/day thereafter to mitigate acute intolerability noted at very young ages in a previous dose range-finding rat study (WIL-779008) and to ensure adequate exposure.

[2] Group denominator includes main and recovery animals.

[3] Group denominator also includes toxicokinetic animals if sacrificed early or found dead due to CCI.

Steady-state exposures (AUC from 0 to 24 hours [AUC_{0-24}]) in rats at the lowest dose (100 mg/kg/day) at which no CCI occurred in the 13-week adolescent rat study were 2.5- to 8-fold greater than that observed in humans at the recommended Phase 2 dose (RP2D; 800 mg twice daily [BID]) from the ongoing Phase 1/2 Study E7438-G000-101. In male juvenile rats, CCI was not seen at 50 mg/kg/day ($AUC_{(0-24h)}$=6340 ng•h/mL). A low incidence of CCI (2/60) was seen at $AUC_{(0-24h)}$ 18,500-67,200 ng-h/mL and greater for juvenile rats, with higher incidence at $AUC_{(0-24h)}$ 125,000- 290,000 ng-h/mL The first incidence of CCI in juvenile rats occurred at a similar AUC_{0-24h} as the single pediatric patient that developed CCI on Study EZH-102. There have been no cases of CCI in any adult patient given tazemetostat.

All patients will be actively monitored for signs or symptoms of abnormal bone formation during the trial. No incidences of new 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 and after the study as described in Section 8.5.11.

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

1.6.2 Hydrobromide Salt Formulation

An analysis of chloride levels in subjects on Study EZH-102 at the 1200 mg/m^2 dose level showed elevated chloride levels (beyond the ULN) in 5/7 subjects who had been treated at this dose level. Reviewing this finding further, subjects at lower dose levels (4/6 subjects at 900 mg/m^2, 4/6 subjects at 700mg/m^2 and 4/6 subjects at 520 mg/m^2) also demonstrated elevated chloride levels.

Hyperchloremia is considered an artifact resulting from interference of serum bromide with the serum chloride assay (tazemetostat is a bromide salt). Artifactually elevated serum chloride was also noted in repeat-dose nonclinical toxicology studies of tazemetostat in rats and monkeys at tazemetostat doses up to 1000 mg/kg/day. Ion exchange chromatography showed increased serum chloride in these nonclinical studies to be pseudo-hyperchloremia, representing increased bromide. Bromide levels were measured in the Phase 1 study of tazemetostat in adults. Bromide was within normal levels (<6.2 mmol/L) for all subjects taking the oral tablet formulation in doses up to 1600 mg BID. However, mean tazemetostat AUC$_{(0\text{-}24)}$ in children at the 1200 mg/m^2 dose level exceeded that observed in the 1600 mg BID dose group in adults from Study E7438-G000-101. Therefore, the assessment of bromide levels was instituted in Amendment No. 5 for all active and new subjects. Refer to Section 8.5.10 and Table 11 for the schedule of bromide level assessments and to Section 6.5.2 for dose modifications due to bromide toxicity. The chloride assay is being collected locally at every visit as part of the electrolyte panel, which is included in the standard blood chemistry assessment (Table 11).

For more details, refer to the tazemetostat Investigator's Brochure, Version 10.0.

1.6.3 Photo-Reactive Potential

There are nonclinical, in vitro 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 sunscreen and sunglasses, wearing protective clothing, and avoiding tanning beds. Refer to the tazemetostat Investigator's Brochure Version 10.0 for details.

1.6.4 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, or CYP2D6, and that have a narrow therapeutic range should be avoided if possible. For more details, refer to the tazemetostat Investigator's Brochure, Version 10.0.

1.6.5 Anticipated Safety Profile

This section summarizes the anticipated safety profile for tazemetostat based on the clinical experience in 90 pediatric subjects treated as of 24 May 2019 in this ongoing study (EZH-102), on nonclinical toxicology studies, and where noted, on 725 adult subjects treated with tazemetostat.

The following treatment-emergent AEs, regardless of causality, have been observed in ≥10% of pediatric subjects in study EZH-102: vomiting, nausea, fatigue, diarrhea, and anemia.

The following nonserious adverse reactions to tazemetostat treatment have been observed in ≥2% of pediatric subjects in study EZH-102: vomiting, nausea, fatigue, diarrhea, anemia, decreased appetite, constipation, thrombocytopenia, and neutropenia.

Tazemetostat treatment-related SAEs have been reported in 9 (10%) pediatric subjects in study EZH-102. The only serious adverse reaction reported in ≥1 pediatric subject has been decreased appetite (2 subjects).

The most common TEAEs that have led to interruption of tazemetostat dosing in pediatric subjects were: platelet count decreased (7%); hydrocephalus (6%); and thrombocytopenia, neutropenia, diarrhea, intestinal obstruction, dyspnea, hypoxia, and pyrexia (each 2%). The most common TEAEs leading to dose reduction in pediatric subjects have been platelet count decreased and thrombocytopenia, reported in 3 (3%) subjects and 2 (2%), respectively.

In addition, as described in Section 10.4, AESIs identified for the tazemetostat development program include: CCI /T-ALL, MDS, AML, and other myeloid malignancies like MPN. Epizyme considers the risk for CCI /T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients. Myeloid malignancies have been reported in 5 of the 725 subjects in the adult population treated with tazemetostat. The risk of myeloid neoplasias as a result of EZH2 inhibition is considered uncertain based on available literature and Epizyme clinical data. Measures are in place to exclude potential subjects who may be predisposed to developing a myeloid neoplasia from participation in clinical studies and for early identification and monitoring of subjects who may be developing a myeloid neoplasia.

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

Additionally, there are unknown risks of abnormal pregnancy outcomes and drug-drug interactions.

Based on the nonclinical toxicology of tazemetostat, the potential risks associated with treatment include: CCI , bone changes, bile duct hyperplasia, lymphoid depletion, teratogenicity, and phototoxicity.

As per Section 1.6.2, there is a potential risk of bromide toxicity related to the hydrobromide salt used in the formulation of tazemetostat. Signs of bromide toxicity consist of CNS AEs including

lethargy, headache, ataxia, and coma. As described in Section 1.4.2 (clinical experience), bromide elevation was reported in 3 (3.3%) of 90 pediatric subjects as of 24 May 2019, all of which were considered to be related to tazemetostat treatment, but there were no AEs suggestive or indicative of bromide toxicity.

1.6.6 Summary

In vitro and in vivo nonclinical xenograft experiments suggest the potential for clinical antitumor activity in INI1-negative tumors, thus providing a rational potential benefit of tazemetostat in the aforementioned pediatric tumors. Furthermore, in the Phase 1 study of tazemetostat in adults, three subjects with MRT, treated with tazemetostat 800 mg BID, have been enrolled to the ongoing adult study and have demonstrated clinical activity.

Given the available safety and initial activity data of tazemetostat in adult subjects, nonclinical safety profile, nonclinical efficacy data in xenograft models, and unmet need in pediatric patients, there is an appropriate potential benefit to risk consideration to study tazemetostat in pediatric subjects with INI1-negative tumors.

2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary: Dose Escalation	
• To determine the MTD or the RP2D of tazemetostat when administered as an oral suspension BID in pediatric subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors, or synovial sarcoma	• Incidence and severity of TEAEs qualifying as protocol-defined DLTs in Cycle 1 • Establishment of the protocol-defined RP2D and/or MTD
Primary: Dose Expansion	
• To evaluate the antitumor activity of tazemetostat as assessed by overall response rate (ORR) in in pediatric subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria	• ORR: CR + PR for each cohort
Secondary: Dose Escalation	
• To evaluate the preliminary antitumor activity of tazemetostat as assessed by ORR, using disease-appropriate standardized response criteria	• ORR: CR + PR
Secondary: Dose Expansion	
• To determine the PFS and overall survival (OS) at 24 and 56 weeks and overall pediatric subjects with relapsed/refractory ATRT (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria	• PFS at 24 and 56 weeks and overall for each cohort • OS at 24 and 56 weeks and overall for each cohort
Secondary: All Subjects	
• To assess the safety and tolerability of tazemetostat administered as an oral suspension BID and tablet three times daily (TID)	• AEs, clinical laboratory tests, and other safety measures
• To assess the pharmacokinetic (PK) parameters of tazemetostat after administrations as suspension or tablets in pediatric subjects	• PK parameters: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time 0 to last measurable concentration [$AUC_{(0-t)}$], area under the concentration-time curve from time 0 to 12 hours post-dose [$AUC_{(0-12)}$], elimination half-life ($t_{1/2}$), oral clearance (CL/F), oral volume of distribution (Vd/F), first-order absorption rate constant (Ka); if data permit
• To evaluate the duration of response in subjects achieving a CR or PR according to disease-appropriate standardized response criteria	• Response duration

Objectives	Endpoints
Exploratory: All Subjects	
CCI [redacted]	

3 STUDY DESIGN

3.1 Overall Experimental Plan

This is a Phase 1, multicenter, open-label, dose escalation and expansion study of tazemetostat in pediatric subjects with select relapsed or refractory INI1- or SMARCA4-negative tumors. Subjects will be screened for eligibility within 14 days of the planned first dose of tazemetostat. A treatment cycle will be 28 days. Treatment with tazemetostat will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Subjects will receive tazemetostat for a cumulative maximum of 2 years.

3.2 Dose Escalation Phase

The starting dose for the dose escalation phase will be 240 mg/m^2/dose administered orally BID for a total of 480 mg/m^2/day. Dose escalation will proceed in increments of 25%-33% and dose de-escalation will proceed in decrements of 50%.

Table 4. Dose Escalation

Dose Level	Dose of Tazemetostat
Level 0	120 mg/m^2 BID = 240 mg/m^2/day
Level 1 (starting dose)	240 mg/m^2 BID (starting dose) = 480 mg/m^2/day
Level 2	300 mg/m^2 BID = 600 mg/m^2/day
Level 3	400 mg/m^2 BID = 800 mg/m^2/day
Level 4	520 mg/m^2 BID = 1040 mg/m^2/day
Level 5	700 mg/m^2 BID = 1400 mg/m^2/day
Level 6	900 mg/m^2 BID = 1800 mg/m^2/day
Level 7	1200 mg/m^2 BID = 2400 mg/m^2/day
Level 8	1600 mg/m^2 BID = 3200 mg/m^2/day

Abbreviation: BID=twice daily.

A “Rolling 6” dose-escalation design (Table 5) (Skolnik, 2008) will be employed whereby up to six subjects may be concurrently enrolled onto the study. Accrual to the study will only be suspended when awaiting data from six subjects. All safety data during dose escalation will be assessed in real time with appropriate adjustments to enrollment if toxicity is seen. For dose-escalation decisions, a minimum of 22 days of toxicity data (80% of one cycle) must be available for each subject.

Decisions as to whether to enroll a new subject onto the current, next highest, or next lowest dose level will be made based on available data at the time of new subject enrollment and will be made by the CSRC (see Section 11). The dose level assigned will be based on the number of subjects currently enrolled in the cohort, the number of DLTs observed, and the number of subjects at risk for developing a DLT (i.e., subjects enrolled, but who were not yet evaluable for toxicity).

Table 5. Rolling 6 Dose Escalation/De-Escalation Parameters

Subjects Enrolled	# Subjects with DLT	# Subjects without DLT	# Subjects with Toxicity Data Pending	Decision When Next Subject Enrolled
2	0, 1	Any	Any	Stay
2	2	0	0	De-escalate
3	0	0, 1, 2	3, 2, 1	Stay
3	0	3	0	Escalate
3	1	0, 1, 2	2, 1, 0	Stay
3	≥2	Any	Any	De-escalate
4	0	0, 1, 2, 3	4, 3, 2, 1	Stay
4	0	4	0	Escalate
4	1	0, 1, 2, 3	3, 2, 1, 0	Stay
4	≥2	Any	Any	De-escalate
5	0	0 1, 2, 3, 4	5, 4, 3, 2, 1	Stay
5	0	5	0	Escalate
5	1	0, 1, 2, 3, 4	4, 3, 2, 1, 0	Stay
5	≥2	Any	Any	De-escalate
6	0	0, 1, 2, 3, 4	6, 5, 4, 3, 2	Suspend
6	0	5, 6	1, 0	Escalate
6	1	0, 1, 2, 3, 4	5, 4, 3, 2, 1	Suspend
6	1	5	0	Escalate
6	≥2	Any	Any	De-escalate

Abbreviation: DLT=dose-limiting toxicity

The MTD will be determined based on the incidence of DLTs in Cycle 1, although toxicities occurring in subsequent cycles will also be reviewed. If serious toxicities are observed at the MTD in later cycles, a reduction of the MTD may be considered.

3.3 Dose Expansion Phase

For new patient dosing, refer to Section 5.3. Subjects will be enrolled into the following cohorts:

- Cohort 1 – Subjects with ATRT (closed to enrollment)
- Cohort 2 – Subjects with MRT/RTK/select tumors with rhabdoid features
- Cohort 3 – Subjects with INI1-negative tumors
- Cohort 4 – Subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (closed to enrollment)

Note, as initially designed, the dose expansion portion of the study was to enroll only subjects with rhabdoid tumors. This group has been divided into two separate cohorts (Cohort 1 and

Cohort 2) as initial subject screening and enrollment trends into the dose-escalation portion of the study indicate that enrollment would be heavily weighted toward ATRT tumor types, therefore, losing the potential to evaluate subjects with non-CNS rhabdoid tumors such as MRT and RTK. Cohort 1 is now closed to enrollment. In addition, as subjects with INI1-negative tumors are being enrolled into the dose-escalation portion of the study, Cohort 3 has been added to the expansion portion of the study in order to evaluate for antitumor response that may be missed in the dose-escalation portion of the study. For these reasons, as well as antitumor activity seen in the current Phase 1 and ongoing Phase 2 studies in adults with INI1-negative tumors and synovial sarcoma, Cohorts 1, 2, and 3 were added as part of Amendment 3. In addition, Cohort 4 was added as part of Amendment 5 to evaluate the administration of tazemetostat in tablet formulation to pediatric subjects who can swallow tablets, which may be more palatable. Cohort 4 is now closed to enrollment.

3.4 Rules for Suspension of Enrollment and Dosing

3.4.1 Rules for Suspension in Any Phase

The Investigators, Institutional Review Board (IRB)/Ethics Committee (EC), regulatory agencies, and CSRC will be urgently informed and the Quarterly Safety Review (QSR) committee promptly convened to review the data and to make recommendations for potential changes in study conduct, including suspension of dose escalation or expansion. The rule will be set in motion 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
- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress)
- CCI /T-ALL

If a new case of CCI /T-ALL occurs, the patient will be discontinued from treatment, and enrollment of new patients will be suspended. The risk/benefit of the drug will be assessed via an ad hoc QSR and a decision will be made (continue the study or not). The study will not be restarted until QSR has made a decision and has agreed upon a course of action. Following the decision, and as per QSR charter, communication to Health Authorities, IRBs/ECs and Investigators will occur. However, patients on study who continue to derive clinical benefit at this time will be maintained on therapy. For more details on AESIs, refer to Section 10.4.

3.4.2 Rules for Suspension of Dose Expansion

The CSRC will convene to review the aggregate safety experience and to assess termination of dose expansion if any of the DLT conditions (see Section 6.3) are met in ≥33% subjects in a cohort. Special attention will be paid to AEs associated with bromide toxicity, as well as bromide values in the range associated with severe bromide toxicity, and AESIs (see Section 10.4). The CSRC may also recommend suspension of tazemetostat dose expansion based upon other conditions as deemed medically appropriate.

3.5 Estimated Study Duration

3.5.1 Study Duration for Participants

The study duration is approximately 24 months for each subject. The duration of screening for each subject will be approximately 14 days. The subject accrual period is planned for approximately 15 months. The duration of treatment will vary for each subject. Subjects may receive tazemetostat for a cumulative maximum of 2 years. Subjects will be followed for safety for approximately 30 days after the last dose of tazemetostat. For subjects that discontinue dosing, participation will continue for survival follow-up and response for 2 years from first dose of tazemetostat.

3.5.2 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 safety follow-up visit or the long-term survival follow-up period, whichever is later. The study may end prior to this if 80% of enrolled subjects are deceased prior to the collection of the last survival follow-up.

4 SUBJECT POPULATION

4.1 Number of Subjects

A total of approximately 120 subjects will be enrolled in this study. Up to 48 subjects are estimated to be enrolled during dose escalation (subjects who discontinue in absence of a DLT prior to the completing of the DLT evaluation period may be replaced). Up to 72 subjects are estimated to be enrolled during Dose Expansion. See Section 14.2.1 for sample size assumptions.

4.2 Inclusion Criteria

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

1. Age (at time of consent/assent): ≥6 months to <18 years of age
   - Cohort 4 only: ≥10 years to <18 years
2. Performance Status:
   - If <12 years of age: Lansky Performance Status >50% (see Appendix 1)
   - If ≥12 years of age: Karnofsky Performance Status >50% (see Appendix 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/assent
4. Has a life expectancy of >3 months
5. Has relapsed or refractory disease and no standard treatment options as determined by locally or regionally available standards of care and treating physician's discretion
6. Is ineligible or inappropriate for other treatment regimens known to have effective potential
7. 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
8. 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
9. Prior therapy(ies), if applicable, must be completed according to the criteria below:

Prior Therapy	Time from Last Prior Therapy
Other investigational agent (any medicinal product that is not approved in the country of treatment for any indication, adult or pediatric)	At least 30 days or five half-lives, whichever is longer, since last dose of an investigational agent prior to the first dose of tazemetostat
Chemotherapy: cytotoxic	At least -14 days since last dose of chemotherapy prior to the first dose of tazemetostat
Chemotherapy: nitrosoureas	At least 6 weeks since last dose of nitrosoureas prior to the 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 the first dose of tazemetostat
Monoclonal antibody(ies)	At least 28 days since last dose of any monoclonal antibody prior to the first dose of tazemetostat
Immunotherapy (e.g., tumor vaccine)	At least 6 weeks since last dose of immunotherapy agent(s) prior to the 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
Hematopoietic growth factor	At least 14 days from last dose of hematopoietic growth factor prior to the first dose of tazemetostat
Hematopoietic cell transplantation (allogeneic or autologous)	At least 60 days from infusion of hematopoietic cells prior to the first dose of tazemetostat

10. Has adequate hematologic (bone marrow and coagulation factors), renal and hepatic function as defined by criteria below:

System	Laboratory Value	
Hematologic (BM Function)		
Hemoglobin[a]	≥8 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		
Calculated Creatinine Clearance[e]	≥50 mL/min/1.73 m^2	
OR		
Serum creatinine based on age/gender		
AGE	**Male**	**Female**
6 months to 1 year	0.6 mg/dL (53 µmol/L)	0.5 mg/dL (44 µmol/L)
1 to <2 years	0.6 mg/dL (53 µmol/L)	0.6 mg/dL (53 µmol/L)
2 to <6 years	0.8 mg/dL (71 µmol/L)	0.8 mg/dL (71 µmol/L)
6 to <10 years	1 mg/dL (88 µmol/L)	1 mg/dL (88 µmol/L)
10 to <13 years	1.2 mg/dL (106 µmol/L)	1.2 mg/dL (106 µmol/L)
13 to <16 years	1.5 mg/dL (133 µmol/L)	1.4 mg/dL (124 µmol/L)

≥16 years	1.7 mg/dL (150 µmol/L)	1.4 mg/dL (124 µmol/L)
Hepatic Function		
Total bilirubin[f]	<1.5 × ULN for age	
ALT or AST[g]	<3 × ULN	

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BM, bone marrow; INR, international normalized ratio; 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 but if only PT can be performed in the testing laboratory that is acceptable
e. Creatinine clearance by 24-hour urine or radioisotope glomerular filtration rate
f. Eligibility can be determined by either total or conjugated bilirubin
g. If attributed to tumor involvement, AST and ALT <5xULN

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.

11. **For subjects with CNS involvement:** Subjects must have:

    - Deficits that are stable for a minimum of 14 days prior to first dose of study drug, or
    - Seizures that are stable, not increasing in frequency or severity and controlled on current anti-seizure medication(s) for a minimum of 7 days prior to first dose of study drug, or
    - Treated brain metastases without evidence of progression (new or enlarging brain metastases by imaging 4 weeks prior to the first dose of study drug), and are on stable or tapering doses of steroids for at least 7 days prior to first dose of study drug.

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

12. Has a left ventricular (LV) fractional shortening of >27% or an LV ejection fraction of ≥50% by echocardiogram (ECHO) or multigated acquisition scan (MUGA) and New York Heart Association Class ≤2.
13. Has a QT interval corrected by Fridericia's formula (QTcF) ≤450 msec
14. Is able to swallow and retain orally administered medication and does not have any uncontrolled gastrointestinal (GI) condition such as nausea, vomiting or diarrhea, or any

clinically significant GI abnormalities that may alter absorption such as malabsorption syndromes, hereditary fructose intolerance, glucose-galactose malabsorption, sucrose-isomaltase insufficiency, or major resection of the stomach and/or bowels.

NOTE: Nasogastric and gastrostomy tube administration of the oral suspension formulation of study drug is permitted.

15. Has sufficient tumor tissue (slides or blocks) available for central confirmatory testing of immunohistochemistry (IHC) and/or cytogenetics/FISH and/or DNA mutation analysis (required for study entry but enrollment based on local results).
16. Is willing and able to comply with all aspects of the protocol as judged by Investigator.
17. **For female subjects of childbearing potential:** Subject must:
    - Have a negative beta-human chorionic gonadotropin (β-hCG) pregnancy test at time of Screening and within 72 hours 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 non-hormonal contraception, as defined in Section 8.5.11 from start of Screening until 6 months following the last dose of study treatment 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 8.5.11), or
    - Have a male partner who is vasectomized with confirmed azoospermia.
18. **For male subjects with a female partner of childbearing potential:** Subject must:
    - Be vasectomized or
    - Agree to use condoms as defined in Section 8.5.11 from the first dose of tazemetostat until 3 months following the last dose of tazemetostat, or
    - Have a female partner who is NOT of childbearing potential
19. **For subjects enrolling at sites in France only:** Is either affiliated with or a beneficiary of a social security category

4.2.1 For Dose Escalation Only

To be eligible for enrollment in dose escalation, a subject must meet ALL of the following criteria in addition to the inclusion criteria listed above for all subjects:

1. Has **evaluable** disease as defined as lesions that can be accurately measured at least in one dimension by radiographic examination or physical examination or other lesions such

as bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis or hepatosplenomegaly from disease.

2. Has one of the following histologically confirmed tumors:

   - Rhabdoid tumor:
     - Atypical teratoid rhabdoid tumor (ATRT) (Closed to enrollment)
     - Malignant rhabdoid tumor (MRT)
     - Rhabdoid tumor of the kidney (RTK)
     - Selected tumors with rhabdoid features
   - INI1-negative tumor:
     - Epithelioid sarcoma (ES)
     - Epithelioid malignant peripheral nerve sheath tumor (EMPNST)
     - Extraskeletal myxoid chondrosarcoma (EMC)
     - Myoepithelial carcinoma
     - Renal medullary carcinoma (RMC)
     - Other INI1-negative malignant tumors (e.g., de-differentiated chordoma)

       NOTE: Requires prior Sponsor approval
   - Synovial sarcoma with SS18-SSX rearrangement (closed to enrollment)

   NOTE: Evidence of diagnostic pathology of original biopsy confirmed by a CLIA/College of American Pathologists (CAP) other Sponsor-approved certified laboratory must be available.

3. **For subjects with ATRT, MRT, RTK, or tumors with rhabdoid features only:** The following test results must be available:

   - Morphology and immunophenotypic panel consistent with rhabdoid tumor, and
   - Loss of INI1 or SMARCA4 confirmed by IHC, or
   - Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss or mutation when INI1 or SMARCA4 IHC is equivocal or unavailable

4. **For subjects with INI1-negative tumor only*:*** The following test results must be available:

   - Morphology and immunophenotypic panel consistent with INI1-negative tumors, and
   - Loss of INI1 confirmed by IHC, or
   - Molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC is equivocal or unavailable

5. **For subjects with synovial sarcoma only*:*** The following test results must be available:

    - Morphology consistent with synovial sarcoma, and
    - Cytogenetics or FISH and/or molecular confirmation (e.g., DNA sequencing) of SS18 rearrangement t(X;18)(p11;q11)

4.2.2 For Dose Expansion Only

To be eligible for enrollment in the Dose Expansion part, a subject must meet ALL of the following criteria in addition to the inclusion criteria for all subjects listed above:

1. Has **measurable** disease as defined in Section 8.5.3
2. Has one of the following histologically confirmed tumors:

    - Cohort 1 (closed to enrollment):
        - Atypical teratoid rhabdoid tumor (ATRT)
    - Cohort 2:
        - Malignant rhabdoid tumor (MRT)
        - Rhabdoid tumor of the kidney (RTK)
        - Selected tumors with rhabdoid features
    - Cohort 3 (INI1-negative tumors):
        - Epithelioid sarcoma (ES)
        - Epithelioid malignant peripheral nerve sheath tumor (EMPNST)
        - Extraskeletal myxoid chondrosarcoma (EMC)
        - Myoepithelial carcinoma
        - Renal medullary carcinoma (RMC)
        - Chordoma (poorly differentiated or de-differentiated)
        - Other INI1-negative malignant tumors **NOTE:** Requires prior Sponsor approval
    - Cohort 4 (closed to enrollment):
        - One of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement

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

3. For subjects with ATRT/MRT/RTK only - have the following test results available:

    - Morphology and immunophenotypic panel consistent with rhabdoid tumor, and
    - Loss of INI1 or SMARCA4 confirmed by IHC, or
    - Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss or mutation when INI1 or SMARCA4 IHC is equivocal or unavailable

4. For subjects with INI1-negative tumors only – have the following test results available:
    - Morphology and immunophenotypic panel consistent with INI1-negative tumors, and
    - Loss of INI1 confirmed by IHC, or
    - Molecular confirmation of tumor bi-allelic INI1 loss/mutation when INI1 IHC is equivocal or unavailable
5. For subjects with synovial sarcoma with SS18-SSX rearrangement (in Cohort 4 only; Cohort 4 is closed to enrollment) - have the following test results available:
    - Morphology consistent with synovial sarcoma, and
    - Cytogenetics or FISH and/or molecular confirmation (e.g., DNA sequencing) of SS18 rearrangement t(X;18)(p11;q11)
6. **For subjects to be enrolled in Cohort 4 (Cohort 4 is closed to enrollment):** Able to swallow and retain orally administered tablets.

4.3 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 EZH2.
2. Is being actively treated for another concurrent malignancy or is less than 5 years from completion of treatment for another malignancy.
3. Has participated in another interventional clinical study and received investigational drug within 30 days or five half-lives, whichever is longer, prior to the planned first dose of tazemetostat.
4. Has had major surgery within 2 weeks prior to enrollment.

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

5. Has 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 at Screening. Cytogenetic testing and DNA sequencing will be conducted by a central laboratory following an abnormal result of bone marrow aspirate/biopsy.
6. Has a prior history of CCI /T-ALL.
7. Has clinically active heart disease including prolonged QTcF (>450 msec).
8. Is currently taking any prohibited medication(s) as described in Section 7.3.

9. 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.
10. Has an active infection requiring systemic treatment.
11. Is immunocompromised (ie, congenital immunodeficiency), including subjects with a known history of infection with human immunodeficiency virus (HIV).
12. Has known history of chronic infection with hepatitis B virus (hepatitis B surface antigen positive) or hepatitis C virus (detectable HCV RNA).
13. Has had a symptomatic venous thrombosis within 14 days prior to study enrollment.

    NOTE: Subjects with a history of a deep vein thrombosis 14 days prior to study enrollment who are on anticoagulation therapy with low molecular weight heparin are eligible for this study.

14. **For subjects with CNS involvement (primary tumor or metastatic disease):** Have any active bleeding, or new intratumoral hemorrhage of more than punctate size on Screening MRI obtained within 14 days of starting study drug, or known bleeding diathesis or treatment with anti-platelet or anti-thrombotic agents.
15. Has known hypersensitivity to any of the components of tazemetostat or other inhibitor(s) of EZH2, or hypersensitivity to Ora-sweet or methylparaben.
16. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements.
17. **For female subjects of childbearing potential:** Is pregnant or nursing

    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.

5 INVESTIGATIONAL PRODUCT

5.1 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). Two formulations will be used in this trial: oral suspension and tablets.

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

Oral Suspension

	Investigational Product
Product name:	Tazemetostat (EPZ-6438)
Formulation description:	Oral Suspension of Tazemetostat API suspended in an Ora-sweet mixture
Dosage form:	Powder for Oral Suspension
Physical Description:	A powder for oral suspension in HDPE bottles or foil-laminate pouches.
Route/Schedule/Duration:	Oral/ BID/Continuous

Abbreviations: BID, twice daily; HDPE, high-density polyethylene

Tablet Formulation (Cohort 4 Only)

	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
Route/Schedule/Duration:	Oral/TID/Continuous

Abbreviations: TID, three times daily

5.2 Preparation, Handling, and Storage of IP

Preparation: The oral suspension is prepared by mixing the tazemetostat powder with Ora-sweet® to produce an oral suspension of 30 mg tazemetostat (as free base) per mL of suspension. Please see Pharmacy Manual for details. No preparation is required for the tablet formulation.

Handling: Please see Pharmacy Manual for details.

Storage: Please see Pharmacy Manual for details.

5.3 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 administered to newly enrolled subjects: Based on benefit-risk assessment of the population studied in this clinical trial, following a report of CCI in a pediatric patient, from the time Amendment 7.0 approval to the completion of enrollment, the following doses will be the starting dose for new enrolled patients: For new patients with ATRT or any INI1-negative tumors with CNS involvement, the starting dose will remain 1200 mg/m^2 BID. For new patients that are non-ATRT, the starting dose will be 520 mg/m^2 BID. (See Section 6.5.3).

Tazemetostat administered as an oral suspension: The starting dose of tazemetostat (for dose escalation only) will be 240 mg/m^2/dose given BID (based on free base) = 480 mg/m^2/day. The amount of suspension per dose is calculated based on the subject's body surface area (BSA) and the assigned dose level. After the completion of Cycle 1, if a subject is unable to continue dosing with the oral suspension formulation due to adherence issues, the Medical Monitor should be contacted to discuss the possibility of switching to tablet dosing options.

Tazemetostat administered as a tablet (subjects in Cohort 4 only; Cohort 4 is closed to enrollment): Tazemetostat will be orally administered at the dose of 800 mg/m^2 TID (2400 mg/m^2/day). Please see CCI for tablet dosing nomogram. This will provide instruction on the number of tablets to be taken based on BSA. After the completion of Cycle 1, if a subject is unable to continue dosing TID with the tablet formulation because of the quantity of tablets or schedule, the Medical Monitor should be contacted to discuss the possibility of switching to BID tablet dosing or BID suspension dosing.

For subjects on the tazemetostat BID oral suspension schedule, doses should be administered as close to 12 hours apart as possible, but there should be no less than 8 hours between doses. For subjects on the TID tablet schedule, doses should be administered as close to 8 hours apart as possible, but there should be no less than 4 hours between doses. Doses may be taken with or without food.

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

Refer to the Pharmacy Manual for more information on drug suspension calculation, preparation, and handling.

Missed Doses

Tazemetostat doses must be taken at least 8 hours apart for BID dosing and at least 4 hours apart for TID dosing. 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 BID dosing or less than 4 hours until the next TID dosing.

5.4 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 FDA 1572, curriculum vitae of principal Investigator 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.

5.5 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 suspension/number 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.

6 STUDY TREATMENT

6.1 Treatment Assignment

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

6.2 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 sun screen and sun glasses, wearing protective clothing, and avoiding tanning beds.

6.3 Dose-Limiting Toxicity (DLT)

A DLT will be determined in the first treatment cycle only (Day 1 to Day 28) of dose escalation and will be graded according to the CTCAE version 4.03. A DLT will be defined as a significant adverse reaction (with the exception of tumor progression) that occurred any time from the initial dose of study treatment though the end of the first cycle of treatment in dose escalation that meets any of the following criteria:

- **Non-hematologic toxicity:** any other Grade 3 or greater **non-hematologic** toxicity except:
    - alopecia
    - fatigue/asthenia
    - transient myalgia/arthralgia
    - Grade 3 vomiting or diarrhea that resolves to ≤Grade 2 within 48 hours (with or without supportive care)
    - Grade 3 nausea that resolves (with or without supportive care) to ≤Grade 2 within 7 days
    - Grade 3 anorexia requiring enteral or parenteral nutrition
- **Hematologic toxicity:** myelosuppression, defined as:
    - Grade 4 thrombocytopenia of any duration (by CTCAE, version 4.03) or Grade 3 thrombocytopenia with bleeding or lasting >7 days
    - Grade 4 neutropenia for five consecutive days (by CTCAE, version 4.03)
- Treatment delay of more than 14 days due to delayed recovery from a toxicity related to treatment with tazemetostat

6.4 Maximum Tolerated Dose (MTD), and Recommended Phase 2 Dose (RP2D)

The MTD and RP2D are defined as the dose level below which >1 subject of 3 or ≥2 subjects of 6 experience a DLT on the dose-escalation portion of the study during Cycle 1. In the event that MTD is not reached, the RP2D will be that dose that results in a mean $AUC_{(0-24)}$ of at least 5900 ng•h/mL (~80% of the mean value observed after administration of 800 mg BID in adults) or provides biologic and/or clinical activity in subjects in this study. For new patient dosing levels, refer to Section 5.3.

6.5 Dose Modification

During dose escalation, dose modifications are not allowed during Cycle 1. Any AE that is severe enough (at the discretion of the Investigator and with permission of the Sponsor/Medical Monitor) to warrant a dose reduction during Cycle 1 will be discussed with the Medical Monitor prior to resumption of study treatment.

Subjects who have an interruption in treatment for >14 days may restart treatment with tazemetostat after consultation with the Medical Monitor.

For any case of CCI /T-ALL, MDS/AML, or other myeloid malignancies like MPN, tazemetostat will be discontinued and the patient will be followed until resolution of the event.

No dose modification 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

For subjects in the dose-escalation portion of the study, refer to Table 4 for a description of dose levels to be used for dose modification. For example, a dose reduction of one dose level for a subject on a dose of 1200 mg/m^2 BID would be 900 mg/m^2 BID and that for a subject at a dose of 900 mg/m^2 BID would be 700 mg/m^2 BID.

For subjects on the dose expansion portion of the study, refer to Section 5.3 for new patient dosing levels.

- For subjects starting at 1200 mg/m^2 BID, refer to Table 6, below, for a description of dose level modifications.
- For subjects on the tablet formulation (Cohort 4), refer to CCI for instructions on how to administer tablets for each dose level.

Table 6. Dose Modification/Dose Reduction for Dose Expansion Portion

Starting Dose	1200 mg/m^2 BID - OR - discontinue
Dose Level - 1	900 mg/m^2 BID - OR - discontinue
Dose Level - 2	700 mg/m^2 BID - OR - discontinue
Dose Level - 3	520 mg/m^2 BID - OR - discontinue

- For subjects starting at the 520 mg/m^2 BID dose level in the dose expansion portion, no dose modifications are permitted. For these subjects, dosing may be interrupted for up to 14 days to allow resolution of AEs, and subjects must be discontinued if the AE does not resolve with dose interruption.

6.5.1 Dose Modification due to Toxicity Not Related to Bromide

Other toxicities that, in the opinion of the Investigator are possible, probably, or definitely related to study treatment, should be managed per Table 5. 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 5. Dose re-escalation is not permitted.

Table 7. Dose Modifications for Treatment-Related Toxicities (Other than Toxicities Related to Bromide)

Toxicity[a]	During Therapy	Dose Adjustment[b,d]
Grade 1		
All occurrences	Continue study treatment	Maintain dose level
Grade 2		
All occurrences	Continue study treatment	Maintain dose level
Grade 3[c] (not including neutropenia)		
1st occurrence	Interrupt study treatment until resolved to Grade ≤1 or baseline[b]	Reduce by one dose level
2nd occurrence (same or new toxicity)		Reduce by two dose levels
3rd occurrence (same or new toxicity)	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
2nd occurrence		Reduce by one dose level
3rd occurrence		Reduce by two dose levels
4th occurrence	Discontinue study treatment	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

Abbreviations: ANC= absolute neutrophil count, BID= twice 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. Exclude Grades 2 and 3 anemia: Subjects are allowed to continue tazemetostat at their current dose level.
d. If more than 2 dose modifications are required, contact Medical Monitor to discuss risk:benefit ratio of continuing on study.

6.5.2 Dose Modification Due to Bromide Toxicity

For toxicities determined to be related to bromide, Table 8 should be used for dose modifications.

Table 8. Dose Modifications for Toxicities Related to Bromide

Bromide Level	Neurologic Findings[a]	Dose Adjustment[b,c]
10-50 mg/dL	None	Continue
	Grade 1	Discuss with Medical Monitor possibility of dose reduction by one dose level
	Grade 2	Reduce one dose level
	Grade 3 and above	• Interrupt dosing and discuss with Medical Monitor increased frequency of bromide monitoring and potential for restarting treatment • Treatment may be restarted if approved by the Medical Monitor • Reduce by at least one dose level if treatment is restarted
>50-75 mg/dL	None	Continue
	Grade 1	Discuss with Medical Monitor possibility of dose reduction
	Grade 2 and above	• Interrupt dosing and discuss with Medical Monitor increased frequency of bromide monitoring and potential for restarting treatment • Treatment may be restarted if approved by the Medical Monitor • Reduce by one dose level if treatment is restarted
	Grade 3 and above	• Interrupt dosing and discuss with Medical Monitor increased frequency of bromide monitoring and potential for restarting treatment • Treatment may be restarted if approved by the Medical Monitor • Reduce by at least one dose level if treatment is restarted
>75 mg/dL	None	• Discuss with Medical Monitor increased frequency of bromide monitoring and potential need for dose reduction. • Reduce by one dose level if deemed appropriate
	Grade 1	• Discuss with Medical Monitor increased frequency of bromide monitoring and potential need for dose interruption and dose reduction by one dose level
	Grade 2	• Interrupt dosing and discuss with Medical Monitor increased frequency of bromide monitoring and potential for restarting treatment. • Treatment may be restarted if approved by the Medical Monitor • Reduce by one dose level if treatment is restarted.
	Grade 3 and above	• Interrupt dosing and discuss with Medical Monitor increased frequency of bromide monitoring and potential for restarting treatment • Treatment may be restarted if approved by the Medical Monitor • Reduce by at least one dose level if treatment is restarted

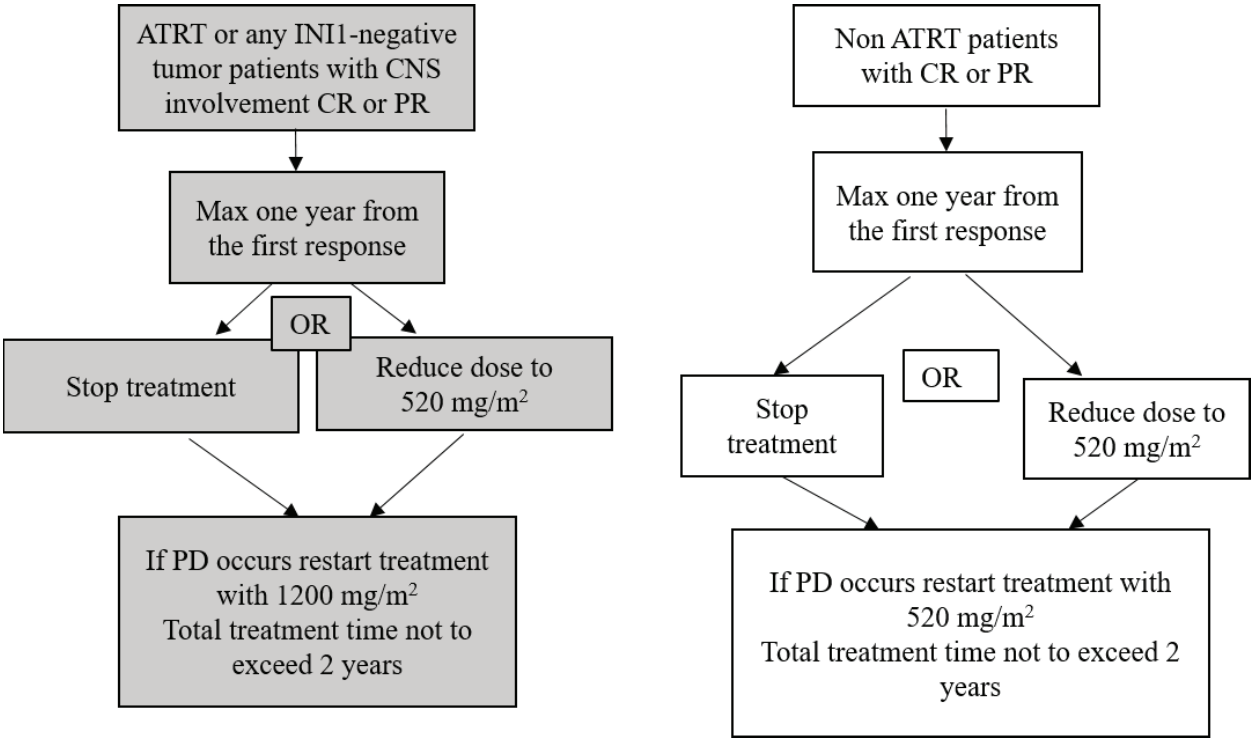
a. Neurologic signs or symptoms not related to disease under study or concomitant medication
b. If the Investigator believes a dose modification or interruption is warranted but not specified in the table above, the Medical Monitor should be contacted to discuss the appropriate treatment plan.
c. If more than 2 dose modifications are required, contact Medical Monitor to discuss risk: benefit ratio of continuing on study.

6.5.3 Dose Modification due to Risk of Adverse Events of Special Interest

6.5.3.1 Dose Modification After Complete or Partial Response

For all responding patients (with CR or PR), regardless of indication, the dose will be either reduced to 520 mg/m^2 BID, or stopped at one year from the first observed response based on the treating Investigator's decision. Patients will remain on study, and upon disease progression, may be rechallenged with treatment at a dose of 520 mg/m^2 BID for non ATRT patients, or at dose 1200 mg/m^2 BID for patients with ATRT or any INI1-negative tumors with CNS involvement. Overall treatment should not exceed 2 years of cumulative dosing (Figure 3).

Figure 3 Dose Modification Schematic for Patients With Complete or Partial Response

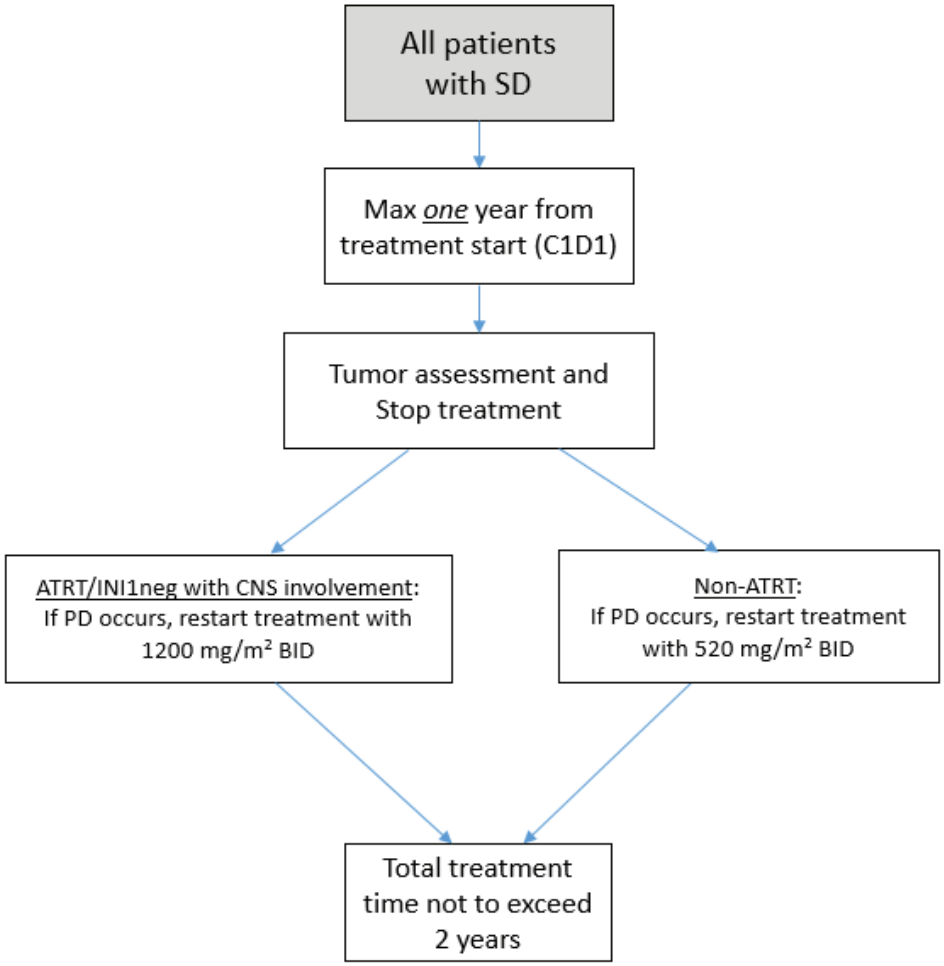


Abbreviations: ATRT= atypical teratoid tumor, CNS= central nervous system, CR= complete response, INI1= Integrase interactor 1, PD= progressive disease.

6.5.3.2 Dose Modification for Patients with Stable Disease

For patients with SD, regardless of indication, after completion of one year of treatment from Cycle 1, Day 1, they will undergo a tumor assessment and discontinue treatment. Patients will remain on study, and upon disease progression, may be rechallenged with treatment at a dose of 520 mg/m^2 BID (for non-ATRT patients) or at a dose of 1200 mg/m^2 BID (for ATRT or any INI1-negative tumors with CNS involvement), based on the treating Investigator's decision. Overall treatment should not exceed 2 years of cumulative dosing (Figure 4).

Figure 4 Dose Modification Schematic for Patients With Stable Disease



Abbreviations: ATRT= atypical teratoid rhabdoid tumor, BID= twice daily, C1D1= Cycle 1, Day 1, CNS= central nervous system, CR= complete response, INI1= integrase interactor 1, PD = progressive disease, PR= partial response, SD= stable disease.

6.6 Treatment Discontinuation

If a new case of [redacted]/T-ALL or MDS occurs, regardless of dose or time on treatment, then the patient will be discontinued from treatment, followed up for resolution, then discontinued from the study (see Section 3.4).

All patients are to discontinue participation on the study after 2 years of cumulative treatment, regardless of whether they came off study due to clinical response or if they reduced dose. For example, if a decision is made by the treating Investigator to pause treatment after 1 year of response, the 2 years of maximum treatment would only be accounted for during the time the patient is receiving therapy. Alternatively, if the decision is made by the treating Investigator to reduce dose, the maximum of 2 years would still apply, regardless of the dose of drug received.

6.7 Continuation of Treatment

In subjects who do not have evidence of clinical or radiographic disease progression and who do not experience unacceptable toxicity, additional cycles of tazemetostat beyond Cycle 1 may be given at the Investigator's discretion with the subject's or his/her legal representative consent.

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.

The required hematologic parameters for continuation of treatment for the second and subsequent cycles are the following:

- 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.

6.8 Duration of Tazemetostat Treatment

Treatment with tazemetostat will continue until disease progression or unacceptable toxicity, for a maximum of 2 years either cumulatively or consecutively, see Section 5.3 for details.

6.9 Treatment Compliance

Compliance for doses taken outside of the clinic may be assessed by the return of study drug to the study site and review of doses taken with the subject (or guardian). This will be recorded in the source documents, which may include the use of a subject medication diary per institutional practice.

6.10 Treatment of Overdose

In the event of an overdose of tazemetostat (defined as administration of more than the protocol-specified dose), 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.

7 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.

7.1 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
- Intermittent use of dexamethasone is permitted as an antiemetic (not to exceed 0.3 mg/kg/dose dexamethasone or maximum dose of 20 mg) every 12 hours as needed
- Blood and platelet transfusions, as needed per the judgment of the Investigator

7.2 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, and have a narrow therapeutic range should be avoided if possible. Medications that are substrates of CYP2C8, CYP2C9, CYP2C19, CYP3A, and CYP2D6, and have a narrow therapeutic range include, but are not limited to, those listed in Table 9, which follows.

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

Table 9. Medications that are CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 Substrates that have a Narrow Therapeutic Range

CYP Enzymes	Substrates with Narrow Therapeutic Range
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus,
CYP2D6	Thioridazine

Please refer to the following websites for a list of these medications or contact the Medical Monitor for additional questions:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

7.3 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 for 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. Medications that are strong inhibitors and strong inducers include, but are not limited to those listed in Table 10, which follows.

Table 10. Medications that are Potent Inhibitors and Inducers of CYP3A4

CYP Enzymes	Strong Inducers	Strong Inhibitors
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, elaprevir, telithromycin, voriconazole

Please refer to the following websites for a comprehensive list of these medications or contact the Medical Monitor for additional questions:

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table3-3

http://medicine.iupui.edu/clinpharm/ddis/

- 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 enrolment in the study or prior to initiating them during the study.

7.4 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.

8 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. Schedules of study assessments and procedures are presented in Section 8.1.

8.1 Schedule of Assessments and Procedures

Table 11. Schedule of Assessments and Procedures

Phase	Pre-treatment[a]	Treatment							
Period	Screening[b]	Cycle 1 (Weeks 1-4) (± 1 day)				Cycles 2 and Beyond (± 3 days)		Post-Treatment/Early Termination[w] (± 3 days)	Follow-up[x,y]
Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	97	98
Day	-14[b] to -1	1	8	15	22	Day 1 of cycle	Day 15 of cycle		
Procedures/Assessments									
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics[c]	X								
Medical History/Current Medical Conditions[d]	X	X	X	X	X	X		X	
Prior and Concomitant Medications	Throughout the study								
Physical examination - Complete	X	X				X		X	
Physical examination - Symptom directed			X	X	X		X		
Focused neurologic history and examination		X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	
Height	X	X				X		X	
BSA[e]		X				X			
Vital signs[f]	X	X	X	X	X	X	X	X	
Performance Status[g]	X	X				X		X	
12-lead ECGs[h]	X	X	X	X	X	X		X	
ECHO or MUGA scan[i]	X							X	
Pregnancy test[j]	X	X				X		X	
Hematology[k]	X	X	X	X	X	X	X	X	
CCI [redacted]	[redacted]	[redacted]				[redacted]			
Blood chemistry[k]	X	X	X	X	X	X		X	

Phase	**Pre-treatment[a]**	**Treatment**							
Period	**Screening[b]**	**Cycle 1 (Weeks 1-4) (± 1 day)**				**Cycles 2 and Beyond (± 3 days)**		**Post-Treatment/Early Termination[w] (± 3 days)**	**Follow-up[x,y]**
Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, etc.**	**7, 9, etc.**	**97**	**98**
Day	**-14[b] to -1**	**1**	**8**	**15**	**22**	**Day 1 of cycle**	**Day 15 of cycle**		
Coagulation Profile[l]	X					X[l]		X	
Bromide level		X (pre-dose)				X		X	
Urinalysis	X	X				X		X	
Creatinine clearance[m]	X								
PGx blood sample[n]	X								
PK blood samples[o,z]						X[o,z]			
PK CSF samples[p]	X					X[p]			
CCI	[redacted]					[redacted]			
Bone monitoring[r]	X					X (every 24 weeks)			
CCI	[redacted]								
Tumor assessments: CT, MRI, bone scan[u, v, x, z]	X[b]	Tumor assessments must be performed every 8 weeks from start of dosing							X[x]
Optional chest ultrasound[aa]	X	Every 8 weeks from start of dosing whilst subject is receiving study drug							
^{18}FDG-PET scan[v]	If clinically indicated								
AEs/SAEs/AESIs[z]	Throughout study								
Tazemetostat administration		Continuous 28-day administration of oral suspension of tazemetostat BID for subjects in Cohorts 1, 2, & 3, and tazemetostat tablets TID for subjects in Cohort 4							
Survival Status and information collection[y]									X[y]
Annual Assessments[z]		X[z]							

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BID = twice daily, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, BSA = body surface area, ^{18}FDG-PET = positron emission tomography with fluorodeoxyglucose, C1D1= Cycle 1 Day 1, CR = complete response, CSF = cerebrospinal fluid, CT = computed tomography, DNA = deoxyribonucleic acid, ECG = electrocardiograms, hr = hour, HR = heart rate, IHC = immunohistochemistry, MRI = magnetic resonance imaging, MUGA = multigated acquisition, PGx = pharmacogenomics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time, RR = respiratory rate, SAE = serious adverse event.

a. **Pre-study procedures** and tumor assessment must be performed within 14 days before first dose of tazemetostat.
b. **Screening:** Screening Period extends from Day -14 to Day -1. Disease assessments, however, are encouraged to be done in this time frame but may be done up to 28 days prior to C1D1 if necessary.
c. **Demographics:** Age at time of enrollment, gender, ethnicity and race will be recorded (as allowed).
d. **Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions, full detailed history of primary diagnosis of the subject's malignancy, including stage of disease at diagnosis and date, therapies and responses to prior antitumor therapies will be recorded at Screening.
e. **BSA:** The determination of tazemetostat doses will be based on BSA (standard institutional formula is acceptable or may be calculated by central Sponsor system) calculated using the subject's current height and weight at the beginning of each treatment cycle. Institutional guidelines for adjusting dose to account for changes in body weight are permissible.
f. **Vital Signs:** Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) will be measured after the subject has been sitting for 5 minutes at Screening and regular intervals during treatment.
g. **Performance Status:** Performance status will be evaluated using either Lansky (Appendix 1) or Karnofsky criteria (Appendix 2) based on the subject's age. If ≤12 years of age, use Lansky criteria; if >12 years of age, use Karnofsky Performance Status criteria.
h. **ECG:** 12-lead ECG must be performed at each visit prior to dosing. ECGs will be recorded in triplicate at least 2 minutes apart. At Cycle 1 Days 1 and 15, and Day 1 of Cycles 2, 3, and 4 (when 1 hour post-dosing PK samples are collected), additional ECGs should be performed at the 1 hour post-dose time. When possible, the ECGs should be obtained prior to the PK sample. See Section 8.2 for window timing allowances.
i. **ECHO:** An ECHO will be performed at Screening as part of the baseline 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.
j. **Pregnancy Test:** A serum or urine pregnancy test will be performed at Screening for all females of childbearing potential. A pregnancy test also should be performed before the first dose of tazemetostat if the Screening pregnancy test was >72 hrs prior. (Urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.)
k. **Laboratory Tests:** Day 1 hematology, chemistry, and urinalysis results must to be reviewed on Day 1 (reconfirming eligibility) prior to dosing. **Chemistries** include: alkaline phosphatase, ALT, AST, either conjugated (direct) bilirubin (where possible) or total bilirubin, blood urea/blood urea nitrogen, electrolytes (sodium, potassium, chloride and bicarbonate), creatinine, albumin, calcium, glucose, phosphorus, total protein, triglycerides, and magnesium.

l. **Coagulation Profile:** Coagulations tests include PT, PTT, and INR. During treatment, to be done as clinically indicated (for example, if started on an anticoagulant during the study or if the total bilirubin increases to >1.5 x ULN).
m. **Creatinine clearance** only required if serum creatinine greater than age and sex ULN.

n. **PGx**: A single 1 mL blood sample will be collected at Screening.
o. **PK**: Blood samples for PK analysis will be collected only at annual assessments. For subjects who are undergoing disease assessment that includes CSF collection for PK (see footnote "p"), draw PK blood sample within 30 minutes of CSF sampling and both samples may be obtained between 0-8 hrs post-dose. A 1 mL blood sample will be collected at the annual time point for subjects ≥ 1 year of age. A 0.5 mL blood sample will be collected at the annual time point for subjects < 1 year of age. All PK blood samples may be drawn from central venous catheter or peripheral blood draw and should be ± 15 min from the scheduled draw time after dosing. The exact time of draw must be recorded. See Section 8.2 for window timing allowances.
p. **CSF PK:** CSF PK samples will be collected only for subjects who require CSF sampling for disease assessment at Screening after consent is signed and at time of the first disease assessment. If a CSF sample is obtained for tumor assessment, 1 mL of CSF should be collected for CSF PK with paired blood sample for PK collected within 30 minutes of the time that the CSF sample is obtained. Both samples should be obtained between 0-8 hours post-dose
q. CCI [redacted]
r. **Bone Monitoring:** Assessment of tibial growth plate, total calcium, phosphorus, magnesium, albumin will be performed during Screening or prior to dosing on Day 1 and then every 6 months while receiving study treatment.
s. CCI [redacted]
t. **Tumor Biopsy:** A tumor biopsy will be requested, where medically feasible, at disease progression.
u. **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, for cycles 1 through 12, a bone or brain scan, respectively, is required every 8 weeks or sooner, if clinically indicated. For cycles 13 and beyond, a bone or brain scan is required every 13 weeks, or sooner, as clinically indicated. Tumor assessments must be performed at Screening and every 8 weeks (±3 days) from start of dosing, irrespective of treatment delays, (during Weeks 8, 16, etc.) or sooner, if clinically indicated. For subjects who stop treatment after one year of first response (CR or PR) or after one year of treatment for subjects with SD, disease assessments should be conducted every 8-12 weeks or according to institutional standards until relapse.
v. **Disease Assessment:** ^{18}FDG-PET scan to be performed if clinically indicated at the Investigator's discretion. It is not a required disease assessment.
w. **Post-Treatment/Early Termination Visit**: A Post-Treatment/Early Termination visit will be conducted within 30 days (±3 days) after last dose of tazemetostat; prior to the start of a new treatment or therapy; or if the subject's participation is terminated early. This may occur at the time of treatment discontinuation (e.g., at the visit at which the decision to discontinue treatment occurs) or up to 30 days after the final dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone as long as the study subject does not require laboratory and/or other assessments related to any new or ongoing AEs, in which case a clinical visit will be required. 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.
x. **Follow-Up** for **Progression-Free Survival**: Subjects who discontinue study treatment for reasons other than disease progression will continue to have disease assessments, when possible, every 8 weeks until disease progression or death.
y. **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 they are lost 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 the survival follow up.

z. **Annual Assessments**: Annual assessments will be conducted including to review for AEs of special interest, tumor response if PD has not been previously reported, and PK (see footnote "o").
aa. **Optional Chest Ultrasound:** An optional chest ultrasound may be performed at the Investigator's discretion to monitor for early signs of CCI /T-ALL.

8.2 Timing Window Allowances for PK Sampling and ECGs

Pharmacokinetic Sampling	
Timepoint	**Tolerance Window**
0 hour	-60 minutes to 0 hour
>0 hour – 2 hour	-15 minutes/+ 15 minutes
4 hour – 8 hour	-30 minutes/+ 30 minutes
Electrocardiograms (ECGs)	
Timepoint	**Tolerance Window**
0 hour	-240 minutes to 0 hour
>0 hour – 1 hour	-15 minutes/+ 15 minutes

8.3 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 include 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., subject ages 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, that adequate provisions are made for soliciting the assent of the child, and whether and how assent 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.

8.4 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 must be performed within 14 days prior to enrollment. Tumor assessments, however, are encouraged to be done in this time frame but may be done up to 28 days prior to cycle 1 day 1, if necessary.

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.

8.5 Study Assessments

For study assessments not included in sections below (e.g., vital signs, performance status, ECHO, bone monitoring), refer to Table 11 for details.

8.5.1 Physical Examinations

8.5.1.1 Comprehensive Physical Examination

Comprehensive physical examinations of all body systems will be performed during Screening and at regular intervals during the study, including neurological examination.

A comprehensive physical examination will be performed at Screening and on Day 1 of each treatment cycle 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)
- Genitourinary
- Musculoskeletal

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.

Height is required at Screening, on Day 1 of each treatment cycle, and at the Post-Treatment/Early Termination visit. Weight is required at Screening, on Day 1 of each treatment cycle, and at the Post-Treatment/Early Termination visit. These assessments will be completed as indicated in the Schedule of Assessments and Procedures (Table 11).

8.5.1.2 Focused Neurologic History and Examination

Focused neurologic history and examinations are to be performed at every visit and are to include sensory testing and seizure status.

8.5.1.3 Symptom-Directed Physical Examination

A symptom-directed physical examination will be performed when a complete physical examination is not required (on Days 8, 15, 22 of Cycle 1, and on Day 15 of each subsequent cycle) 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 (Table 11).

8.5.2 Electrocardiograms (ECGs)

ECGs will be performed as indicated in the Schedule of Assessments and Procedures (Table 11)Additionally, see Section 8.2 for timing allowances. Machine read ECGs should be reviewed by the Investigator at the time of assessment.

ECGs will be read by a central reader within 72 business hours and data from the central reader should be entered in the clinical database.

8.5.3 Disease Assessment

Disease assessment will be performed and assessed by disease-appropriate standard criteria and evaluated by appropriate response criteria:

- **Solid tumors:** The RECIST 1.1 (Appendix 4) will be used with measurement of up to 5 target lesions. PET will be used only to confirm CR. Response must be sustained for a minimum of 2 consecutive imaging assessments no less than 4 weeks (28 days) apart.
- **CNS Tumors:** RANO criteria will be used (Appendix 5)

Measurable Disease (Dose Expansion Only) Will Be Defined As:

- Tumor lesions: accurately measured in at least one dimension (longest diameter in the plane of measurement) with a minimum size as follows:
    - 10 mm by MRI or computed tomography (CT) (CT slice thickness no greater than 5 mm)
    - 10 mm caliper measurement by clinical examination
    - 20 mm by chest X-ray
- Lymph node: >15 mm in short axis by CT (with CT slice thickness no greater than 5 mm)
- Bone lesions: measured by MRI (bone scan, PET scan, or plain film can be used to confirm presence or disappearance of bone lesions)
- Cystic lesions: considered measurable disease if they represent cystic metastatic or primary lesions, it is preferred that solid lesions are defined as the target lesion

Disease status will be reassessed after the completion of every 8 weeks of tazemetostat treatment with appropriate assessment (MR and/or CT of primary and metastatic site, PET scan for soft tissue sarcomas, refer to [Table 11] 8.1). During the period following 1 year of first response (CR or PR) or 1 year of treatment for subjects with SD, disease status will be reassessed every 8 to 12 weeks, or per institutional standard, until relapse occurs.

Optional Chest Ultrasound

An optional chest ultrasound may be performed at screening and every 8 weeks at the investigator's discretion to monitor for early signs of [redacted]/T-ALL.

8.5.4 Confirmation Criteria for Objective Response

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

8.5.5 Pharmacokinetics

8.5.5.1 PK Blood Samples

Blood samples for PK analysis will be drawn per the Schedule of Assessments and Procedures (see Table 11). Additionally, see Section 8.2 for timing allowances.

A blood sample for PK analysis will be required at the time of annual assessments. A 1 mL sample should be collected for subjects ≥ 1 year of age and a 0.5 mL sample should be collected for subjects < 1 year of age for the annual assessments (see Table 11).

A Laboratory Manual detailing the PK sample collection, preparation, storage, and shipping process will be provided.

8.5.5.2 CSF PK Samples

CSF samples for PK analysis will be collected only from subjects who require CSF sampling for disease assessment per the Schedule of Assessments and Procedures (see Table 11). A paired blood sample for plasma PK analysis should be collected within 30 minutes of the time that the CSF sample is obtained.

Refer to the Laboratory Manual detailing the CSF PK sample collection, preparation, storage, and shipping process.

8.5.6 Pharmacodynamics (PD)

Blood samples for PD analysis will no longer be collected.

8.5.7 Pharmacogenomics (PGx)

A single whole blood sample will be collected during the Screening phase to provide DNA for analysis of genes involved in drug disposition (i.e., ADME). This will support investigation of whether subject genotype, specifically of ADME genes, is related to the PK of tazemetostat.

8.5.8 Tumor Sampling

8.5.8.1 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 will be 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 instead be provided.

Study entry and eligibility will be based upon local diagnostic criteria. Independent central confirmation will not be required for study entry.

If archive tumor material is not available, tumor biopsy obtained during Screening is also acceptable. Adequate tissue must be available to prepare or provide 10-20 unstained paraffin-embedded tumor tissue slides.

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. CCI [redacted]

8.5.8.2 Tumor Biopsy to Assess Tazemetostat PD

If biopsy done for disease management during the course of treatment, any additional tissue will be requested for exploratory studies for subjects who have disease response and are beyond Week 8 of treatment.

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

8.5.8.3 Tumor Biopsy to Assess the Mechanisms of Relapse/Resistance

Subjects who progress while on study will be requested to have a tumor biopsy, if medically feasible. For any subject who undergoes a repeat tumor biopsy for disease assessment, tumor tissue will be requested at any time point after Week 8 for those subjects who achieve a PR or better.

8.5.9 Circulating Tumor DNA

CCI [redacted]

8.5.10 Clinical Laboratory Assessments

All clinical laboratory assays will be performed at local laboratories according to the laboratory's normal procedures. Chloride levels will be analyzed at both local and central laboratories. Bromide will be collected and sent only to a central laboratory for analysis. Please see Laboratory Manual for details. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. 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, and platelet count assessments are performed at Screening and at regular intervals during each treatment cycle. Also, a peripheral blood smear will be collected along with normal hematology testing at screening and on day 1 of each cycle and assessed for abnormal morphology and potential bone marrow aspirate/biopsy (see below).

Coagulation Profile: Partial thromboplastin (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) are performed at Screening, as clinically indicated (for example, when an anticoagulant is started or when total bilirubin increases to 1.5 X ULN), and at Post-treatment/Early Termination.

Serum Chemistry: Serum chemistries will be performed at Screening and at regular intervals during each treatment cycle.

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

Bromide Levels: Bromide levels will be measured pre-dose on Day 1 of Cycle 1; on Day 1 of every cycle thereafter; and at Post-Treatment/Early Termination visit.

Urinalysis: Urinalysis testing to include at minimum: glucose, blood, protein, and pH will be performed at Screening, on Cycle 1, Day 1, and on Day 1 every cycle thereafter and at Post-Treatment/Early Termination visit.

NOTE: Day 1 hematology, chemistry, and urinalysis results must to be reviewed on Day 1 (to reconfirm eligibility) prior to dosing.

NOTE: It is anticipated that Microtainers™ will be used (as appropriate) for routine standard of care testing to minimize blood loss. All research samples have also been minimized to the smallest volume required to adequately perform the testing.

Creatinine Clearance: Only required if serum creatinine is above the normal range for age/gender. Creatinine clearance may be calculated by radioisotope measure or 24-hour urine creatinine clearance and must be $\geq$50 mL/min/1.73 m^2.

Bone Marrow Aspirate/Biopsy: As noted above, peripheral blood smear will be collected along with normal hematology testing at screening and on day 1 of each cycle and assessed for abnormal morphology. If peripheral blood smear morphology results are abnormal, a bone marrow aspirate/biopsy will be required for cytogenetic testing and DNA sequencing by the central laboratory to closely monitor patients for abnormalities associated with MDS/AML/MPN. If the results are abnormal (per the central laboratory) and are associated with myeloid malignancies, the patient will be excluded from the study.

Refer to the Schedule of Assessment and Procedures (Table 11) for additional details.

8.5.11 Pregnancy

There has been no experience to date of the use of tazemetostat during pregnancy or lactation. In an embryofetal development study, evidence of increased skeletal developmental abnormalities in fetuses from the pregnant rats and rabbits relative to fetuses from control rats and rabbits were 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.

Sexually active male subjects must ensure that acceptable methods of contraception are used throughout the study period, including the post-treatment period as described in the sections below, if their partner is or could become pregnant.

8.5.11.1 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 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

8.5.11.2 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)

8.5.11.3 Pregnancy Testing

All female subjects of childbearing potential must have a negative pregnancy test (urine or serum) at Screening and within 72 hours of 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.

8.5.11.4 Prevention

8.5.11.4.1 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 least 7 days before starting tazemetostat, 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 contraceptive.

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.

8.5.11.4.2 Male Subjects

Male subjects of childbearing potential must agree to use condoms with their female partner of child bearing potential starting from the first dose of tazemetostat, throughout study treatment, and for 3 months after the final dose of study treatment.

8.5.11.5 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 eight 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.

9 WITHDRAWAL AND REPLACEMENT OF SUBJECTS

9.1 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)

9.2 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

9.3 Replacement of Subjects

A subject will be replaced during dose escalation if the subject:

- Is removed from a cohort during Cycle 1 for reasons other than toxicity (opinion of the Investigator will be consulted) or
- Has an interruption in dosing during Cycle 1 of more than 14 days total.

Subjects will not be replaced during the Dose Expansion portion of the trial.

9.4 Survival Follow-Up

Subjects who discontinue study treatment for reasons other than disease progression will continue to have disease assessments, when possible, every 8 weeks until disease progression or death. In addition, 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 they are lost to follow-up. AESI and subsequent anti-cancer therapy information will be collected throughout the survival follow up.

Survival follow-up will continue for 2 years for each subject or until 80% of subjects enrolled have died.

9.5 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 Post-Treatment/Early Termination follow-up visit prior to initiating any subsequent anticancer therapy (approved or investigational). Post-study anticancer therapy will not be provided as part of this study. The subject may receive subsequent anticancer therapy at the discretion of the treating physician. The subsequent anticancer therapy should be documented on the eCRF.

9.6 Evaluation of Response to Subsequent Anticancer 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 induction therapy should be followed for response whenever possible. Data to be recorded on the subsequent regimen should include:

- Agents received
- Best response
- Duration of response

10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

10.1 Definitions

10.1.1 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, whether or not related to the investigational product.

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.

10.1.2 Serious Adverse Event (SAE)

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

- Results in death
- 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.
- 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

out-patient 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.

- 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.

- Is a congenital anomaly/birth defect.
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as 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. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions (in subjects without pre-existing seizure disorder) that do not result in hospitalization, or development of drug dependency or drug abuse.

10.1.3 Adverse Drug Reaction (ADR)

Adverse drug reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

10.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any AE that is both unexpected (not consistent with the applicable product information) and also meets the definition of a serious adverse reaction would be considered a suspected unexpected serious adverse reaction (SUSAR).

10.2 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.

10.3 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 10.1.1 and Section 10.1.2, 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.

10.3.1 Disease-Related Events

Events that meet the criteria for serious but are thought to be associated with the progression of the disease under study should be reported as SAEs. **NOTE: Disease progression *per se* should not be reported as an SAE.**

10.4 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.

10.4.1 T-Cell Lymphoblastic Lymphoma/T-Cell 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). CCI 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 CCI includes a mediastinal mass or lymphadenopathy with <25% bone marrow blasts. Adult CCI 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, an event of CCI was observed in a pediatric subject on study EZH-102. This event was reported to regulatory authorities as a 7-day 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 event of CCI.
- 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, benefit-risk across tumor types in adults and children.
- Consultation with well recognized external experts in T-cell malignancies and pediatric/adult oncology.

Based on this evaluation, tazemetostat is considered to be a clinically active drug and has the potential to benefit both adult and pediatric patients across different tumor types where there are unmet medical needs. The risk assessment identifies a possible direct association between tazemetostat and CCI/T-ALL at doses >900 mg/m^2 BID for treatment lasting ≥1 year.

Epizyme considers the risk for CCI/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients based on: 1) higher $AUC_{0\text{-}24h}$ exposures in pediatric patients, and 2) increases over time in age-related thymic involution. The risk of CCI/T-ALL in adults is not known; however, the incidence of treatment-related CCI/T-ALL in adults is expected to be uncommon.

CCI Case

The event of CCI in a 9-year-old (at the time of enrollment) female subject diagnosed with poorly differentiated chordoma occurred on Study Day 432 of treatment with tazemetostat 900 mg/m^2 BID. At the time of the event of CCI, the subject was in complete response of her target lesions of the disease under study, yet due to presence of 1 of 2 non-target lesion in her lung (1 lesion disappeared), was considered overall as a partial responder. The first response was

observed and measured at Day 54 on treatment. The steady-state $AUC_{0\text{-}24h}$ at Cycle 1 Day 15 in this subject was 18,784 ng•h/mL and is similar to the mean $AUC_{0\text{-}24h}$ at Cycle 1 Day 15 for the 900 mg/m^2 dose group overall (21,000 ng•h/mL, n=5). The study medication was discontinued and the subject withdrawn from the study due to the event.

Induction therapy was initiated on 06 April 2018 with the following regimen: cytrarabine, daunorubicin, dexamethasone, dexrazoxane. Methotrexate was subsequently started on 13 April 2018. The 9-year-old subject has since experienced a partial clinical response following standard induction chemotherapy, and is expected to have a good overall prognosis as is typical of CCI in children when treated appropriately.

The SUSAR of CCI resulted in the Sponsor initiating a temporary global halt in enrollment for the pediatric study EZH-102. For further details, see the Investigator's Brochure, Version 10.0. In the event of suspicion of CCI /T-ALL or related concerns, please refer to Section 6.5 for evaluation and discontinuation.

Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of CCI /T-ALL so that tazemetostat may be discontinued in the subject and treatment can be initiated for these malignancies. If a case of adult CCI /T-ALL occurs, enrollment will be suspended and the benefit-risk of the drug will be assessed by the QSR committee and the External Safety Committee (ESC) and will be communicated to all Health Authorities and Ethics Committees.

10.4.2 Myelodysplastic Syndrome/Acute Myeloid Leukemia/Myeloid Proliferative Neoplasm

As of the 24 May 2019 data cut, 5 cases of MDS/AML/MPN have been reported in the adult population. A high-level tabular summary of the AESIs in the is provided in Table 12. The 3 AML cases were reported in 1 subject each with rhabdoid sarcoma, DLBCL, and FL and the 2 cases of MDS were reported in 1 subject each with DLBCL and FL. One case was reported as fatal (transformation to AML; PT: second primary malignancy).

Table 12. By-Subject Listing of Adverse Events of Special Interest in the Adult Population

Study	Patient ID	Sex/Age[a]	Original Diagnosis	Diagnosis/Relationship	Time of Onset[b]
E7438-G000-101	PPD		FL	MDS/ Possibly related	Day 465
E7438-G000-101 EZH-501[c]			DLBCL	MDS; later transformed to AML/ Possibly related	Day 843
E7438-G000-101 EZH-501[c]			DLBCL	MDS/ Possibly related	Day 1163
E7438-G000-101			FL	AML/ Not related	Day 786
E7438-G000-101 EZH-501[c]			Rhabdoid sarcoma	AML/ Not related	Day 1591

Abbreviations: AML = acute myeloid leukemia; DLBCL = diffuse large B-cell lymphoma; ID = identified; MDS = myelodysplastic syndrome.
[a] Age at study entry.
[b] Relative to first dose of tazemetostat.
[c] Long-term follow-on study.

A summary of these 5 cases is described in the Investigator's Brochure, Version 10.0. In the event of suspicion of these malignancies or related concerns, please refer to Section 6.5 for evaluation and dose adjustments. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any MDS/AML and other myeloid malignancies like MPN. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be discontinued in the subject.

10.4.3 Tazemetostat Safety Committees

The Tazemetostat safety committees include the CSRC, the QSR committee and the ESC. These committees will review all AESI cases, including CCI /T-ALL, MDS/AML and other myeloid malignancies like MPN (both related and unrelated), and other solid tumor malignancies. Recommendations for next steps will be taken by the QSR and communicated to all stakeholders by the Epizyme Chief Medical Officer.

10.5 Other Adverse Event (OAEs)

Adverse events 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: Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
- 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 AEs associated with an overdose should be captured on the AE eCRF. Both the AEs associated with the exposure and the overdose, misuse, abuse, or medication error should be reported using the procedures for reporting SAEs (Section 10.10), even if the AE associated with overdose, misuse, abuse, or medication error does not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner, but it should be noted as nonserious on the SAE form and the AE eCRF.

In addition, the following events are considered events of clinical interest (ECI) and should be reported in the same manner as SAEs, regardless of seriousness:

- Events considered related to new abnormal bone formation and confirmed by radiologic scan.
- Elevated bromide

For each serious OAE, a narrative will be written and included in the CSR.

10.6 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 v4.03 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 an SAE when it meets one of the pre-defined outcomes as described in Section 10.1.2.

10.7 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.

10.7.1 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 which 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 possibly, probably 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.

10.8 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 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).

10.9 Timeframe for Reporting AEs and SAEs

AEs: Adverse events 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 anticancer therapy.

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. Up until 30 days after the last dose of study treatment or until the initiation of subsequent anticancer 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 lymphoma, even if occurring more than 30 days after the last dose of study drug, will be reported to the Sponsor as in Section 10.4.

10.10 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 (inconsistent 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 expediting reporting according to local regulatory requirements and are forwarded to Investigators as applicable. 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 SAE(s) 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.

10.11 Reporting of Adverse Events of Special Interest

These AESIs are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the seriousness criteria. All AESIs are to be reported on the SAE eCRF and sent to Epizyme within 24 hours, whether or not they meet the criteria for an SAE.

10.11.1 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 CECs 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			
EU Medical Monitor				

SAE REPORTING HOTLINE INFORMATION

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

11 SAFETY REVIEW COMMITTEES

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

The CSRC will review safety data from Cycle 1 (Days 1−28) from each cohort. The CSRC will review the following safety data:

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

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

12 CORRELATIVE ASSESSMENTS

12.1 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.

CCI

[redacted]

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.

12.2 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 collection of 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.

12.3 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 (EMA/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.

13 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.

13.1 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 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.

14 STATISTICAL METHODS

14.1 Hypotheses

14.1.1 Dose Escalation

No specific hypotheses will be tested in dose escalation. The primary focus will be on determining the MTD and/or RP2D (based on available safety, PK and response data), the safety profile and the PK profile of tazemetostat in pediatric subjects with relapsed/refractory CNS and solid tumors. Most analyses will be descriptive or exploratory.

14.1.2 Dose Expansion

The null hypothesis for Dose Expansion is that the ORR (percentage of subjects achieving either a confirmed CR or PR) of 5% or less would have no clinical benefit over existing therapies. The alternative hypothesis is that the ORR is clinically meaningful (≥20%) and therefore, the study treatment warrants further development.

14.2 Study Design Considerations

14.2.1 Determination of Sample Size

Dose Escalation: The sample size is not based on a statistical consideration. The number of subjects will be determined based in part on the number of dose escalations required to determine the protocol-defined MTD and/or RP2D. It is expected that approximately 48 subjects will be enrolled with the "Rolling 6" dose-escalation design (subjects who discontinue in absence of a DLT prior to the completing of the DLT evaluation period may be replaced).

Dose Expansion: The sample size for dose expansion (Cohorts 1 to 3) is based on the hypothesized improvement in ORR over historical rates. An ORR no higher than 5% would have no clinical benefit over existing therapies; an ORR of 20% is considered of clinical interest. For each Dose Expansion cohort separately, using a one-sided test and targeting a Type I error rate of 10% and a Type II error rate of 20% requires a total of 20 pediatric subjects to be enrolled per cohort in Cohorts 1 to 3. To establish that the data support tazemetostat, at least 3 of 20 subjects will be required to have an objective response (i.e., an observed 15% ORR) within a cohort. Due to the discrete nature of the primary endpoint, this statistical test achieves a Type I error rate of 8% (i.e., probability of deciding for tazemetostat when the true ORR is 5%), and a Type II error rate of 21% (i.e., probability of deciding against tazemetostat when the true ORR is 20%). Twelve subjects were to be enrolled in dose expansion Cohort 4 to evaluate the PK of tazemetostat when administered as a tablet formulation to pediatric subjects. Sufficient information to describe the PK of tazemetostat was obtained after administration of tazemetostat tablets to 4 pediatric subjects. Therefore, Cohort 4 was closed to further enrollment. Approximately 72 subjects will be enrolled across the 4 Dose Expansion cohorts.

14.3 Data Analysis Considerations

14.3.1 Analysis Sets

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

The **Safety Population** will consist of all subjects in the ITT population set 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.

Dose-Limiting Toxicity (DLT) Population set will consist of all subjects in the Safety Population set who:

- Experience a DLT during Cycle 1 as defined in the Section 6.3.

OR

- Are not removed from Cycle 1 for reasons other than toxicity and did not have an interruption in study treatment for more than 14 days during Cycle 1

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.

14.3.2 Interim Analyses

Dose Expansion: No interim analysis will be performed.

14.3.2.1 Sample Size Re-Estimation

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

14.3.3 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 dose level and cohort(s) within study part and overall.

14.4 Efficacy Analyses

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

- For solid tumors: RECIST 1.1 (Appendix 4)
- For CNS tumors: RANO criteria (Appendix 5)

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

14.4.1 Analysis of Primary Endpoint by Cohort

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

In Dose Expansion, the ORR will be summarized by cohort and overall. An exact 95% CI for ORR in each cohort and overall will be calculated.

14.4.2 Analysis of Secondary Efficacy Endpoints

In dose escalation, the ORR will be summarized by dose level and overall.

In addition, the ORR will be summarized by dose level across the dose escalation and dose expansion parts (including cohorts) and overall. For each dose level and cohort with at least 20 subjects and overall across the study, an exact 95% CI for ORR will be calculated.

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

For subjects who progressed or died after an extended period without adequate assessment, the time of PFS will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate

assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring. Specific rules for identifying extended loss to follow-up or extended time without an adequate assessment are provided in the SAP.

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

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

Overall Survival (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 and overall, PFS and OS will be calculated using the Kaplan-Meier method. PFS and OS at 24 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 90% 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 overall, the ORR and an exact 95% CI will be provided.

Response Duration, for the subset of subjects with confirmed CR or PR response, is defined as the interval of time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, using disease-appropriate standardized response criteria (i.e., RECIST 1.1 or RANO).

The duration of response will be calculated for each subject with a confirmed CR or PR. If sample size permits, for each dose level within and across study parts, cohorts (if more than one) and overall, 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.

14.5 Safety Analyses

14.5.1 Analysis of Primary Safety Endpoint

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

14.5.2 Extent of Exposure

The data on exposure to tazemetostat will be listed by study part, dose level and cohort(s). 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.

14.5.3 Adverse Events

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

- Emerge after the time of the administration of the first dose, having been absent prior to the first dose.
- Re-emerge, having been present but stopped prior to the time of the administration of the first dose.
- 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 date of first administration).

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 TEAEs 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

Listings will be provided for the following:

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

14.5.4 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).

Low, normal, and high (LNH) classifications will be applied to determine whether the laboratory test value was below (L), within (N), or above (H) its reference range. Shifts from baseline in LNH classification and 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.

14.5.5 Other Safety Measures

The results of scheduled assessments of physical examination, vital signs, ECG, ECHO, and Karnofsky/Lansky 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.

14.6 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, if data are sufficient. Non-compartmental PK parameters C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(0-12)}$ and $t_{1/2}$ will be calculated for tazemetostat and its metabolite on Cycle 1, Day 1 and Cycle 1, Day 15 if data are sufficient. All plasma tazemetostat concentrations will be used to determine population estimates of CL/F, Vd/F and Ka with a non-linear mixed-effects model using NONMEM® 7 software as data warrant. The effect of subject characteristics such as age, weight, BSA, and gender on tazemetostat 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.

All derived PK parameters will be listed. For each of the non-compartmental PK parameters, except T_{max}, the following summary statistics will be calculated, for each dose level within and across study parts and cohorts (if more than one), and for each study day for which PK parameters were calculated: median, minimum, maximum, arithmetic mean, 95% CI for the arithmetic mean, SD, coefficient of variation, geometric mean, 95% CI for the geometric mean and SD of logarithmically transformed data. For T_{max}, median, maximum, minimum, arithmetic mean, 95% CI, and SD will be calculated. Population PK parameters will be summarized across all subjects.

14.7 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 CSR.

CCI

15 STUDY CONDUCT CONSIDERATIONS

15.1 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before subject enrollment begins.

15.2 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 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.

15.2.1 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.

15.2.2 Informed Consent Process

It is the responsibility of the Investigator to obtain written informed consent (and assent in accordance with applicable regulations and GCP) from each subject before any protocol-specific assessments and/or procedures are performed. All consent or assent 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) and assent, if applicable, must be given to the subject or the subject's legally authorized representative. If applicable, the ICF and assent will be provided in a certified translation of the subject's local language. Signed ICFs and assents, if applicable, 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.

15.3 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.

15.4 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.

15.5 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.

15.6 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.

15.7 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.

16 ADMINISTRATIVE PROCEDURES

16.1 Recording, and Access to Study Records

As described in the ICH GCP Guidelines (ICH E6 Section 8.3), 'essential documents', including eCRFs, source documents, consent forms, laboratory test results and the investigational product inventory records must be maintained by the Investigator.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US CFR, 21 CFR 312.68, or other regulatory authorities in accordance with regulatory requirements.

16.2 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 has been entered and all queries resolved. Once the Study Monitor has verified the contents of the completed eCRFs against the source data, queries may be raised if the data are unclear or contradictory. The Investigator must address all queries.

16.3 Quality Assurance and Quality Control

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.

16.4 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.

16.5 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 age at study entry 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.

16.6 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must 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.

16.7 Record Retention

Essential documents should be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor or its designee. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Investigator must obtain written permission from the Sponsor or its designee prior to the destruction of any study document.

16.8 Provision of Study Results and Publication

A summary of the study results should be made publicly available within 12 months of reaching the end of the study, defined as the date of the last subject's last visit (LSLV). A full CSR should be made publicly available no later than 18 months after the end of the study.

If a manuscript is planned to be 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 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.

17 REFERENCES

Alimova I, Birks DK, Harris PS, et al. Inhibition of EZH2 suppresses self-renewal and induces radiation sensitivity in atypical rhabdoid teratoid tumor cells. *Neuro Oncol.* 2013;15(2):149-160.

Baleydier F, Decouvelaere AV, Bergeron J, et al. T cell receptor genotyping and HOXA/TLX1 expression define three T lymphoblastic lymphoma subsets which might affect clinical outcome. *Clin Cancer Res.* 2008;14(3):692-700.

Bourdeaut F, Chi SN, Frühwald MC. Rhabdoid tumors: integrating biological insights with clinical success: a report from the SMARCB1 and Rhabdoid Tumor Symposium, Paris, December 12-14, 2013. 2014/09//, 2014.

Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. *Biometrics.* 1982;38:29-41.

Burkhardt B, Reiter A, Landmann E, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the berlin-frankfurt-muenster group. *J Clin Oncol.* 2009;27(20):3363-3369.

Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood.* 2011;117(19):5019-5032.

Chan-Penebre E, Armstrong K, Drew A, et al. Selective Killing of SMARCA2- and SMARCA4-deficient Small Cell Carcinoma of the Ovary, Hypercalcemic Type Cells by Inhibition of EZH2: In Vitro and In Vivo Preclinical Models. *Mol Cancer Ther.* 2017;16(5):850-860.

Chase A, Cross NC. Aberrations of EZH2 in cancer. *Clin Cancer Res.* 2011;17(9):2613-2618.

Chbani L, Guillou L, Terrier P, et al. Epithelioid sarcoma: a clinicopathologic and immunohistochemical analysis of 106 cases from the French sarcoma group. *American journal of clinical pathology.* 2009;131(2):222-227.

Cheng JX, Tretiakova M, Gong C, et al. Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. *Mod Pathol.* 2008;21(6):647-652.

Chi SN, Zimmerman MA, Yao X, et al. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. *J Clin Oncol.* 2009;27(3):385-389.

Copeland RA. Molecular pathways: protein methyltransferases in cancer. *Clin Cancer Res.* 2013;19(23):6344-6350.

Cortelazzo S, Ferreri A, Hoelzer D, et al. Lymphoblastic lymphoma. *Crit Rev Oncol Hematol.* 2017;113:304-317.

Council for International Organizations of Medical Sciences. Management of Safety Information From Clinical Trials: Report of CIOMS Group VI. In: Gordon AJ, ed. Geneva, Switzerland: Council for International Organizations of Medical Sciences; 2005.

Errico A. Genetics: SMARCA4 mutated in SCCOHT. *Nat Rev Clin Oncol.* 2014;11(6):302.

Fisher C. Synovial sarcoma. *Annals of diagnostic pathology.* 1998;2(6):401-421.

Foulkes WD, Clarke BA, Hasselblatt M, et al. No small surprise - small cell carcinoma of the ovary, hypercalcaemic type, is a malignant rhabdoid tumour. *The Journal of pathology.* 2014;233(3):209-214.

Ginn KF, Gajjar A. Atypical teratoid rhabdoid tumor: current therapy and future directions. *Frontiers in oncology.* 2012;2:114.

Guadagnolo BA, Zagars GK, Ballo MT, et al. Long-term outcomes for synovial sarcoma treated with conservation surgery and radiotherapy. *International journal of radiation oncology, biology, physics.* 2007;69(4):1173-1180.

Harrison ML, Hoskins P, du Bois A, et al. Small cell of the ovary, hypercalcemic type -- analysis of combined experience and recommendation for management. A GCIG study. *Gynecologic oncology.* 2006;100(2):233-238.

Jackson EM, Sievert AJ, Gai X, et al. Genomic analysis using high-density single nucleotide polymorphism-based oligonucleotide arrays and multiplex ligation-dependent probe amplification provides a comprehensive analysis of INI1/SMARCB1 in malignant rhabdoid tumors. *Clin Cancer Res.* 2009;15(6):1923-1930.

Jelinic P, Mueller JJ, Olvera N, et al. Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. *Nat Genet.* 2014;46(5):424-426.

Jelinic P, Schlappe BA, Conlon N, et al. Concomitant loss of SMARCA2 and SMARCA4 expression in small cell carcinoma of the ovary, hypercalcemic type. *Mod Pathol.* 2016;29(1):60-66.

Kadoch C, Crabtree GR. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell.* 2013;153(1):71-85.

Karnofsky DA, Burchenal JH. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. . Presented at: Evaluation of Chemotherapeutic Agents: Symposium, 1949; New York, New York, USA.

Kawaguchi S, Wada T, Nagoya S, et al. Extraskeletal myxoid chondrosarcoma: a Multi-Institutional Study of 42 Cases in Japan. *Cancer.* 2003;97(5):1285-1292.

Kawano S, Grassian AR, Tsuda M, et al. Preclinical Evidence of Anti-Tumor Activity Induced by EZH2 Inhibition in Human Models of Synovial Sarcoma. *PLoS One.* 2016;11(7):e0158888.

Knutson SK, Kawano S, Minoshima Y, et al. Selective inhibition of EZH2 by EPZ-6438 leads to potent antitumor activity in EZH2-mutant non-Hodgkin lymphoma. *Mol Cancer Ther.* 2014;13(4):842-854.

Knutson SK, Warholic NM, Wigle TJ, et al. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *Proc Natl Acad Sci U S A.* 2013;110(19):7922-7927.

Lai C, Dunleavy K. NK/T-cell lymphomas in children. *Best Pract Res Clin Haematol.* 2013;26(1):33-41.

Lansky SB, List MA, Lansky LL, et al. The measurement of performance in childhood cancer patients. *Cancer.* 1987;60:1651-1656.

Le Loarer F, Watson S, Pierron G, et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. *Nat Genet.* 2015;47(10):1200-1205.

Lones MA, Heerema NA, Le Beau MM, et al. Chromosome abnormalities in advanced stage lymphoblastic lymphoma of children and adolescents: a report from CCG-E08. *Cancer Genet Cytogenet.* 2007;172(1):1-11.

Mahdi Y, Zouaidia F, Zouhair A, et al. Combined myoepithelial carcinoma and myoepithelioma in soft tissue: a case report and review of the literature. *Journal of Medical Case Reports.* 2014;8(1):317.

Margol AS, Judkins AR. Pathology and diagnosis of SMARCB1-deficient tumors. *Cancer genetics.* 2014;207(9):358-364.

Margueron R, Reinberg D. The Polycomb complex PRC2 and its mark in life. *Nature.* 2011;469(7330):343-349.

Minagawa T, Shioya R, Sato C, et al. Advanced epithelioid malignant peripheral nerve sheath tumor showing complete response to combined surgery and chemotherapy: a case report. *Case reports in oncological medicine.* 2011;2011:705345-705345.

Morgenstern DA, Gibson S, Brown T, et al. Clinical and pathological features of paediatric malignant rhabdoid tumours. *Pediatric blood & cancer.* 2010;54(1):29-34.

Patel B, Kang Y, Cui K, et al. Aberrant TAL1 activation is mediated by an interchromosomal interaction in human T-cell acute lymphoblastic leukemia. *Leukemia.* 2014;28(2):349-361.

Portell CA, Sweetenham JW. Adult lymphoblastic lymphoma. *Cancer J.* 2012;18(5):432-438.

Ramos P, Karnezis AN, Craig DW, et al. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. *Nat Genet.* 2014;46(5):427-429.

Reed NS, Pautier P, Avall-Lundqvist E, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian small cell cancers. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* 2014;24(9 Suppl 3):S30-34.

Roberts CW, Galusha SA, McMenamin ME, et al. Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. *Proc Natl Acad Sci U S A.* 2000;97(25):13796-13800.

Skolnik JM, Barrett JS, Jayaraman B, et al. Shortening the timeline of pediatric phase I trials: the rolling six design. *J Clin Oncol.* 2008;26(2):190-195.

Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol.* 2009;27(19):3126-3132.

Stacchiotti S, Zuco V, Tortoreto M, et al. Comparative Assessment of Antitumor Effects and Autophagy Induction as a Resistance Mechanism by Cytotoxics and EZH2 Inhibition in INI1-Negative Epithelioid Sarcoma Patient-Derived Xenograft. *Cancers (Basel).* 2019;11(7).

Sullivan LM, Folpe AL, Pawel BR, et al. Epithelioid sarcoma is associated with a high percentage of SMARCB1 deletions. *Mod Pathol.* 2013;26(3):385-392.

Sultan I, Qaddoumi I, Rodriguez-Galindo C, et al. Age, stage, and radiotherapy, but not primary tumor site, affects the outcome of patients with malignant rhabdoid tumors. *Pediatric blood & cancer.* 2010;54(1):35-40.

Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* 4th, Volume 2 ed. Lyon, France: IARC Press; 2008.

van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012;379(9829):1879-1886.

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963-1972.

Wetmore C, Boyett J, Li S, et al. Alisertib is active as single agent in recurrent atypical teratoid rhabdoid tumors in 4 children. *Neuro-oncology.* 2015;17(6):882-888.

Wilson BG, Wang X, Shen X, et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell.* 2010;18(4):316-328.

Witkowski L, Carrot-Zhang J, Albrecht S, et al. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. *Nat Genet.* 2014;46(5):438-443.

Young RH, Oliva E, Scully RE. Small cell carcinoma of the ovary, hypercalcemic type. A clinicopathological analysis of 150 cases. *Am J Surg Pathol.* 1994;18(11):1102-1116.

Zisowsky J, Krause A, Dingemanse J. Drug Development for Pediatric Populations: Regulatory Aspects. *Pharmaceutics.* 2010;2(4):364.

APPENDIX 1: LANSKY PERFORMANCE STATUS

The Lansky Performance Scale is designed for subjects <12 years old (Lansky, 1987).

Score	Description
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

APPENDIX 2: KARNOFSKY PERFORMANCE SCALE

The Karnofsky Performance Scale is designed for subjects ≥12 years old (Karnofsky, 1949).

Condition	Percent	Description
Able to carry on normal activity and to work. No special care needed.	100	Normal, no complaints, no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home and care for most personal needs. A varying degree of assistance is needed.	70	Cares for self, unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his/her needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospice care. Disease may be progressing rapidly.	40	Disabled, requires special care and assistance.
	30	Severely disabled, hospitalization indicated. Death not imminent.
	20	Very sick, hospitalization indicated. Death not imminent.
	10	Moribund, fatal processes progressing rapidly.
	0	Dead.

CCI

APPENDIX 4: MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST 1.1

General Guidelines

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.

Clinical Examination: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph node) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography including a ruler or calipers to estimate the size of the lesion is recommended.

CT and MRI: Contrast enhanced CT with 5 mm contiguous slices is recommended. Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used.

X-ray: X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray.

Bone Scans (Bone Scintigraphy)

For subjects without bone disease at baseline: baseline and subsequent bone scans should only be performed as clinically indicated (e.g., presentation of bone pain).

For subjects with bone disease at baseline: For Cycles 1 through 12, a bone scan is required every 8 weeks or as clinically indicated. For Cycles 13 and beyond, a bone scan is required every 12 weeks or as clinically indicated. In addition, in order to assign a response of CR in a subject with bone disease at baseline, a bone scan must be performed within 4 weeks after the first set of images showing CR. If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT scan, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Brain Scans

For subjects without CNS disease at baseline: subsequent brain scans should only be performed as clinically indicated (e.g., symptoms suggestive of CNS progression).

For subjects with CNS disease at baseline: For Cycles 1through 12, a brain scan is required every 8 weeks or as clinically indicated. For Cycles 13 and beyond, a brain scan is required every 12 weeks or as clinically indicated. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed within 4 weeks after the first set of images showing CR.

If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT scan.

Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) Scan

- A FDG-PET scan will be performed as clinically indicated.
- FDG-PET is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the eCRF.
- New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Disease Evaluation Guidelines

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- ≥20 mm (≥2 cm) by chest X-ray
- ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes (LN) can be considered pathologically enlarged and measurable, a LN must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and follow-up, only the short axis will be measured and followed.

Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological LN with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next

largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If a LN(s) is to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Response Criteria

Target Lesion Evaluation

Assessment of target lesion(s) response is defined as:

- Complete Response (CR): Disappearance of all target lesions. Any pathological LN must be <10 mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g., percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Notes:

- If LN(s) is documented as a target lesion(s) the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When LN decrease to non-pathological size (short axis <10 mm) they should still have a measurement reported in order not to overstate progression.

- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Non-Target Lesion Evaluation

Assessment of non-target lesion(s) response is defined as:

- Complete Response (CR): The disappearance of all non-target lesions. All LN identified as a site of disease at baseline must be non-pathological (e.g., <10 mm short axis).
- Non-CR/Non-PD: The persistence of one or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Notes:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (e.g., non-target response does not have to be "NE").

New Lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the Investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of Overall Response

The best overall response is the best response recorded from the start of study treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Best Overall Response for Subjects with Target (+/- Non-Target lesions) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 weeks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 weeks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease
* Refer to RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Best Overall Response for Subjects with Non-Target Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not Evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR, complete response; PD, progressive disease; SD, stable disease
*'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Notes:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Confirmation Criteria

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

APPENDIX 5: RESPONSE ASSESSMENT IN NEURO-ONCOLOGY (RANO)

As discussed in (Wen, 2010).

Measurable disease is defined as bi-dimensionally contrast-enhancing or enhancing lesions with clearly defined margins by magnetic resonance imaging (MRI) scan, with 2 perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0 mm skip.

Non-measurable disease is defined as either uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

All measurable and non-measurable lesions must be assessed using the same techniques as at baseline.

Complete response (CR): Requires all of the following:

- complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
- no new lesions
- stable or improved non-enhancing (T2/fluid-attenuated inversion recovery [FLAIR]) lesions
- subjects must be off corticosteroids (or on physiologic replacement doses only)
- stable or improved clinically

Note: Subjects with non-measurable disease only cannot have a CR; the best response possible is SD.

Partial response (PR): Requires all of the following:

- ≥50% decrease compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks
- no progression of non-measurable disease; no new lesions
- stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan
- corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan
- stable or improved clinically

Note: Subjects with non-measurable disease only cannot have a PR; the best response possible is SD.

Stable disease (SD): Requires all of the following:

- does not qualify for CR, PR, or progression
- stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan

In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression (PD) on neuro-imaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of PD, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Note: Stable doses of corticosteroids include subjects not on corticosteroids.

Disease progression (PD): PD is defined by any of the following:

- ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids
- significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by co-morbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects)
- any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection) or changes in corticosteroid dose
- failure to return for evaluation as a result of death or deteriorating condition
- clear progression of non-measurable disease

Summary of RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium-enhancing disease	None	≥50% decrease	<50% decrease but <25% increase	≥25% increase[a]
T2/FLAIR	Stable or decrease	Stable or decreasing	Stable or decrease	Increase
New Lesion	None	None	None	Present
Corticosteroids	None	Stable or decreasing dose	Stable or Decreasing dose	NA[b]
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease
Requirement for Response	All	All	All	Any

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; NA, not applicable; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology: SD, stable disease (Wen, 2010).

a. Progression occurs when this criterion is present.
b. Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

CCI