STATISTICAL ANALYSIS PLAN

Protocol EZH-202

A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma

Prepared By: Epizyme, an Ipsen Company

Version Number and Date: V3.0, 30 NOV 2022

STATISTICAL ANALYSIS PLAN FOR EZH-202

SIGNATURE PAGE

The undersigned have reviewed this plan and find it meets the protocol requirements for the reporting of this study.

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MODIFICATION HISTORY

After approval of version 1.0 of the statistical analysis plan, subsequent versions should be documented below with a brief description of the change from the previous version, as well as, the rationale for the change.

Version, Date	Made by	Brief Description of Change and Rationale
3.0, 15 NOV 2022	PPD	• Section 2: Rephrased objectives and endpoints for clarity • Section 2: Updated the exploratory objectives and endpoints regarding pharmacodynamics • Section 3.2.1: Specified the duration of treatment and survival follow-up for this study for clarity • Revised Sections 15 and 17 for efficacy and safety analysis plan, accordingly, due to the updates of objectives and endpoints • Updated information of the medical monitor and statistician of study • Made editorial changes of all contents, accordingly, to align with PA version 11.0
2.0, 17 MAR 2020	PPD	• Revised based on the change of the primary objective of Cohort 6 and the addition of Cohort 8 • Changed in study schema • Updated definition of time to response • Updated definition of time to treatment failure
1.2, 18 MAR 2019	PPD	• Removed analysis of TEAEs of cardiotoxicity specified in EZH-202 SAP and ISS SAP due to lack of observed toxicity in the clinical data of pooled or pivotal study • Removed certain subgroup analyses due to 1) all patients being INI1 negative in ITT population 2) duplicated ECOG group 3) tumor subtype demonstrating inconsistency as an established prognostic factor and varying reports effects on treatment outcomes • Add time to response analysis • Removed imputation rule based on missing severity of TEAE • Special data handling rule for hematology and biochemistry: lab data are collected in different local laboratories with potential missing normal ranges and units. Two procedures have been applied to handle the issue: 1) conversion to standard international unit and 2) Standard Lab Normal Ranges are used to replace missing ones. • Added time to treatment failure analysis as an exploratory
1.1, 17 DEC 2018	PPD	• Modify protocol deviation section • Add description of Green-Dahlberg as an extension to Simon's two stage design • Remove response evaluable population as it was not defined in the protocol. • Add a rational for adding 30 subject's expansion for Cohort 5 based on the meeting with the FDA. • Add a reference for Green-Dahlberg two-stage design
1.1, 24 OCT 2018	PPD	• Change the protocol amendment (PA) 5 to 6 • Remove the text "Cohort 5 will be summarized by original cohort and by expansion for all analyses excluding prior/concomitant medications

		and safety" in grouping of subjects and table presentation. • Remove the text about the study day calculation when the assessment date is after the last dose date. • Update the confidence interval calculation as 95% CI in the whole study. • Add response evaluable population definition and defined the efficacy parameters to be analyzed in RE population. • Update the text "time (in months) from date of last disease progression until the informed consent date" as "time (in months) from date of last disease progression until the start of study treatment". • The concomitant medication definition is updated as "Concomitant medications will include medications taken any time from the start of the first dose of study drug through 30 days following end of study drug administration". • Update radiotherapy instead of palliative radiotherapy will be analyzed in the study. • Update the definition of Best Overall Response (BOR), Stable Disease (SD), and Overall Response Rate definition. • Update the censor rule for PFS and DOR: No progression (or death) and new anticancer treatment or cancer-related surgery documented will be censored on the date of last 'adequate' assessment of response on or prior to starting anti-cancer therapy or cancer-related surgery; Death or progression after two missed visit (with 2 week window) will censored on the date of last 'adequate' assessment of response prior to missed assessments • Define the subgroup analyses for best overall response, objective response rate, and response duration. • Update the definition of TEAEs as "AEs that started or worsened in severity on or after the day of the first dose of study drug through 30 days after the end of study drug" • Update the Adverse Event summary list, add the definition of cardiotoxicity of TEAEs. • Remove the urinalysis shift tables. • Clarify the Creatinine Clearance calculation formula and the criteria for subject with creatinine clearance rate. • Add liver function analysis in laboratory evaluation The changes are based on FDA guidance and updated protocol

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
SIGNATURE PAGE 2
MODIFICATION HISTORY 3
TABLE OF CONTENTS 5
LIST OF TABLES 6
LIST OF FIGURES 7
LIST OF ABBREVIATIONS AND DEFINITIONS 8
1. INTRODUCTION 10
2. STUDY OBJECTIVES AND ENDPOINTS 10
3. STUDY DESIGN 12
3.1. General Description 12
3.2. Estimated Study Duration 15
3.2.1. Study Duration for Participants 15
3.2.2. End of Study 15
3.3. Changes to Analyses from Protocol 15
4. PLANNED ANALYSES AND SAMPLE SIZE 16
4.1. Interim Analysis 16
4.2. Primary Analysis 17
4.3. Final Analysis of Progression-Free Survival (PFS) and Overall Survival (OS) 17
4.4. Determination of Sample Size 17
4.5. Sample Size Re-estimation 20
5. ANALYSIS POPULATIONS 20
6. GENERAL CONSIDERATIONS 20
6.1. Grouping of Subjects and Table Presentation 20
6.2. Time Point Conventions 21
7. STATISTICAL CONSIDERATIONS 21
7.1. Common Conventions 21
7.2. Missing Data 22
8. ANALYSIS POPULATIONS AND ENROLLMENT 23
9. DISPOSITION 23
10. PROTOCOL DEVIATIONS 23
11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 29
12. PRIOR SURGICAL AND MEDICAL HISTORY 29
13. MEDICATIONS AND PROCEDURES 30

13.1. Prior Anticancer Therapy and Radiotherapy 30
13.2. Prior and Concomitant Medications 30
13.3. Concurrent Surgery and Radiotherapy 31
13.4. Post-Treatment Anticancer Therapy 31
14. STUDY DRUG EXPOSURE AND COMPLIANCE 31
14.1. Study Drug Exposure 31
14.2. Study Drug Compliance 32
15. EFFICACY ANALYSES 32
15.1 Primary and Secondary Endpoints 33
15.2 Other Endpoints 37
15.3 Subgroup Analysis 37
16. PERFORMANCE STATUS ANALYSIS 38
17. SAFETY OUTCOMES 38
17.1. Adverse Events 38
17.2. Laboratory Evaluations 40
17.3. Electrocardiogram Evaluations 41
17.4. Vital Signs 42
17.5. ECHO/MUGA 43
18. REFERENCES 43
APPENDIX 1. PARTIAL DATES CONVENTIONS 45
Algorithm for Treatment Emergence of Adverse Events 45
Algorithm for Prior and Concomitant Medications 46
APPENDIX 2. SCHEDULE OF EVENTS 3
APPENDIX 3. PHARMACODYNAMICS AND GENETICS ANALYSES 52

LIST OF TABLES

Table 1: Decision Rules for Each Cohort at the End of Stage 1 16
Table 2: Numbers of Subjects Enrolled in Each Stage 17
Table 3: 95% exact binomial (CI) for potential point estimates of DCR and/or ORR 19
Table 4: Number of subjects enrolled in each cohort 20
Table 5: Date of Event or Censoring for PFS 35
Table 6: ECG Measures and Markedly Abnormal Criteria 42
Table 7: Vital Signs and Markedly Abnormal Criteria 43
Table 8: Algorithm for Treatment Emergence of Adverse Events 45
Table 9: Algorithm for Prior / Concomitant Medications 46

Table 10: Schedule of Events 3
Table 11: Timing Window Allowances for ECGs and PK Collection.....51

LIST OF FIGURES

Figure 1: Study Schema 13

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AEs	Adverse Events
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATRT	atypical teratoid rhabdoid tumors
BID	twice daily
BOR	Best Overall Response
BP	Blood pressure
Brookmeyer	Brookmeyer-Crowley method
CI	confidence interval
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMC	Extraskeletal myxoid chondrosarcoma
EMPNST	Epithelioid malignant peripheral nerve sheath tumor
ES	epithelioid sarcoma
EZH2	enhancer of zeste homolog 2
F	absolute bioavailability
GOF	gain of function
H3K27	histone 3 lysine 27
HLGT	high-level group term
HR	heart rate
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
INI1	integrase interactor 1
ITT	Intent-to-Treat
IV	intravenous
LLN	lower limit of normal
MDS	myelodysplastic syndrome

MedDRA	Medical Dictionary for Regulatory Activities
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MRT	malignant rhabdoid tumors
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	objective response rate
OS	overall survival
PA	protocol amendment
PD	pharmacodynamics
PFS	progression-free survival
PGx	pharmacogenetic(s)
PK	pharmacokinetics
PR	partial response
PT	preferred term
PTT	partial thromboplastin time
QTc	corrected QT interval
QTcF	QTc, Fridericia
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RMC	renal medullary carcinoma
RR	respiration rate
RTK	rhabdoid tumors of the kidney
SAEs	serious adverse events
SAP	statistical analysis plan
SD	Stable Disease
SET	sun(var)3-9, enhancer-of-zeste and trithorax
SI	International System of Units
SOC	system organ class
SS	synovial sarcoma
T	temperature
T-ALL	T-cell acute lymphoblastic leukemia
TEAEs	treatment emergent adverse events
T-LBL	T-cell lymphoblastic lymphoma
TTF	Time treatment failure
TTR	Time to Response
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses to be included in the Clinical Study Report for the phase 2 Protocol EZH-202. This SAP is based on Protocol Amendment (PA) 11.0, dated 05 October 2022. This SAP must be approved, the database locked, analysis populations defined, and protocol deviations identified prior to performing the primary analyses described in this document.

Analyses of the Phase 2 pharmacokinetics (PK), pharmacodynamics (PD), genetics, and pharmacological data will be conducted under the auspices of Epizyme and will be governed by separate SAPs.

2. STUDY OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary:	
Cohorts 1 (rhabdoid tumors), **3** (other integrase interactor 1 [INI1]-negative tumors or any solid tumor with enhancer of zeste homolog-2 [EZH2] gain of function [GOF] mutation), **4** (renal medullary carcinoma [RMC]), **5** (epithelioid sarcoma [ES]), **6** (ES with optional tumor biopsy), and **7** (chordoma): To assess the objective response rate (ORR) following oral administration of tazemetostat 800 mg twice daily (BID).	ORR (confirmed complete response [CR] + partial response [PR]) for tazemetostat in subjects with INI1-negative tumors using disease-appropriate standardized response criteria (primary CNS tumors: Response Assessment for Neuro-Oncology [RANO] and all others: RECIST 1.1)
Cohort 2 (relapsed/ refractory [R/R] synovial sarcoma): To determine the progression-free survival (PFS) rate after 16 weeks of oral administration of tazemetostat 800 mg BID	PFS rate after 16 weeks of treatment with tazemetostat. This is the number of subjects with confirmed CR or PR, or stable disease (SD) at the Week 16 assessment.
Cohort 8 (ES treated with tazemetostat 1600 mg once daily [QD]): To assess the safety and tolerability of tazemetostat 1600 mg QD	AEs and clinical laboratory test
Secondary:	
To evaluate the duration of response (DOR) in subjects with rhabdoid tumors (Cohort 1), R/R synovial sarcoma (Cohort 2), other INI1-negative tumors or any solid tumor with EZH2 GOF mutation (Cohort 3), RMC (Cohort 4), ES (Cohort 5), ES undergoing optional biopsy (Cohort 6), chordoma (Cohort 7), and ES receiving 1600 mg tazemetostat QD (Cohort 8) and to evaluate the DOR in Cohorts 1, 3, 4, 5, 6, and 7 combined.	DOR, defined as the time from the first documented evidence of CR or PR to the time of first documented disease progression or death due to any cause, whichever comes first, using disease-appropriate standardized response criteria

To assess the disease control rate (DCR) in subjects with ES (Cohort 5) and ES undergoing optional biopsy (Cohort 6) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD.	DCR for tazemetostat (defined as the number of subjects who achieve confirmed response [CR+PR] or who have SD lasting at least 32 weeks)
To assess the ORR in subjects with R/R synovial sarcoma (Cohort 2) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD.	ORR (defined as the number of subjects who achieve confirmed response [CR+PR] per RECIST 1.1)
To determine the PFS and overall survival (OS) at Weeks 24, 32, and 56 and overall in subjects with rhabdoid tumors (Cohort 1), R/R synovial sarcoma (Cohort 2), other INI1-negative tumors or any solid tumor with EZH2 GOF mutation (Cohort 3), RMC (Cohort 4), ES (Cohort 5), ES undergoing optional biopsy (Cohort 6), and chordoma (Cohort 7) following oral administration of tazemetostat 800 mg BID, and in subjects with ES (Cohort 8) following oral administration of tazemetostat 1600 mg QD.	PFS at Weeks 24, 32, 56, and overall for each cohort. PFS is defined as the time from the date of first dose of study treatment to the earlier of the date of first documented disease progression or date of death due to any cause. OS at Weeks 24, 32, 56, and overall for each cohort. OS is defined as the time from the date of the first dose of study treatment to the date of death due to any cause.
<u>Exploratory:</u>	
To explore the relationship between plasma PK and tumor pharmacodynamic (PD) markers as permitted by the data.	Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation and cell proliferation, and their correlation with activity
To assess tumor tissue and blood for somatic mutations, germline variants, messenger ribonucleic acid (mRNA), and/or proteins as candidate markers of response to tazemetostat.	Somatic mutation analysis of tumor tissue and blood derived circulating deoxyribonucleic acid (DNA) Germline DNA analysis for INI1 or SMARCA4 variants

Cohort 6 only: To assess the effects of tazemetostat on tumor immune priming (e.g., PD-L1 and CD8 IHC)	Assessment of pre- and post-dose biopsies for immune priming (e.g. PD-L1 and CD8 IHC)
Cohort 6 only: To investigate the PD effects of tazemetostat in tumor tissue, if a post-dose tumor sample is available.	Assessment of pre- and post-dose biopsies for H3K27me3 and for changes in gene expression.

3. STUDY DESIGN

3.1. General Description

This is a Phase II, multicenter, open-label, single-arm, 2-stage study of tazemetostat 800 mg BID or 1600 mg QD (Cohort 8) administered orally in continuous 28-day cycles. Screening of subjects to determine eligibility for the study will be performed within 21 days of the first planned dose of tazemetostat. As shown in Figure 1 below, eligible subjects will be enrolled into one of eight cohorts based on tumor type:

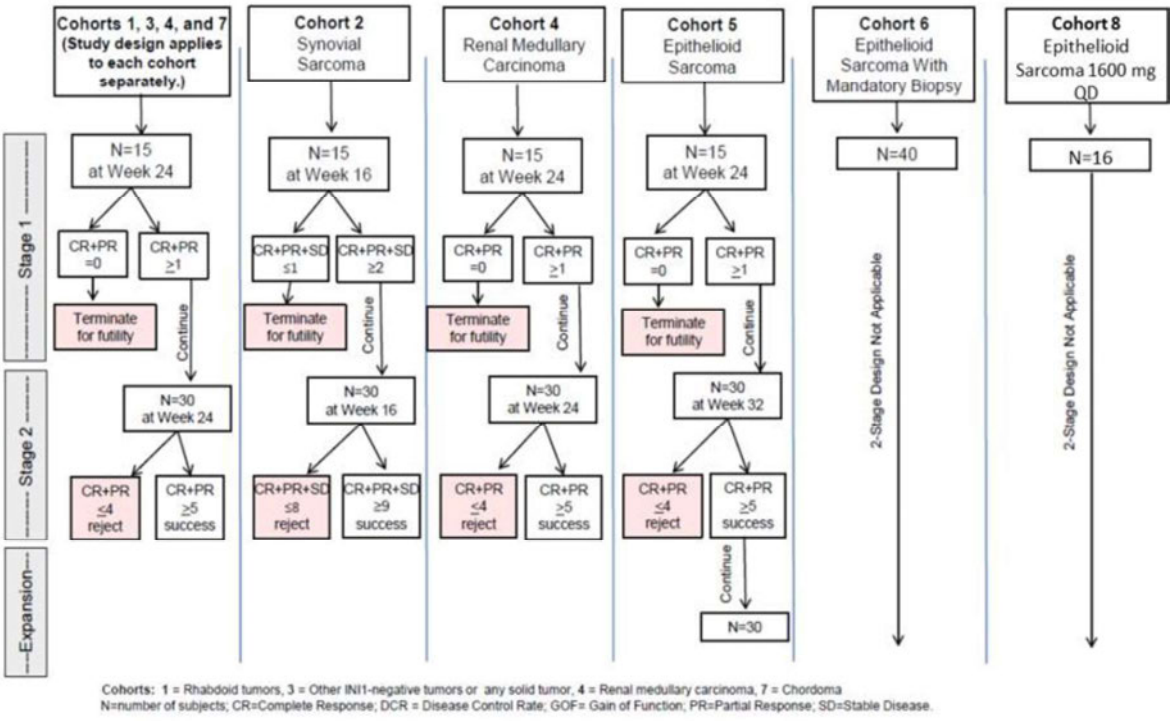
Cohorts using tazemetostat 800 mg BID:

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

Cohort using tazemetostat 1600 mg QD:

Cohort 8: ES (closed to enrollment).

Figure 1: Study Schema



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

Response assessment was to be evaluated after 8 weeks of treatment and then every 8 weeks thereafter while on study.

Note: Changes to Cohorts:

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

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

Amendment 5 added 2 additional cohorts: Cohort 6 (ES undergoing mandatory biopsy) and Cohort 7 (chordoma). Cohort 6 was added to further explore the immune-priming effects of tazemetostat (see Section 5.4.5 of protocol amendment [PA] 11.0). Cohort 7 was added to allow the inclusion of subjects with chordoma, a very rare sarcoma with a large percentage of the poorly differentiated variants having loss of INI1, based on observed clinical activity in the Phase 1 pediatric dose-escalation Study EZH-102 “A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric

Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma." Subjects with chordoma who were enrolled in Cohort 3 prior to Amendment 5 were moved to Cohort 7.

Amendment 7 added Cohort 8, which uses a new dosing schedule of tazemetostat 1600 mg QD in ES subjects. It was hypothesized that 1600 mg QD may achieve a higher AUC at steady-state of approximately 7000 ng*h/mL (see dose justification in Section 5.4.6 of protocol v 11).

Interim Analyses

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

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

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

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

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

Treatment

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

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

Rollover Study

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

3.2. Estimated Study Duration

3.2.1. Study Duration for Participants

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

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

3.2.2. End of Study

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

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

See Appendix 2 for the schedule of events.

3.3. Changes to Analyses from Protocol

Section 17.5.3 of PA 11.0 indicates that laboratory analytes will be summarized descriptively as value and change from baseline, as well as, shifts from baseline (based on low, normal, high categorization) at each visit. To allow for more focused presentation of values most likely to represent a safety concern, laboratory analytes will be summarized as shift from the baseline to the worst post-baseline category (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] severity grades). When an NCI CTCAE category is undefined for an analyte, a multiple of the nearer normal limit will be used.

Though not identified within the protocol, DCR at different time points (e.g. 24 weeks) may be

explored.

If warranted, additional exploratory analyses of efficacy and/or safety endpoints by supportive analytical data may be performed.

4. PLANNED ANALYSES AND SAMPLE SIZE

4.1. Interim Analysis

As part of the two-stage design, an initial assessment for strong evidence of lack of efficacy will be conducted within each cohort (except Cohorts 6 and 8) when 15 subjects have been treated and completed at least the Week 16 (Cohort 2) or Week 24 (all other cohorts) assessment. Futility will be reviewed by an IDMC. Futility stopping rules are further detailed in Section 4.4. Details governing the conduct and data review of the IDMC are covered in a separate Charter and IDMC Reporting Plan.

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

Table 1: Decision Rules for Each Cohort at the End of Stage 1

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

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

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

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

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

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

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

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

4.2. Primary Analysis

The primary analysis for each cohort of the study may occur separately when each cohort has at least met its primary objective (further described in Section 15.1). Details regarding the timing of the PK, and cellular pharmacologic analyses will be described in detail under separate SAPs.
Details regarding the timing of pharmacodynamics (PD) and genetics analyses will be in Appendix 3 (which will be inserted into this SAP post finalization).

4.3. Final Analysis of Progression-Free Survival (PFS) and Overall Survival (OS)

Depending on the maturity of PFS and OS data at the time of the primary analysis, analyses of PFS and OS may be repeated when data are mature, i.e. not having high percentage of censoring (e.g. >50%) or having stable duration of response with estimable medians.

4.4. Determination of Sample Size

Each cohort (exception: Cohorts 6 and 8) will be evaluated separately using a Green-Dahlberg two-stage design, to allow early termination of the cohort due to the lack of efficacy. The sample size of each cohort is calculated on the primary endpoint. Within each cohort, the hypothesis will be tested using a one-sided test with α=0.05 and the type II error rate will be controlled at 0.2. The numbers of subjects to be enrolled in each stage of the Green-Dahlberg two-stage design for each cohort are listed in the Table 2 below.

Typically, one tests the null hypothesis H_0: $p = p_0$ against the alternative H_A: $p = p_A$, where p is the probability of response, p0 is the response rate below which one considers the drug insufficiently active and p_A is the assumed response rate of the new drug. In a well-known two-stage design, Simon proposed method of choosing n_1, n, r1 and boundary at final analysis (r) via binomial distribution when p0, p_A, type I and II errors (a and b) are specified. A number of extensions to Simon Two-Stage Design have been proposed. Green and Dahlberg (1992) proposed several approaches to adapting interim stopping rules when the actual sample size is not the planned size. The authors summarize the operating characteristic of the design comparing with others including Simon's two stage design.

Table 2: Numbers of Subjects Enrolled in Each Stage

	Each Cohort Separately: **Cohort 1**[a] (Rhabdoid tumors) **Cohort 3**[a] (Other INI1-negative	**Cohort 2**[a] (R/R synovial sarcoma)	**Initial Design:** **Cohort 5**[a] (ES)	**Amended Design:** **Cohort 5**[b] (ES)

	tumors or any solid tumor with EZH2 GOF mutation) **Cohort 4**[a] (RMC) **Cohort 7**[a] (Chordoma)			
Stage 1: Null hypothesis	CR + PR ≤5%	CR + PR + SD at Week 16 ≤15%	CR + PR ≤5%	DCR ≤5%
Stage 1: Alternative hypothesis	CR + PR ≥20%	CR + PR + SD at Week 16 ≥35%	CR + PR ≥20%	DCR ≥20%
Stage 1 sample size (n1)[c]	15	15	15	
Stage 1 rejection of study treatment (r1)[c]	0	1	0	
Stage 2 sample size (n2)	15	15	15	15
Stage 2 rejection of study treatment (r)	4	8	4	4
Total sample size (n)	30	30	30	30
Expansion[a]	NA	NA	NA	30

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

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

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

For Cohorts 1, 3, 4, 5, and 7:

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

For Cohort 2:

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

The expanded sample size **for Cohort 5**:

An additional 30 subjects may be enrolled for expanded evaluation of efficacy and safety. Enrollment in the expansion stage may be opened once the Stage 2 rejection criterion has been surpassed. If this occurs prior to the full enrollment of Stage 2, the total cohort sample size (Stage

1 + Stage 2 + expansion) will remain unchanged at 60 subjects. The additional 30 subjects will allow for increased precision for the point estimates of DCR and ORR. The table below shows the 95% exact binomial confidence interval (CI) for potential point estimates of DCR and/or ORR.

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

Table 3: 95% exact binomial (CI) for potential point estimates of DCR and/or ORR

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

For Cohort 6:

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

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

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

For Cohort 8:

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

Total Sample Size:

The total number of subjects to be enrolled for the entire study is approximately 291 (180 subjects in the 2-stage design with each cohort 30 subjects from Cohorts 1-5 and 7, respectively, 30 subjects from the Cohort 5 expansion, 65 subjects from Cohort 6, and 16 subjects from Cohort 8). The number of subjects to be enrolled in each stage are provided in the table below.

Table 4: Number of subjects enrolled in each cohort

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

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

4.5. Sample Size Re-estimation

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

5. ANALYSIS POPULATIONS

The agreement and approval of subjects to be included/excluded from each analysis population will be established prior to database lock. The analysis population definitions are as follows:

- The **Enrolled population** will consist of all subjects who sign informed consent and were entered into the electronic case report form for the study. The Enrolled population will be used for summaries of subject disposition and protocol deviations.
- The **Intent-to-Treat (ITT) population** will consist of all subjects who receive at least one dose of tazemetostat. The ITT population will be used for summaries and analysis of the efficacy endpoints (excluding PK and PD).
- The **Safety population** will consist of all subjects in the ITT population who have at least one post-dose safety observation recorded (safety observations are those identified in Section 17). The Safety population will be used for summaries and analysis of the safety and tolerability.
- The **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.
- The **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.

6. GENERAL CONSIDERATIONS

6.1. Grouping of Subjects and Table Presentation

Subjects will be grouped and summarized by each cohort and overall in table presentations.

Epithelioid sarcoma (ES) subjects will be further summarized and presented by Cohorts 5 and 6 combined.

6.2. Time Point Conventions

6.2.1. Study Day Conventions

Start Day of study treatment will use the date of first dose of tazemetostat.

Depending on the context, listings may present assessments in terms of 'Study Day' label where the first day of treatment is identified as 'Day 1' and the day prior to the first day of treatment is identified as 'Day -1' (with no intervening 0). Study Day will be calculated as follows:

- Study Day = (assessment date/event date – first dose date) + 1 if assessment date or event date ≥ first dose date of study drug.
- Study Day = (assessment date/event date – first dose date of study drug) if assessment date or event date < first dose date of study drug.

Study Day will appear as missing in the listings if the event date is partial.

6.2.2. Baseline Assessments

Baseline will be defined as the last non-missing (including unscheduled) assessment prior to starting study drug. Unless the collection time or label indicates otherwise, assessments performed on the same day as the first dose of tazemetostat will be considered as performed prior to treatment. AEs and medications with a start date on the date of first dose of tazemetostat will be considered to have occurred after the start of treatment. Baseline will be determined separately for each laboratory analyte.

6.2.3. Visit Assessments

For by-visit summaries, nominal visits will be presented (i.e. visit windowing will not be applied). Unscheduled measurements will not be included in by-visit table summaries but will contribute to worst-case values table summaries. Listings will include both scheduled and unscheduled data.

7. STATISTICAL CONSIDERATIONS

7.1. Common Conventions

Unless noted otherwise, the statistical considerations below will be applied.

- 1 pound = 0.454 kg.
- 1 inch = 2.54 cm.
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded up to 1 significant digit for purposes of presentation.
- 1 month = 30.4375 days. Month is calculated as (Days / 30.4375) and will be rounded up to 1 significant digit for purposes of presentation.
- Body mass index (BMI) calculated as [weight (kg)/height $(m)^2$].
- Dates, time, and date/time fields will be displayed in data listings in ISO 8601 formats.

- Data from all centers within each cohort will be pooled for analyses.
- The issue of statistical multiplicity will not apply to this study; therefore, all analyses will be conducted at the nominal 1-sided alpha 0.05 significance level.
- Confidence interval (CI) will be presented as 2-sided 95% CI.
- Safety data will not be imputed except for incomplete dates associated with AEs and medications (rules in Appendix 1) and missing severity or relationship (rules in Section 17.1).
- Missing response data will be handled as described in Section 15.1.
- Summary statistics will include the number and percentage of subjects in each category for discrete variables and the sample size, mean, median, standard deviation (SD), minimum, and maximum for continuous variables.
- When the denominator includes subjects with missing values, a "missing" category may be added for completeness and displayed last in the category summary.
- Time-to-event statistics will include the minimum, 25th percentile, median, 75th percentile, and maximum, provided they are estimable.
- In summary tables of continuous variables (except for weight, height and BMI), the minimum and maximum values will be displayed to the same number of decimal places as the raw data; all mean, median, and percentile values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value, unless otherwise specified. The maximum number of decimal places is 3 and values will be truncated to 3 decimal places in situations where there are more than 3 decimal places. Wherever possible data will be decimal aligned. For weight, height and BMI, only one decimal place will be kept for summary results (except N).
- The number and percentage of responses will be presented in the form XX (XX.X%) with percentage rounded to one decimal place.
- Change from baseline = value (post-baseline visit) – value (baseline).
- Percent change from baseline = 100 × [value (post-baseline visit) – value (baseline)]/ value (baseline).
- Post Baseline Duration in days = end date – start date + 1 (divide by 7 to convert to weeks, divide by 30.4375 to convert to months, and divide by 365.25 to convert to years; Round result to 1 decimal place)
- Listings typically will be sorted by cohort, subject identification number (concatenated site and subject number), date, and time, if collected.
- P-values, if applicable, will be presented to 3 decimal places. If the rounded result is a value of 1.000, it will be displayed as > 0.999.
- All analyses will be conducted using SAS version 9.4 or higher. Any date in the listings will use the *date9.* format, for example, 07MAY2002.

7.2. Missing Data

Unless noted otherwise, missing data will not be imputed. All analyses will be based on observed data only. The effective sample size at each assessment visit will be based on the total number of subjects with non-missing data for the parameter of interest at that visit.

Missing or partially missing start or end dates for adverse events (AEs) and medications will be imputed based on the conventions described in Appendix 1. The purpose of the imputation for AEs is to determine if an AE with an incomplete date is treatment-emergent, as defined in Section 17.1. Similarly, the purpose of the imputation for medications is to determine if a medication with an incomplete date was given concomitantly with study drug, as defined in Section 13.2.

Missing or partially missing dates for initial disease diagnosis will be imputed. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1st for the calculation.

8. ANALYSIS POPULATIONS AND ENROLLMENT

The number of subjects in each analysis population (Enrolled, ITT, and Safety populations) will be summarized on the Enrolled population. Similarly, the number of subjects enrolled will be also summarized by country and site. Subjects in the Enrolled population but not in the ITT population will be counted in a 'Not Treated' column for table summaries on the Enrolled population.

A subject listing indicating analysis population and country of enrollment will be presented for the Enrolled population.

9. DISPOSITION

Subject disposition, including reasons for study withdrawal, will be summarized and listed based on the Enrolled population.

Cause of death during and until 30 days after the last dose of study drug will be summarized on the Safety population. The number of subjects who died due to Treatment Related Adverse Event during and until 30 days after the last dose of study drug will be summarized on the Enrolled population. The number of subjects who died due to Treatment Related Adverse Event after 30 days after the last dose of study drug will be summarized on the Enrolled population.

10. PROTOCOL DEVIATIONS

Protocol deviation reports will be reviewed, and the severity of each protocol deviation will be assigned by the study team. A complete list of important protocol deviations in the following categories can be found in the CRO Medpace's Protocol Deviation Guidance Document.

- Inclusion and exclusion criteria
- Study drug
- Assessment – safety
- Lab/Endpoint data
- Visit window
- Informed consent
- Prohibited Co-Medication
- Overdose and/or Misuse
- Other

Below is a list (not exhaustive) of Inclusion and exclusion criteria for protocol deviations in general and refer to Section 4 of Protocol v 11 in detail.

Inclusion Criteria

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

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

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

10. **For Cohort 6 (ES undergoing optional tumor biopsy) only:**
    - Morphology and immunophenotypic panel consistent with epithelioid sarcoma (e.g., CD34, EMA, Keratin, and INI1)
    - If providing optional biopsy: Willingness to provide informed consent to undergo pre- and post-dose biopsy
11. Has all prior treatment (i.e., chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per CTCAE, version 4.03 or are clinically stable and not clinically significant, at time of enrollment
12. Prior anti-cancer therapy(ies), if applicable, must be completed according to the criteria below:

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

13. Has sufficient tumor tissue (slides or blocks) available for central confirmatory testing of IHC and/or cytogenetics/FISH and/or DNA mutation analysis (required for study entry but enrollment based on local results).
14. Has **measurable** disease based on either RECIST 1.1 for solid tumors or RANO for CNS tumors as defined in Section 12.5.5 of PA 11.0.
15. Has adequate hematologic (bone marrow and coagulation factors), renal and hepatic function as defined by criteria below:

System	Laboratory Value
Hematologic (Bone Marrow Function)	
Hemoglobin[a]	≥9 g/dL
Platelets[b]	≥100 000/mm^3 (≥100 × 10^9/L)
ANC[c]	≥1000/mm^3 (≥1.0 × 10^9/L)
Hematologic (Coagulation Factors)	
INR/PT[d]	≤1.5 ULN
PTT	≤1.5 ULN
Renal Function	
Serum creatinine[e]	≤1.5 × ULN
Hepatic Function	
Total[f] bilirubin	≤1.5× ULN
AST[g]	≤3 × ULN
ALT[g]	≤3 × ULN

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

a. May receive transfusion
b. Should be evaluated after at least 7 days since last platelet transfusion
c. Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
d. INR is the preferred value to be measured. However, if only PT can be performed in the testing laboratory that i acceptable
e. If creatinine is not ≤1.5×ULN, then calculate by Cockcroft-Gault methods or local institutional standard and CrC must be >50 mL/kg/1.73 m^2 (see Appendix 3 of PA 11.0)
f. If attributed to documented Gilbert's disease, total bilirubin < 2.5 × ULN. Eligibility can be determined by total o conjugated bilirubin.
g. If attributed to tumor involvement, AST and ALT ≤5×ULN
h. Subjects a history of hepatitis (Exclusion Criterion No. **13**) must have ALT within the normal range

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

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

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

17. Has a shortening fraction of >27% or an ejection fraction of ≥50% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan and New York Heart Association (NYHA) Class ≤2 (see **Error! Reference source not found.** of protocol)
18. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec
19. **Female subjects of childbearing potential must:**

- Have a negative beta-human chorionic gonadotropin (β-hCG) pregnancy test at time of screening and within 14 days prior to planned first dose of tazemetostat (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing), **and**
- Agree to use effective contraception, as defined in Section 12.6.1 of PA 11.0, from a minimum of 7 days prior to first dose until 6 months following the last dose of tazemetostat and have a male partner who uses a condom, **or**
- Practice true abstinence, (when this is in line with the preferred and usual lifestyle of the subject, see Section 12.6.2 of PA 11.0) **or**
- Have a male partner who is vasectomized

20. **Male subjects with a female partner of childbearing potential must:**
    - Be vasectomized, **or**
    - Agree to use condoms as defined in Section 12.6.2 of PA 11.0, from first dose of tazemetostat until 3 months following the last dose of tazemetostat, **or**
    - Have a female partner who is NOT of childbearing potential

Exclusion Criteria

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

1. Has had prior exposure to tazemetostat or other inhibitor(s) of enhancer of zeste homologue-2 (EZH2)
2. Has participated in another interventional clinical study and received investigational drug within 30 days or 5 half-lives, whichever is longer, prior to the planned first dose of tazemetostat
3. Has known active CNS or any leptomeningeal metastasis of primary extracranial tumor. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging 4 weeks prior to the first dose of study drug and any neurologic symptoms have stabilized), have no evidence of new or enlarging brain metastases, and are on stable or tapering doses of steroids for at least 7 days prior to first dose of study drug.

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

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

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

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

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

7. Has a prior history of T-LBL/T-ALL.
8. Is unwilling to exclude grapefruit juice, Seville oranges and grapefruit from the diet and all foods that contain those fruits from time of enrollment to while on study.
9. Has cardiovascular impairment, history of congestive heart failure greater than NYHA Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of tazemetostat; or ventricular cardiac arrhythmia requiring medical treatment
10. Is currently taking any prohibited medication(s) as described in Section 11.3 of PA 11.0.
11. Has an active infection requiring systemic treatment
12. Is immunocompromised (i.e., has a congenital immunodeficiency), including subjects known history of infection with human immunodeficiency virus (HIV)
13. Has known active infection with hepatitis B virus or hepatitis C virus

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

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

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

15. **For subjects with CNS involvement (primary tumor or metastatic disease):** Have any active bleeding, or new intra-tumoral hemorrhage of more than punctate size on screening MRI obtained within 14 days of starting study drug or known bleeding diathesis or treatment with anti-platelet or anti-thrombotic agents.
16. Has known hypersensitivity to any of the components of tazemetostat or other inhibitor(s) of EZH2
17. Is unable to take oral medications, or has malabsorption syndrome or any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea or vomiting) that might impair the bioavailability of tazemetostat
18. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements.
19. **For female subjects of childbearing potential:** Is pregnant or nursing
20. **For male subjects:** Is unwilling to adhere to contraception criteria from time of enrollment in study to at least 3 months after last dose of tazemetostat.

Incidence of important protocol deviations will be summarized by deviation categories. A listing will be provided with protocol deviation details. None of the deviations will lead to subjects being

excluded from any analysis populations described in Section 5. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed.

Major protocol deviations will be listed for the Enrolled population. Predefined categories of major protocol deviations will include:

- Major violation of inclusion/exclusion criteria such as no baseline measurable disease per RECIST 1.1.
- Prohibited medications, as defined in Section 7.3 of PA 11.0, while on tazemetostat (inclusive of the first and last days of treatment)

Additional categories may be added during the course of the study but will be determined prior to the primary analysis. Sensitive analysis may be planned according to the final protocol deviation list, especially the major ones.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized and listed for the ITT population. Demographics will include age (in years), sex, race, ethnicity, hepatic impairment status, renal impairment status, and baseline Eastern Cooperative Oncology Group (ECOG) performance status.

Baseline disease characteristics will include tumor type (Advanced solid tumor, ES), location of primary tumor at diagnosis, disease subtype (ES only; proximal vs. classic), and tumor stage (0, I, II, III, IV, or unknown). All cases of ES will be centrally reviewed for disease confirmation. Progressive disease (PD) prior to study entry (yes/no) and time (in months) from date of last disease progression until the start of study treatment, inclusive, will be summarized as a continuous measure. Partial dates will be interpreted as July 1 when only a year is recorded and as the 15th of the month when only a month and year are recorded. If this interpretation yields a date of last progression after the informed consent date, then the partial date of last progression will be interpreted as January 1 when only a year is provided and the 1st of the month when only a month and year are provided. Other combinations of missing date elements will be handled as missing values.

Baseline tumor burden will include descriptive statistics on the criteria used for response evaluation (RECIST or RANO), the sum of target lesion diameters (RECIST), the sum of target lesion cross products (RANO), as well as, presence of target lesions (RECIST or RANO; yes/no), presence of lymph node target lesions (RECIST; yes/no), presence of non-target lesions (RECIST or RANO; yes/no), and presence of non-target lesions evaluable by T2/FLAIR (RANO; yes/no).

12. PRIOR SURGICAL AND MEDICAL HISTORY

Significant prior surgical and medical history will be summarized and listed for the ITT population.

Terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. The number and percentage of subjects with any significant surgical and medical history will be summarized. Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Surgical history will be summarized by the MedDRA high-level group term (HLGT) and PT. Prior surgeries will be defined as surgeries performed on or prior to the date of first dose of study drug. Partial dates that cannot conclusively be identified as occurring after the

start of treatment will be assumed to have occurred prior to start of treatment. Listings will include start date and stop date or notation of ongoing for conditions continuing into treatment.

13. MEDICATIONS AND PROCEDURES

Medications will be coded using World Health Organization (WHO) Drug Dictionary (version September 2020). For incidence summaries of medications by coded WHO Anatomical Therapeutic Chemical (ATC) category, a subject will be counted once per specific ATC category (likewise for preferred drug name).

13.1. Prior Anticancer Therapy and Radiotherapy

Prior anticancer therapy and radiotherapy will be summarized and listed for the ITT population.

The summary for prior anticancer therapies will include:

- Number of regimens (0, 1, 2, 3, 4, or more than 4 prior regimens)
- Number of regimens in the advanced/metastatic setting (0, 1, 2, 3, 4, or more than 4 prior regimens)
- Number of prior anticancer therapies with progression
- Therapy setting (Neoadjuvant, Adjuvant, Therapeutic for Advanced/Metastatic Disease, Consolidation, Maintenance, or Unknown); A subject may be counted in multiple categories
- Incidence of prior anticancer therapies by WHO Drug ATC level 4 and preferred drug name

The summary for the prior radiotherapy will include:

- Number of prior lines (0, 1, or 2 or more lines)
- Sites of prior radiotherapy (subdivisions of those sites will be listed); A subject may be counted in multiple categories

Prior radiotherapy will be defined as radiotherapy performed on or prior to the date of first dose of study drug. Partial dates that cannot conclusively be identified as occurring after the start of treatment will be assumed to have occurred prior to start of treatment.

13.2. Prior and Concomitant Medications

Medications will be summarized and listed for the Safety population. Summary tables will include incidence (number and percentage) of subjects receiving any medication and incidence of specific medications by WHO Drug ATC level 4 and preferred drug name.

Prior and concomitant medications will be summarized separately. Categorization will be defined as follows:

- Prior medications will include medications which stopped prior to the first dose of study drug.
- Concomitant medications are defined as medications that were started at any time after the start of first dose of any study drug through 30 days after the last dose of study drug administration or until the start of a subsequent anticancer therapy, whichever is earlier.
- Medications that started prior to the first dose of study drug but continued into study

treatment period until the end of study treatment or the start of a subsequent anticancer therapy, whichever is earlier, are considered as both prior and concomitant.

- Post-treatment anticancer therapies will include anticancer therapies which started after discontinuation of study drug.

Medications with missing or partially missing start or end dates will be handled according to the conventions described in Appendix 1. If it cannot be determined whether a medication was a prior medication due to partial medication start date or end date, the medication will be considered concomitant. If medication's start date and end date are missing, the medication will be considered concomitant.

13.3. Concurrent Surgery and Radiotherapy

Concurrent anticancer surgery and radiotherapy will be summarized for coded terms in the same manner as prior surgeries and prior radiotherapy. Concurrent anticancer surgery and radiotherapy are those procedures that conclusively can be identified as occurring after the date of first dose of study drug up to, and including, the date of last dose of study drug.

13.4. Post-Treatment Anticancer Therapy

Post-treatment anticancer therapies will include anticancer therapies which started after discontinuation of study drug. The number and percentage of subjects with post-treatment anticancer therapy noted during survival follow up, as well as, the incidence (number and percentage) of anticancer therapies by WHO Drug ATC level 4 and preferred drug name will be summarized.

14. STUDY DRUG EXPOSURE AND COMPLIANCE

Study drug exposure and compliance will be summarized and listed for the Safety population.

14.1. Study Drug Exposure

The following summaries of study drug exposure will be presented:

- Duration of exposure (weeks) = [(last dose date of tazemetostat – first dose date of tazemetostat) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.
- Total number of cycles of study drug categorized as follows:
  - Cycle 1 (Days 1-28; weeks 1-4)
  - Cycle 2 (Days 29-56; weeks 5-8)
  - Cycle 3 (Days 57-84; weeks 9-12)
  - Cycle 4 (Days 85-112; weeks 13-16)
  - Cycle 5 (Days 113-140; weeks 17-20)
  - Cycle 6 (Days 141-168; weeks 21-24)
  - Cycle 7 (Days 169-196; weeks 25-28)

  - Cycle 8 or more (Day 197 and beyond; week 29 and beyond)

- Total amount of study drug taken (mg)
- Average dose intensity (mg BID/day) = total amount of study drug taken (mg) / [2 * duration of exposure (days)] (mg BID/day)

  where duration of exposure (days) = (last dose date of tazemetostat – first dose date of tazemetostat) + 1
- For assessment of tolerability, numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)

14.2. Study Drug Compliance

The following summaries of study drug compliance will be presented:

- Percentage study drug taken (summarized as a continuous variable) = 100% * Average dose intensity (mg BID/day) / 800 (mg BID/day).
- Category of percentage of study drug taken (using categories ≥ 90%, 80% to < 90%, 70% to < 80%, and < 70%).

15. EFFICACY ANALYSES

Investigator assessments and Central imaging assessments of best overall response (BOR), Overall Response Rate (ORR), Duration of Response (DOR), and Disease Control Rate (DCR) will be summarized and listed for the ITT population. The results by investigator assessments will be considered as primary and those performed by central imaging assessment will be supportive.

BOR, ORR, DOR, DCR, progression-free survival (PFS) and overall survival (OS) will be summarized and listed for the ITT population based on both investigator and central imaging assessments (only Cohort 5).

PFS rate at week 16 will be summarized and listed for Cohort 2. Provided sufficient data exists, additional cohort summaries may be presented. All central imaging data will be listed for the ITT population.

OS will be summarized by Kaplan-Meier method for the ITT population. The same analysis will be performed for Cohort 6 and combined Cohorts 5 and 6 (epithelioid sarcoma (ES) population) when Cohort 6 data is mature.

Best Overall Response (BOR)

BOR is defined as the best response designation (in the order of CR, PR, SD, PD) for each subject that is recorded between the date of the first dose of tazemetostat and the date of documented disease progression per RECIST 1.1 or RANO criteria or the date of subsequent anticancer therapy or cancer-related surgery (i.e., surgical resection of tumor) whichever occurs first.

The summaries of BOR will include number and percentage of subjects in each of these categories:

- Complete response (CR)
- Partial response (PR)

- Stable disease (SD) (includes Non-CR/Non-PD for subjects with non-measurable disease only)
- Progressive disease (PD)
- Not Evaluable, Unknown, Missing

Confirmation of CR/PR is required at least 28 days after the initial CR/PR was first met. Stable disease (SD) is required at least 4 weeks after the first dose of study drug for investigator assessments and central imaging assessments. Subjects will be evaluated for response based on the following disease appropriate criteria:

- For primary brain tumors, response will be assessed based on RANO (Wen et al., 2010). Primary central nervous system tumors outside of the brain may use RECIST version 1.1.

All other advanced solid tumors will be assessed based on RECIST version 1.1 (Eisenhauer et al., 2009).

15.1 Primary and Secondary Endpoints

Objective Response Rate (ORR)

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

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

Within **Cohort 5**, the data cut-off for the analysis at the end of Stage 2 will occur after all enrolled subjects have completed at least the Week 32 assessment, completed the final study visit, or terminated early from the study. DCR is defined as the percentage of subjects who achieve a confirmed response (CR or PR, as per RECIST 1.1 criteria) or who have SD lasting at least 32 weeks from the start of treatment until disease progression or the start of subsequent anti-cancer therapy. For subjects with a confirmed response, the onset and duration of the response may be of any length as long as the response is confirmed per RECIST 1.1. An unconfirmed response (CR or PR) will be considered SD at that time point. Subjects with a best response of unknown/non-evaluable response will be treated as non-disease control, i.e., they will be included in the denominator when calculating the percentage. Subjects with a time point response of

unknown/non-evaluable response on or before Week 32 will still be classified as having disease control as long as there is a response of CR, PR, or SD on or after Week 32.

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

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

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

A plot of the maximum percent tumor reduction from baseline in target lesions for each subject will be provided by cohort. Each plot will be color coded for best overall response.

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

Duration of Response (DOR)

DOR, for the subset of subjects with confirmed CR or PR response, **is defined** as the time from the first documented evidence of CR or PR to the time of first documented disease progression or death due to any cause, whichever comes first, using disease-appropriate standardized response criteria. Within each cohort and for Cohorts 1, 3, 4, 5, 6, and 7 combined, DOR will be calculated for subjects with a confirmed CR or PR. DOR is defined as the time from the first documented evidence of CR or PR to the time of first documented PD or death due to any cause, whichever occurs first, using disease-appropriate standardized response criteria.

DOR censoring rules will follow those of the PFS analysis defined below.

Provided there are a sufficient number of DOR events, DOR will be analyzed using Kaplan-Meier methods and the median DOR, first quartile, and third quartile will be presented for each group/cohort noted above. The associated 2-sided 95% CIs will be estimated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982).

Disease Control Rate (DCR)

DCR is defined as the percentage of subjects who achieve a confirmed response (CR or PR, as per RECIST 1.1 criteria) or who have SD lasting at least 32 weeks from the start of treatment until disease progression or the start of subsequent anti-cancer therapy. For Cohort 5 and Cohort 6, DCR at the specified time point (Week 12, Week 24, Week 32, and Week 48) is defined as the

percentage of subjects who achieve either a confirmed CR or PR of any duration or who have SD lasting at least the number of weeks indicated from the start of treatment until disease progression or the start of subsequent ant-cancer therapy, according to the appropriate disease evaluation criteria. Subjects with a best response of unknown/non-evaluable response on or before the specified time point will be handled as not achieving disease control, i.e., they will be included in the denominator when calculating the percentage. Subjects with a time point response of unknown/non-evaluable response on or before the specified time point will still be classified as having disease control as long as there is a response of CR, PR, or SD on or after the specified time point. Disease control rate will be analyzed and summarized in the same manner as ORR.

For Cohort 5, DCR also will be analyzed by prior systemic anticancer therapy (with, without), by adult subjects (age >= 18 years), and by prior systemic anticancer therapy (with, without) for adult subjects for investigator and central imaging assessments.

Progression-Free Survival (PFS)

PFS is defined as the interval of time (in weeks) between the date of the first dose of study drug and the earliest date of disease progression or death due to any cause, whichever comes first. A subject alive and progression free at the time of the analysis will be right-censored at the last date where the subject met CR, PR, or SD based on appropriate response criteria. PFS censoring rules are defined in Table 5 below. If a subject meets more than one of these conditions, then the scenario that occurs first will be used for analysis.

PFS will be calculated as follows:

PFS (weeks) = (Event or Censoring Date – Date of 1st Dose of Study Drug + 1) /7.

Within each cohort, PFS will be calculated using the Kaplan-Meier method. PFS rate at 24, 32, and 56 weeks and overall, along with the associated 2-sided 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 associated 95% 2-sided CIs, will be estimated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982). Kaplan-Meier curves for PFS also will be provided. Figures and listings of PFS will also be provided.

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

Table 5: Date of Event or Censoring for PFS

	Situation	Date of Event (PD/Death) or Censoring	Outcome: Event (PD/Death) or Censored
1	No baseline tumor assessments and the subject has not died	Date of Study Day 1	Censored

2	No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Date of Study Day 1	Censored
3	Progression documented between scheduled visits	Date of assessment of progression[1]	Event
4	No progression *(or death)* and no new anticancer treatment and no cancer-related surgery documented	Date of last 'adequate' assessment of response[2]	Censored
5	No progression *(or death)* and new anticancer treatment or cancer-related surgery documented	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy or cancer-related surgery	Censored
6	New anticancer treatment started or cancer-related surgery documented *(prior to documented disease progression or death).*[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy or having cancer-related surgery	Censored
7	Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
8	Death between adequate assessment visits	Date of death	Event
9	Death or progression after two or more consecutive missed visits (with 2-week window)	Date of last 'adequate' assessment of response[2] prior to missed assessments	Censored
10	Alive and without documented disease progression	Date of last radiological assessment	Censored
11	Progression *(or death)* after an extended period without adequate assessment	Date of last 'adequate' assessment of response[2] prior to progression or death	Censored

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)

[2] An adequate assessment is defined as a radiological assessment where CR, PR, or SD was determined by investigator.

[3] If PD and subsequent anti-cancer therapy occur on the same day assume the progression was documented first, e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of Study Day 1.

PD = progressive disease; PFS = progression-free survival.
Note: If a subject meets more than one of these conditions, then the scenario that occurs first will be used for analysis.

As a secondary endpoint, PFS will be analyzed by cohort and listed for the ITT population. For Cohort 5, PFS also will be analyzed by prior systemic anticancer therapy (with, without), by adult subjects (age >= 18 years), and by prior systemic anticancer therapy (with, without) for adult subjects for investigator and central imaging assessments.

Depending on the maturity of PFS data at the time of the primary analysis, the PFS analysis may be repeated when data are mature.

Overall Survival (OS)

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.

OS will be analyzed by cohort and listed for the ITT population. For Cohort 5, OS also will be analyzed by DCR endpoint (i.e. subjects with disease control vs. non-disease control), by prior systemic anticancer therapy (with, without), by adult subjects (age >= 18 years), and by prior systemic anticancer therapy (with, without) for adult subjects.

Within each cohort, OS will be calculated using the Kaplan-Meier method. OS rate at 24, 32, and 56 weeks and overall, along with the associated 2-sided 95% CIs, will be provided. If there are a sufficient number of OS events (i.e., deaths), median OS, first and third quartiles and associated 95% 2-sided CIs, will be estimated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982). Kaplan-Meier curves for OS also will be provided. Figures and listings of OS will also be provided.

Depending on the maturity of OS data at the time of the primary analysis, OS may be repeated when data are mature.

15.2 Other Endpoints

Time to Response (TTR)

Defined only for subjects who have a response. **Time to first response is defined** as [(date of first response of confirmed CR or PR - first dose date of tazemetostat) + 1]/7, and will be calculated using the Kaplan-Meier method. The median, 25th percentile and 75th percentile and associated 95% 2-sided CIs will be estimated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982). Response is based on RANO for primary CNS tumors and RECIST 1.1 for all other solid tumors.

Time to Treatment Failure (TTF)

Time to treatment failure is defined as [(last dose date of tazemetostat - first dose date of tazemetostat) + 1]/7 and will be calculated using the same method as for TTR.

If the treatment is ongoing at the time of the analysis, the last visit date will be used as the last dose date and the subject will be censored at the last visit date.

Concordance

Concordance of investigator and central imaging assessments for BOR, ORR and DCR will be summarized for Cohorts 5 and 6 (and for other cohorts provided if sufficient data exists).

15.3 Subgroup Analysis

Subgroup Analysis will be performed for best overall response (BOR), Overall Response Rate (ORR), Duration of Response (DOR) for investigator and central imaging assessments. The following subgroup factors will be used:

- Prior systemic anticancer therapy (with, without)
- Prior systemic anticancer therapy (with, without) for adult subjects (age >= 18 years)
- Gender (Female, Male)
- Baseline ECOG 0 vs. 1 or 2
- Age (>= 18 years, < 18 years)
- Stage at disease diagnosis
- Baseline sum of target lesion by median (≤ median, > median)
- Geographic region (US vs. Non-US)
- Geographic region (US vs. Non-US) for adult subjects (age >= 18 years)

16. PERFORMANCE STATUS ANALYSIS

ECOG performance status score will be analyzed and listed for the ITT population. ECOG performance status will be summarized categorically at baseline, best post-baseline value, and worst post-baseline value. A summary of baseline, best post-baseline and worst post-baseline status as well as change from baseline (improved, no change, deteriorated) for the best post-baseline value and the worst post-baseline value during the study will be provided. Best and worst post-baseline values will be flagged in the listing.

17. SAFETY OUTCOMES

Safety summaries will be based on the Safety population.

17.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1. Summary tables will be based on treatment emergent adverse events (TEAEs) which are defined as AEs that started or worsened in severity on or after the day of the first dose of study drug through 30 days after the end of study drug. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Missing or partially missing start and end dates for AEs and SAEs will be handled according to the conventions described in Appendix 1. For cases in which it is not possible to ascertain treatment-emergence, the event will be classified as treatment-emergent.

Each summary table will include the incidence (number and percentage) of subjects reporting any TEAE, as well as, by SOC and PT. A subject will be counted once within an SOC, even if the subject experienced more than one TEAE within a specific SOC (likewise for PT).

Investigator assessed severity grade will be based on the National Cancer Institute CTCAE, version 5.0. A subject will be counted once at the worst severity grade within an SOC and/or PT.

Investigator assessed causality to study drug will be categorized as “not related,” “unlikely related,” “possibly related,” or “related” to study drug. For summary purposes, treatment-related TEAEs will include events with relationship to study drug classified as “possibly related” or

"related". A TEAE with a missing causality will be classified as "possibly related" to study drug. A subject will be counted once at the strongest causality within an SOC and/or PT.

TEAEs of special interest are defined in Section 14.4 of protocol amendment 11. In consultation with study clinicians, this subset of TEAEs will be identified using MedDRA terms.

In accordance with the TEAE table presentation described above, AEs will be summarized as follows:

- TEAEs
- TEAEs with ≥ 10% incidence overall based on PT
- TEAEs of grade 3 or higher
- TEAEs of grade 3 or 4
- Treatment-related TEAEs
- Treatment-related TEAEs of grade 3 or higher
- Treatment-related TEAEs of grade 3 or 4
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to discontinuation of study drug
- TEAEs leading to discontinuation from study
- Treatment-emergent serious adverse events (SAEs)
- Treatment-related treatment emergent SAEs
- TEAEs leading to death
- Treatment-related TEAEs leading to death
- TEAEs of special interest (provided a sufficient number of events occur)
- TEAEs by Hepatic Impairment Status
- TEAEs of grade 3 or higher by Hepatic Impairment Status
- Treatment-related TEAEs by Hepatic Impairment Status
- Treatment-emergent serious adverse events (SAEs) by Hepatic Impairment Status
- Treatment-related treatment emergent SAEs by Hepatic Impairment Status
- TEAEs by Potential Renal Impairment Status
- TEAEs of grade 3 or higher by Potential Renal Impairment Status
- Treatment-related TEAEs by Potential Renal Impairment Status
- Treatment-emergent serious adverse events (SAEs) by Potential Renal Impairment Status
- Treatment-related treatment emergent SAEs by Potential Renal Impairment Status

Additional separate listings of SAEs, TEAEs leading to discontinuation of study drug, and TEAEs

with an outcome of death will be provided. A listing of TEAEs of special interest will be provided.

Adverse events with CTCAE Grade 5 or outcome of death are excluded from AE summary tables and summarized under death related tables.

Subject deaths will be summarized and listed as follows:

- Summary and listing of subjects who died during and till 30 days after last dose of study drug with the reason for death as follows.
  - Any AE (by MedDRA preferred Term)
  - Any treatment related TEAE
  - Progressive Disease
  - Disease under Study
  - Unknown/Other causes
- Summary and listing of subjects who died during and till 30 days after last dose of study drug with treatment-related TEAEs
- Summary and listing of subjects who died after 30 days after the last dose of study drug with treatment-related AEs.

17.2. Laboratory Evaluations

Section 12.5.14 of the protocol identifies the hematology, chemistry, and urinalysis analytes collected for the study. Laboratory evaluations will be performed by local laboratories.

Summaries and listings of laboratory data will be represented in international system (SI) of units, where applicable.

Laboratory values that are reported as 'below the detectable limit' of an assay will be analyzed as half the detectable limit when required for analysis purposes but listed as originally reported. The following summaries will be provided for selected hematology and chemistry data:

- Shift from baseline grade to worst post-baseline grade based on NCI CTCAE v4.03 (for analytes where CTCAE grading applies). A missing baseline grade will be assumed to be grade 0. For laboratory tests with both low and high values, summaries will be provided separately.
- Shift from baseline to worst post-baseline value that is < 0.25 x lower limit of normal (LLN) or > 2.5 x upper limit of normal (ULN) for analytes not gradable by NCI CTCAE v4.03.

In addition to the analysis for serum creatinine, the number and percentage of subjects with creatinine clearance rate during the treatment period meeting the following categories will be presented:

- Normal: Glomerular filtration rate (creatinine clearance [CrCl]) ≥90 mL/min
- Mild Impairment: CrCl ≥ 60 - < 90 mL/min
- Moderate Impairment: CrCl ≥ 30 - < 60 mL/min
- Severe Impairment: CrCl ≥ 15 - < 30 mL/min
- Kidney Failure: CrCl < 15 mL/min

Creatinine clearance rate will be calculated using serum creatinine and the Cockcroft-Gault formula.

The number and percentage of subjects with the following potentially clinically significant abnormal liver function test will be summarized:

- ALT ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- Potential Hy's Law cases: ALT or AST ≥3 xULN, total bilirubin ≥2xULN, and ALP < 2xULN

All above abnormal overlapping liver analytes have to be within a 7-day timeframe. All laboratory data will be listed. Additional listings of grade 3 or higher (per NCI CTCAE) values and values < 0.25 x LLN or > 2.5 x ULN for analytes not gradable by NCI CTCAE will be provided. For subjects with a post-baseline analyte that is grade 3 or higher, all values for that analyte will be listed. Similarly, for subjects with a post-baseline analyte value that is < 0.25 x LLN or > 2.5 x ULN, all values for that analyte will be listed.

Special data handling rule for hematology and biochemistry: lab data are collected in different local laboratories with potential missing normal ranges and units. Two procedures have been applied to handle the issue: 1) conversion to standard international units and 2) Standard Lab Normal Ranges are used to replace missing ones.

17.3. Electrocardiogram Evaluations

Single electrocardiogram (ECG) measures will be collected according to the schedule of events in Appendix 2 unless there is an abnormality. Triplicates or additional unscheduled time points may be collected, if clinically indicated. When triplicates are collected, the averages (as calculated by the central ECG vendor ERT) will be used in the summaries.

The following pre-dose and post-dose ECGs parameters will be collected at select scheduled time points and presented as continuous statistics:

- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Bazett [QTcF] Interval (mesc)
- QTc, Fridericia [QTcF] Interval (msec)
- HR (bpm)

The QTcF interval will be the primary ECG measure of interest with other parameters as secondary.

The following summaries will be provided for ECG measurements listed above:

- ECG values and changes from baseline (and changes from pre-dose) by planned visit
- Shift from baseline to worst post-baseline in QTcF status categorized as markedly

abnormal or not (defined in the table below)

- Number and percentage of subjects whose worst-case changes from baseline in QTcF measurements meet markedly abnormal criteria (described in the table below).

Table 6: ECG Measures and Markedly Abnormal Criteria

QTcF Measure	Markedly Abnormal Criteria
Observed	450–480 msec, inclusive [CTCAE grade 1] 481–500 msec, inclusive [CTCAE grade 2] > 500 msec [CTCAE grade 3 or higher]
Change from Baseline	31–60 msec, inclusive, increase from baseline >60 msec increase from baseline

The listings will include the individual ECG values, the calculated averages, and other information collected from the ECG. QTcF measures meeting the markedly abnormal criteria as defined in the table above will be flagged on the listing.

17.4. Vital Signs

Weight (kg) and height at screening (cm). The following vital signs were measured following the initiation of study drug:

- systolic and diastolic blood pressures (mmHg)
- heart rate (bpm)
- body temperature (degrees Celsius, ^{0}C)

Each of these vital signs will be summarized descriptively by calculating the mean, standard deviation, median, and range (minimum and maximum) of the following values that are derived for each subject:

- baseline value
- minimum post-baseline value and corresponding change from baseline
- maximum post-baseline value and corresponding change from baseline
- last post-baseline value and corresponding change from baseline

In addition, summaries of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be based on markedly abnormal criteria defined below:

Table 7: Vital Signs and Markedly Abnormal Criteria

Vital Sign	Abnormal Criteria
Heart rate (bpm)	< 60 bpm at post-baseline and ≥ 60 bpm at baseline > 100 bpm at post-baseline and ≤ 100 bpm at baseline
Temperature (ºC)	≤ 35 ºC at post-baseline and > 35 ºC at baseline ≥ 38 ºC at post-baseline and 38 ºC at baseline
Systolic blood pressure (mmHg)	120-139 mmHg, inclusive (CTCAE grade 1) at post-baseline and < 120 mmHg at baseline 140–159 mm Hg, inclusive (CTCAE grade 2) at post-baseline and < 140 mmHg at baseline ≥ 160 mmHg (CTCAE Grade 3) at post-baseline and < 160 mmHg at baseline
Diastolic blood pressure (mmHg)	80–89 mmHg, inclusive (CTCAE grade 1) at post-baseline and < 80 mmHg at baseline 90–99 mm Hg, inclusive (CTCAE grade 2) at post-baseline and < 90 mmHg at baseline ≥ 100 mmHg (CTCAE grade 3) at post-baseline and < 100 mmHg at baseline

Incidence of markedly abnormal worst-case values will be presented. For heart rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories. Markedly abnormal vital sign values will be flagged as such on a vital signs listing.

17.5. ECHO/MUGA

For ECHO/MUGA left ventricular ejection fraction, results will be listed by subject along with the type of assessment (MUGA or echocardiogram).

18. REFERENCES

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APPENDIX 1. PARTIAL DATES CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

Table 8: Algorithm for Treatment Emergence of Adverse Events

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date and < (end of treatment + 30 days) or start date of new anticancer therapy, whichever is sooner, then TEAE If start date > (end of treatment + 30 days) or start date of new anticancer therapy, whichever is sooner, then not TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR AND CONCOMITANT MEDICATIONS

Table 9: Algorithm for Prior / Concomitant Medications

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment+30 days or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.** If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as **post-treatment.**
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment+30 days or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.** If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as **post-treatment.**
	Missing	If stop date is missing could never be assumed a prior medication. If start date <=end of study treatment+30 days or discontinued date of study drug, assign as **concomitant**. If start date > 30 days after the end of treatment, assign as post-treatment.
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment+30 days or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.** If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment.

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment+30 days or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.** If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment.
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication. If start date <=end of study treatment+30 days or discontinued date of study drug, assign as **concomitant**. If start date > 30 days after the end of treatment, assign as post-treatment.
Missing	Known	If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date, assign as **concomitant**. Cannot be assigned as post-treatment.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date, assign as **concomitant**. Cannot be assigned as post-treatment.
	Missing	Assign as concomitant.

APPENDIX 2. SCHEDULE OF EVENTS

Table 10: Schedule of Events

Visit Description / Study Weeks	Screen[a]	Cycle 1		Cycle 2		Cycles 3+	End of treatment[b]	Survival follow- up[c, d]
		Day 1	Day 15	Day 1	Day 15	Day 1		
Visit		1	2	3	4	5+		
Study Day Procedures/Assessments[b]	-21 to -1	1	15 (±3 days)	29 (±3 days)	43 (±3 days)	57 (Every 28 Days Thereafter) (±3 days)	Up to 30 days post-treatment	
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics[f]	X							
Medical history/Current medical conditions[g]	X	X	X	X	X	X	X	
Prior and concomitant medications	Throughout the study							
Physical examination - Complete	X	X		X		X (Day 1 of each Cycle)	X	
Physical examination - Symptom directed			X		X			
Weight	X	X		X		X	X	
Height	X							
Vital signs[h]	X	X	X	X	X	X	X	
ECOG performance status	X	X		X		X	X	
12-lead ECGs[i]	X	X	X	X	X	X	X	
ECHO or MUGA scan[j]	X	If clinically indicated					X	
Pregnancy test[k]	X	X		X		X	X	
Hematology[l]	X	X	X	X	X	X	X	
Blood chemistry[l]	X	X	X	X	X	X	X	
Hepatitis titers for subjects with history of hepatitis (per Exclusion Criterion No. 11)[l]	X	X		X		X	X	
Coagulation profile[m]	X	If clinically indicated					X	
Urinalysis	X	X		X		X	X	
PGx blood sample[n]	X							
Circulating DNA blood sample[o]	X	X At the time of tumor assessment from Cycle 3 on						
Archival tissue for confirmation[p]	X							

Visit Description / Study Weeks	Screen[a]	Cycle 1		Cycle 2		Cycles 3+	Post-Treatment[b]	Survival follow-up[c, d]
		Day 1	Day 15	Day 1	Day 15	Day 1		
Visit		1	2	3	4	5+		
Study Day **Procedures/Assessments[e]**	**-21 to -1**	**1**	**15 (±3 days)**	**29 (±3 days)**	**43 (±3 days)**	**57 (Every 28 Days Thereafter) (±3 days)**	**Up to 30 days post-treatment**	
~~Optional tumor biopsy (Cohort 6 only)[g]~~	X	~~X~~ C2D1 (± 7 days)				~~X~~ (optional - at disease progression)		
~~Tumor biopsy for H3K27 PD[t]~~						~~X~~ (any time after Cycle 2)		
Tumor biopsy at disease progression[s]	At disease progression							
~~Tumor assessments: CT and/or MRI[t,u]~~	X	X (Tumor assessments every other cycle beginning at start of Cycle 3, Cycle 5, Cycle 7 etc.)						
Optional chest ultrasound[v]	X	An optional chest ultrasound may be performed every 8 weeks from start of dosing						
CT or MRI of the brain	X	If clinically indicated						
AEs/SAEs	Throughout the study							
Tazemetostat administration		800 mg tazemetostat BID or 1600 mg tazemetostat QD (Cohort 8 only) in continuous 28-day cycles						
Overall survival	X							

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

a. **Error! Reference source not found.Screening:** Screening Period extends from Day -21 to Day -1.
b. **End of Treatment:** An EOT visit will be conducted up to 30 days (±3 days) after last dose of tazemetostat or prior to the start of a new treatment or therapy at the end of study or if the subject's participation is terminated early. The EOT assessments will be required and, in the event of a continuing AE, the subject will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely.
c. **Follow-Up for Progression-Free Survival:** Subjects who discontinue study treatment for reasons other than disease progression will continue to have disease assessments when possible, every 8-12 weeks until disease progression or death.
d. **Follow-Up for Overall Survival:** Subjects who permanently discontinue study treatment will be followed (by phone, email, or clinic visit) for survival every 16 weeks until death, withdrawal of consent, or loss to follow-up. Survival follow-up will continue for 2 years for each subject or until 80% of subjects enrolled have died. All anticancer therapies will be collected (the Sponsor may choose to stop the collection of therapies after the first anticancer treatment). Additionally, AESI and subsequent anti-cancer therapy information will be collected throughout survival follow up.
e. Pre-study procedures and tumor assessment must be performed within 21 days before first dose of study treatment.

f. **Error! Reference source not found.Demographics:** Year of birth, gender, ethnicity and race (as allowed) must be recorded.
g. **Error! Reference source not found.Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions, full history of the course of the subject's malignancy including primary diagnosis, stage and date, and information on prior antitumor therapies including response to prior therapies must be recorded at Screening.
h. **Error! Reference source not found.Vital Signs:** Blood pressure (BP), heart rate (HR), and temperature (T) must be measured after the subject has been sitting for five minutes at screening and at regular intervals during treatment.
i. **Error! Reference source not found.ECG:** 12-lead ECG must be performed at each visit prior to dosing. On Days 1 and 15, an additional ECG should be performed at the 1-hour post-dose time. A single ECG will be recorded unless there is an abnormality such as prolonged QTc(F) ≥ 480 msec, new arrhythmia, or other clinically significant finding. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. See Section 12.2 for window timing allowances.
j. **Error! Reference source not found.ECHO:** An ECHO must be performed at screening as part of the screening cardiac assessment for study entry. If an ECHO cannot be performed, a MUGA scan is acceptable for assessment of cardiac function, but is not required.
k. **Error! Reference source not found.Pregnancy Test:** A serum or urine pregnancy test must be performed at Screening for all females who are of childbearing potential. A urine pregnancy test should be performed before the first dose of study treatment if the negative screening pregnancy test is >72 hours prior to dosing. For subsequent testing, either a urine or serum pregnancy test is to be performed every 4 weeks (monthly) after first dose of study treatment. Positive urine tests should be confirmed with serum testing.
l. **Error! Reference source not found.Laboratory Tests:** Chemistries include: alkaline phosphatase, ALT, AST, bilirubin (conjugated bilirubin when possible or total bilirubin), electrolytes (including sodium, potassium, chloride and bicarbonate when possible), Blood urea/blood urea nitrogen, creatinine, albumin, calcium, magnesium, glucose, phosphorus, total protein, and triglycerides. A complete peripheral blood smear morphology assessment needs to be collected along with normal hematology testing. If the morphology results are abnormal, a bone marrow aspirate/biopsy will be required for cytogenetic testing and DNA sequencing to closely monitor subjects for abnormalities associated with MDS/AML/MPN. Bone marrow aspirate/biopsy will be conducted following an abnormal peripheral blood smear morphology assessment conducted by the central laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy. See Section 12.5.14 of protocol for further details. Creatinine clearance only required if serum creatinine greater than age and sex ULN. Creatinine clearance by Cockcroft-Gault formula (**Error! Reference source not found.** of protocol) or institutional standard. For subjects with a history of hepatitis per Exclusion Criterion No. 11, hepatitis titers should be drawn if ALT exceeds the ULN at any time during treatment with tazemetostat.
m. **Coagulation Profile:** Coagulations tests include: prothrombin time (PT), partial thromboplastin time (PTT), and INR.
n. **Error! Reference source not found.PGx:** A single 6 mL blood sample will be collected at Screening. Do not collect samples for PGx from subjects enrolled after Amendment 7.
o. **Error! Reference source not found.Circulating DNA:** 20 mL circulating tumor DNA blood samples to be obtained at Screening and at time of each disease assessment including at time of disease progression.
p. **Error! Reference source not found.Tumor Tissue:** Archival tissue (block or slides) will be requested for central confirmation of pathology, IHC, and additional molecular testing, e.g. detection of somatic mutations and/or candidate biomarkers of response. If archived tumor material is not available tumor biopsy obtained during Screening is also acceptable.
q. **Error! Reference source not found.Optional Tumor Biopsy for Tazemetostat:** An optional tumor biopsy is requested at screening and C2D1 (± 7 days) to assess the immune priming effect of tazemetostat
r. **Error! Reference source not found.Tumor Biopsy for Tazemetostat PD:** An optional tumor biopsy to assess H3K27 is requested from all subjects, when medically feasible, any time after 15 days of continuous dosing. This may coincide with the Week 8 tumor assessment.
s. **Tumor Biopsy at Disease Progression:** An optional Tumor biopsy is requested, where medically feasible, at disease progression in all subjects.
t. **Error! Reference source not found.**Disease Assessment: Tumor assessments by disease-appropriate standard criteria (RECIST 1.1 or RANO) using CT, MRI of known sites of disease as clinically indicated. For subjects with bone disease or CNS disease at baseline, a bone or brain scan, respectively, is required every 8 weeks or sooner, if clinically indicated. Tumor assessments must be performed at Screening and every other odd numbered cycle beginning at Cycle 3 Day 1 (±3 days) from start of dosing (every 8 weeks and irrespective of treatment delays) or sooner, if clinically indicated.

u. **Disease Assessment:** 18FDG-PET scan should be performed as clinically indicated at the Investigator's discretion, and is not a required tumor assessment.
v. **Optional Chest Ultrasound:** An optional chest ultrasound may be performed every 8 weeks at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL..

Table 11: Timing Window Allowances for ECGs and PK Collection

ECG	
Timepoint	**Tolerance Window**
pre-dose	-240 minutes to 0 hour
1 hour post-dose	-15 minutes/ +15 minutes
PK	
Timepoint	**Tolerance Window**
0 – 8 hr	-10 minutes/+10 minutes
10-12 hr	-30 minutes/+30 minutes
24 hr	-1 hour/+1 hour

APPENDIX 3. PHARMACODYNAMICS AND GENETICS ANALYSES

The analysis will specify and will be provided in a separate report.

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In Person Signer Events	Signature	Timestamp

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	9/12/2023 11:07:45 AM
Certified Delivered	Security Checked	9/12/2023 11:12:37 AM
Signing Complete	Security Checked	9/12/2023 11:13:21 AM
Completed	Security Checked	9/12/2023 11:13:21 AM

Payment Events	Status	Timestamps

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