1. TITLE PAGE

TAZEMETOSTAT

EZH-1401

SYMPHONY II: A PHASE II OPEN-LABEL, MULTICENTER TRIAL OF ORAL TAZEMETOSTAT IN COMBINATION WITH RITUXIMAB IN SUBJECTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

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

Original Protocol (conducted by Swedish Cancer Institute): 29 January 2020
Amendment 1 (conducted by Epizyme, Inc.): 29 January 2021
Amendment 2 (conducted by Epizyme, Inc.): 21 October 2021

GCP Statement: This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Epizyme, Inc.

Sponsor's Authorized Officer:

PPD

24-Oct-2021 | 10:22 EDT

Date

Epizyme, Inc.
400 Technology Square, 4th Floor
Cambridge, MA02139 USA
Telephone Number: PPD

Responsible Medical Officer:

PPD

22-Oct-2021 | 11:01 EDT

Date

400 Technology Square, 4th Floor
Cambridge, MA 02139 USA
Telephone Number: PPD

INVESTIGATOR'S AGREEMENT

Protocol Title: Symphony II: **A Phase II Open-Label, Multicenter Trial of Oral Tazemetostat in Combination with Rituximab in Subjects with Relapsed/Refractory Follicular Lymphoma**

Protocol Number: EZH-1401

I have read the **EZH-1401** protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

_____

Name/Address of Institution

PROCEDURES IN CASE OF EMERGENCY

Protocol Title:	Symphony II: A Phase II Open-Label, Multicenter Trial of Oral Tazemetostat in Combination with Rituximab in Subjects with Relapsed/Refractory Follicular Lymphoma
Compound Name (Number):	Tazemetostat (EPZ-6438)
Protocol Number:	EZH-1401
IND Number:	124025
Sponsor:	Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA
Sponsor Medical Monitor:	PPD Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA Telephone: PPD Email: PPD
SAE Hotline:	PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2 (conducted by Epizyme, Inc.):	**21 October 2021**
Amendment 1 (conducted by Epizyme, Inc.):	29 January 2021
Original Protocol (conducted by Swedish Cancer Institute):	29 January 2020

Amendment 2 (21 October 2021)

Overall Rationale for the Amendment:

This amendment is being made primarily for the following reasons:

- To update the safety information for tazemetostat to align with Investigator Brochure version 11.0
- To allow subjects who are benefiting from treatment with tazemetostat to continue to have access to treatment
- For administrative changes and clarifications

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

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

Section # and Name	Description of Substantial Change	Rationale
Title Page Investigator's Agreement Procedures in Case of Emergency Section 2 (Clinical Protocol Synopsis)	Updated study title to include "Symphony II"	To include study branding information.
Signature Page Procedures in Case of Emergency	Updated Sponsor's Medical Monitor	To align with current study management.
Investigator's Agreement	Removed the statement, "I have received and read the Investigator's Brochure for tazemetostat."	Investigators will receive a separate signature page to acknowledge reading the Investigator's Brochure (IB) for tazemetostat.
Procedures in Case of Emergency	Corrected the Investigational New Drug Application (IND) number Updated contact details for the Serious Adverse Event Hotline	To provide the correct information

Section # and Name	Description of Substantial Change	Rationale
Section 2 (Clinical Protocol Synopsis) Section 6 (Trial Objectives and Endpoints) Section 14 (Statistics)	Defined the endpoint of progression-free survival (PFS) and clarified the remaining endpoints. Added the secondary endpoint of duration of response (DOR). Added the exploratory objective and endpoint of Overall Survival (OS).	PFS was defined and remaining endpoints were updated for clarity. DOR was added to allow this study to explicitly determine the durability of responses to treatment. OS was added to allow this study to help better understand the effects of treatment.
Section 2 (Clinical Protocol Synopsis) Section 6 (Trial Objectives and Endpoints)	Updates to ensure the objectives listed in the Clinical Protocol Synopsis match those listed in Trial Objectives and Endpoints and updates for clarity	For consistency and clarity
Section 2 (Clinical Protocol Synopsis) Section 7.1 (Overall Study Design and Plan)	Updated to include additional details, including the number of subjects and responses needed for futility stopping, plans for stratification by subpopulation, and an overview of the study visits	For clarity
Section 2 (Clinical Protocol Synopsis) Section 7.2 (Number of Subjects) Section 14 (Statistics)	Changes to sample size and its determination, including updates to the number of subjects needed for futility analysis, the range for success for the primary and secondary endpoints, the type I error rate, and the study's power. Updated criteria for evaluation and statistical methods to align with the updated endpoints. Added that sample and power calculations are based on nQuery 8.0.	To more recalculate the sample size using Simon's 2-stage design based on the revised assumptions
Section 2 (Clinical Protocol Synopsis) Section 8.1 (Inclusion Criteria) Section 8.1.2 (Exclusion Criteria)	Updated to reorder inclusion and exclusion criteria	To make the inclusion/exclusion criteria clearer and easier for sites to use
	Updated to add inclusion criterion 4 , "Life expectancy (in the opinion of the Investigator) of ≥3 months before enrollment"	To clarify that subjects enrolled into the study should be expected, within reason, to complete treatment
	Updated to add laboratory parameters for hemoglobin in inclusion criterion 7.c.	For subject safety and to align across the tazemetostat program.
	Updated to clarify Grade 3b and mixed histology follicular lymphomas are excluded from this study	For clarity
	Added exclusion criteria regarding prior treatment washout periods, prior medical history, and strong CYP3A inhibitors	For subject safety and to align across the tazemetostat program

Section # and Name	Description of Substantial Change	Rationale
Section 2 (Clinical Protocol Synopsis) Section 7.7 (Schedule of Procedures/ Assessments) Section 8.1 (Inclusion Criteria) Section 12.1.6 (Laboratory Assessments) Section 12.1.7 (Viral Serology/ Virology) Appendix 7 (Interpretation of Hepatitis B Serologic Test Results) Appendix 8 (Interpretation of Results of Tests for Hepatitis C Virus [HCV] Infection and Further Actions)	Updated to include viral serology/virology testing	To align with the safety requirements used across tazemetostat protocols
Section 2 (Clinical Protocol Synopsis) Section 7.7 (Schedule of Procedures/ Assessments) Section 8.1 (Inclusion Criteria) Section 9.3 (Contraception and Pregnancy) Section 12.1.9 (Pregnancy Testing)	Updated contraception language to clarify the timeframes and requirements for male and female subjects, respectively	For clarity and to align with the contraception requirements used across tazemetostat studies
Section 2 (Clinical Protocol Synopsis) Section 7.1 (Overall Study Design and Plan) Section 7.3 (Treatment Assignment) Section 7.5 (Continuation of Treatment) Section 7.7 (Schedule of Procedures/ Assessments) Section 8.2 (Subject Withdrawal Criteria) Section 10.5 (Administration) Section 11 (Assessment of Efficacy)	Updated to allow subjects to continue on tazemetostat therapy until 24 months of therapy or until disease progression, unacceptable toxicity, or withdrawal of consent.	To allow subjects who are benefiting from treatment with tazemetostat to continue to have access to treatment.
Section 2 (Clinical Protocol Synopsis) Section 7.3 (Treatment Assignment) Section 10.5 (Administration)	Added information regarding subcutaneous rituximab	To clarify that either intravenous or subcutaneous rituximab can be administered during the clinical trial
Section 2 (Clinical Protocol Synopsis)	Updated to provide additional details on the safety criteria for evaluation.	To provide more comprehensive and up-to-date information.

Section # and Name	Description of Substantial Change	Rationale
Section 3 (Table of Contents)	Added a list of figures.	To provide a link to the figure added in this amendment.
Section 5 (Introduction)	Updated existing information on the indication and study rationale.	To provide more comprehensive and up-to-date information.
	Added additional information on the investigational products.	To provide information on each of the investigational products.
Section 5.2.2 (Tazemetostat Clinical Experience) Section 12.2.2 (AESIs) Section 12.2.4 (Other Risks) Section 12.4 (Reporting of Adverse Events)	Updated based on the latest version of the tazemetostat IB and remove repetition in Section 12.2.4 (Other Risks)	To align with the current tazemetostat IB, version 11.0.
Section 7.4 (Dose Adjustment Criteria)	Updated the dose modification for tazemetostat Updated the dose modifications for rituximab.	To align with the inclusion criteria and retreatment For clarity
Section 7.7 (Schedule of Procedures/ Assessments)	Included rows and footnotes to clarify which visits will be on site versus phone calls. Update to include informed consent, include/exclusion criteria, demographics and medical history, prior and concomitant medications, pregnancy testing, height and weight measurements, viral serology/virology, serum chemistries & coagulation, urinalysis, bone marrow aspirates, scans, ect. Clarified information on adverse events (AEs) and concomitant medications/ procedure. Added End-of-Treatment and Safety Follow-up visits.	Updated to clarify the order of assessments and procedures
Section 7.7 (Schedule of Procedures/ Assessments) Section 12.1.6 (Laboratory Assessments) Section 12.1.8 (Peripheral Blood Smear and Bone Marrow Aspirate/Biopsy)	Added peripheral blood smears to test for abnormal morphology.	Added as a safety assessment to align with prior safety commitments.
Section 8.2 (Subject Withdrawal Criteria)	Added additional information regarding subject withdrawal.	Add for clarity and alignment across tazemetostat protocols
Section 9.1 (Description of Study Drug)	Added tazemetostat FDA-approval information and updated the chemical name, structural formula of tazemetostat.	To provide more comprehensive and up-to-date information.
Section 9.2 (Concomitant Medication)	Updated to include additional information and guidance.	To provide more comprehensive and up-to-date information as well as for alignment across tazemetostat protocols.

Section # and Name	Description of Substantial Change	Rationale
Section 9.4 (Treatment Compliance) Section 12.2.5 (Special Situations: Overdose, Misuse, Abuse and Medication Error)	Moved and updated information regarding special situations.	For improved readability and to align with tazemetostat IB, version 11.0
Section 10.1 (Study Drug)	Added a table descripting the study drugs.	To provide more comprehensive and up-to-date information.
Section 10.2 (Study Drug Packaging and Labeling)	Updated to include additional information and guidance.	To provide more comprehensive and up-to-date information.
Section 10.3 (Study Drug Storage)	Updated to include additional information and guidance.	To provide more comprehensive and up-to-date information.
Section 10.5 (Administration)	Removed text stating that subjects enrolled will receive a prophylaxis treatment for *Pneumocystis jirovecii* (eg, sulfamethoxazole 800 mg plus trimethoprim 160 mg 3 times a week or acceptable alternative) for a total of 24 weeks, starting on Cycle 1 Day 1.	Removed as it is already stated in Section 9.2 (Concomitant Medications)
Section 11 (Assessment of Efficacy)	Updated to include additional information and guidance.	To provide more comprehensive and up-to-date information.
Section 11.3 (Independent Review Committee)	Updated to clarify timing of IRC	To clarify that an IRC will be formed if the data is promising and warrants label expansion for tazemetostat.
Section 11.4 (Survival Follow-up)	Updated to clarify timeframe and extent of survival follow-up.	To more accurately describe the role of survival follow-up in this study.
Section 12.1 (Safety Parameters)	Updated to include additional information and guidance.	For clarity and to align with the tazemetostat program.
Section 12.1.6 (Laboratory Assessments)	Updates to list clinical laboratory tests.	For clarity.
Section 12.5 (Quarterly and External Safety Review: The Tazemetostat Safety Committees)	Removed the sentence “Monitoring for AESI and other safety concerns will also be evaluated during SRC and by the IDMC” and other clarifications	To more accurately describe the role of the Quartery Safety Committee and External Safety Committee in this study.
CCI [redacted]		
Section 14 (Statistics)	Re-defined analysis sets. Added a section on futility analysis.	For clarity and to better align with the planned analyses.
Section 19 (Publication Policy)	Clarified timeline for clinical study report results.	To align with the tazemetostat program.

Section # and Name	Description of Substantial Change	Rationale
Appendix 2 (COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS)	Updated to use the most up-to-date language	To align with the tazemetostat program
Appendix 3 (LUGANO 2014 RESPONSE CRITERIA IN LYMPHOMA)	Replaced with a more detailed appendix	To provide more information regarding the Lugano Response Criteria
Appendix 4 (COCKCROFT-GAULT FORMULA) Appendix 6 (NEW YORK HEART ASSOCIATION CARDIAC DISEASE CLASSIFICATION) Appendix 7 (INTERPRETATION OF HEPATITIS B SEROLOGIC TEST RESULTS) Appendix 8 (INTERPRETATION OF RESULTS OF TESTS FOR HEPATITIS C VIRUS (HCV) INFECTION AND FURTHER ACTIONS)	Added new appendices	To provide sites with additional information

2. CLINICAL PROTOCOL SYNOPSIS

Name of Sponsor/Company: Epizyme, Inc.		
Name of Investigational Product: Tazemetostat (EPZ-6438)		
Name of Active Ingredient: Tazemetostat		
Protocol Number: EZH-1401	**Phase:** 2	**Country:** US
Title of Study: Symphony II: A Phase II Open-Label, Multicenter Trial of Oral Tazemetostat in Combination with Rituximab in Subjects with Relapsed/Refractory Follicular Lymphoma		
Study Center(s): Approximately 24 US sites.		
Study Period (years): The study duration is estimated to be approximately up to 5 years including enrollment time and follow-up.		
Background and Rationale for Study Subjects with follicular lymphoma (FL) who fail to achieve response after at least 2 prior lines of systemic therapy have a poor prognosis when treated with salvage chemotherapy alone or phosphoinositide 3-kinase (Pi3K) inhibitors. However, preclinical and clinical data indicate an opportunity for improved treatment response with the addition of targeted therapies inhibiting the enhancer of zeste homolog 2 (EZH2) pathway. The goal of this study is to examine the safety and efficacy of adding the EZH2 inhibitor, tazemetostat, compared to standard second line or beyond therapy as a means to improve disease response.		
Objectives: **Primary:** To assess the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in combination with rituximab in subjects with relapsed/refractory (R/R) FL and with wild-type (WT) EZH2 status. **Secondary:** • To evaluate the safety of the combination of tazemetostat and rituximab by assessing the incidence of adverse events (AEs)/serious adverse events (SAEs), change of vital signs, lab results, and physical exam findings from baseline • To estimate median progression-free survival (PFS) of tazemetostat in combination with rituximab at 2 years in subjects with R/R FL and WT EZH2 status, and in the pooled group regardless of mutation status. • To explore the response rate in a subset of subjects with mutant (MT) EZH2. • Evaluation of efficacy outcomes in rituximab refractory subjects **Exploratory:** • To estimate the overall survival (OS) of subjects receiving tazemetostat in combination with rituximab		
Endpoints **Primary Endpoint:** ORR, defined as the proportion of all subjects with WT EZH2 status achieving a CR or PR according to the 2014 Lugano Classification (Appendix 3) as assessed by Investigator and blinded independent review committee (IRC) at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24. **Secondary Endpoints:** • Type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent AEs or abnormalities of laboratory tests; SAEs; dose limiting toxicities (DLTs), or AEs leading to discontinuation of study treatment or death. • PFS, defined as the time from first dose of study drug to the time of the earliest date of CR or PR per the 2014 Lugano Classification (Appendix 3) or death, whichever occurs first, as assessed by an IRC.		

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- Duration of response (DOR), defined as the time from the earliest date of CR or PR per the 2014 Lugano Classification (Appendix 3) to documented progression or death, whichever comes first, as assessed by an IRC.
- ORR in the pooled group regardless of mutation status and in a subset of subjects with MT EZH2 at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24 for tazemetostat in combination with rituximab using 2014 Lugano Classification (Appendix 3).
- ORR in rituximab refractory subjects at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24 for tazemetostat in combination with rituximab using 2014 Lugano Classification (Appendix 3).

Exploratory:

- OS, 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

Study Design:

This is a phase 2, multicenter, open-label study of oral tazemetostat in combination with rituximab in subjects with R/R FL. Subjects will enroll into a single, open-label arm of the study where they will each be stratified based on EZH2 mutation status (MT or WT). Additionally, subjects will be stratified by previous experience with rituximab (rituximab refractory or rituximab-naïve). Stratification will occur during data analysis rather than at enrollment. This study is designed to evaluate the safety and efficacy of tazemetostat in combination with rituximab in subjects previously treated with at least 2 prior systemic lines of therapy for FL and features early futility stopping to maintain subject safety.

The first stage will enroll 15 subjects regardless of EZH2 mutational status. If there are 8 or fewer responses in these 15 subjects, the study will be considered futile. Enrollment will continue during the interim futility analysis. If 9 responses or greater are seen in the initial 15 subjects, additional subjects will be accrued for a total of 54 evaluable subjects regardless of mutation status. Futility analysis will be performed when the Cycle 6 Day 1 tumor assessment data are available for the first 15 subjects.

Based on Simon's 2-stage design, the primary analysis will occur after 43 evaluable subjects regardless of mutation status are available. Enrollment will continue during the primary analysis. Full set analysis will occur once data from 54 evaluable subjects regardless of mutation status are available.

Methodology:

This study includes a 28-day screening period, a 2-year (24-cycle) treatment period, and a follow-up period. During the treatment period, subjects will receive tazemetostat in combination with rituximab in 28-day cycles for the first 6 cycles followed by tazemetostat alone in 28-day cycles for the remaining 18 cycles, or until disease progression, unacceptable toxicity, or withdrawal of consent. Disease assessments will be performed at screening, Cycle 3 Day 1, Cycle 6 Day 1, Cycle 12 Day 1, Cycle 18 Day 1, and Cycle 24 Day 1.

Tazemetostat 800 mg twice daily will be administered daily starting on Cycle 1 Day 1 (C1D1). Tazemetostat is supplied by Epizyme in pre-counted, appropriately labeled bottles. Tazemetostat will be administered from C1D1 to the end of Cycle 24, for 24 months of therapy or until disease progression, unacceptable toxicity, or withdrawal of consent.

Rituximab will be administered by either subcutaneous injection or IV infusion according to the regional product prescribing information, labeling, and institutional guidelines. For subjects receiving rituximab via IV infusion, rituximab will be administered at a dose of 375 mg/m^2 on Day 1, 8, 15, and 22 of Cycle 1, and then on Day 1 of Cycles 3 through 6, accounting for an additional 4 doses (ie, a total of 8 doses of rituximab in 6 cycles).

For subjects receiving rituximab subcutaneously, rituximab will be administered at a dose of 375 mg/m^2 via IV infusion on Cycle 1 Day 1. Subcutaneous rituximab hyaluronidase will be administered as 1,400 mg rituximab and 23,400 Units hyaluronidase per 11.7 ml total volume (120 mg/2,000 Units per mL) on Cycle 1 Days 8, 15, and 22 and on Day 1 of Cycles 3 through 6, for a total of 8 doses of rituximab in 6 cycles (7 doses of SC rituximab after the initial IV infusion). Rituximab will be procured by the clinical sites from commercial sources.

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Sample Size Justification:

The primary objective of this study is to evaluate the overall response rate obtained in subjects with R/R FL, treated with the combination of rituximab and tazemetostat. Given the historical data with single agent rituximab (McLaughlin, 1998; Leonard, 2019), the Sponsor would consider the combined regimen to be of no further interest if the ORR were 50% or less, but of considerable interest if the ORR were at least 70%.

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 50% will be tested against the one-sided alternative. In the first stage, 15 subjects will be accrued. If there are 8 or fewer responses in these 15 subjects, the regimen will be considered as futile.

Subject enrollment will continue during futility analysis. If 9 responses or greater (CR + PR) are seen in the initial 15 subjects, additional subjects will be accrued for a total of 54 evaluable subjects. The Sponsor expects 80% of enrolled subjects to have WT EZH2 status. Consequently, the study will enroll approximately 43 WT subjects as well as approximately 11 MT subjects. With an estimated early dropout rate of 10%, this study estimates a total accrual of 59 subjects.

For the primary analysis, the null hypothesis will be rejected if 27 or more responses (CR + PR) are observed in the first 43 evaluable subjects regardless of mutation status. This design yields a one-sided type I error rate of 0.05 and power of 0.801 when the true response rate is 70%.

If the primary analysis is successful, full set analysis will be conducted once 54 evaluable subjects are available regardless of mutation status. Subjects in the Full Analysis Set (FAS) will be stratified to 2 subgroups depending on their EZH2 mutation status (WT vs MT).

With an estimated 54 eligible subjects in the combined FAS, rates of individual AEs can be estimated to within at most ± 14% (95% confidence interval). Any AE with a true rate of at least 5% is likely to be observed at least once (93% chance).

Assuming accrual takes place over 24 months, with at least an additional 12 months of follow-up for progression, there would be approximately 65% power to rule out a benchmark median PFS of 12 months against the alternative of a true PFS of 18 months (one-sided, 0.05 level test) in the primary analysis subset of approximately 43 subjects with at least 26 PFS events. If PFS is similar in both subsets regardless of EZH2 status, then there would be 80% power for the same analysis in the combined FAS of approximately 54 subjects with at least 33 PFS events.

The reporting of response rate in the MT EZH2 subset (anticipated to be 11 subjects) will have very little precision and is exploratory only. Note, the subjects with MT EZH2 will be included in all safety analyses.

Sample and power calculations are based on nQuery 8.0.

Number of Subjects (planned):

Approximately 59 subjects (assuming a 10% early drop-out rate resulting in approximately 54 evaluable subjects)

- Approximately 43 evaluable subjects with WT EZH2 (primary study population) and
- Approximately 11 evaluable subjects with MT EZH2

Diagnosis and Main Criteria for Eligibility

Inclusion Criteria:

1. Men and women of 18 years of age and older
2. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Appendix 1)
4. Life expectancy (in the opinion of the Investigator) of ≥3 months before enrollment
5. Have histologically confirmed FL, Grades 1 to 3a. Subjects may have R/R disease following at least 2 standard prior systemic treatment regimens where at least 1 anti-CD20-based regimen was used
6. Treatment recommended in accordance with the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria due to the presence of at least one of the following:

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a. Any nodal or extranodal tumor mass >7 cm diameter
b. Involvement of at least 3 nodal sites, each with diameter >3 cm
c. Presence of any systemic or B symptoms
d. Splenic enlargement with inferior margin below the umbilical line
e. Compression syndrome (ureteral, orbital, gastrointestinal)
f. Pleural or peritoneal serous effusion (irrespective of cell content)
g. Leukemic phase (>5.0 x 10^9/L circulating malignant cells)
h. Cytopenias (granulocyte count <1.0 x 10^9/L and/or platelets <100 x 10^9/L)

7. Meet the following laboratory parameters:
   a. Absolute neutrophil count (ANC) ≥ 750 cells/µL (0.75 x 10^9/L), or ≥ 500 cells/µL (0.50 x 10^9/L) in subjects with documented bone marrow involvement
   b. Platelet count ≥ 50,000 cells/µL (50 x 10^9/L), or ≥ 30,000 cells/µL (30 x 10^9/L) in subjects with documented bone marrow involvement, and without transfusion dependence
   c. Hemoglobin ≥ 8 g/dL
   d. Serum alanine aminotransferase (AST) and aspartate aminotransferase (ALT) ≤ 3.0 x ULN, unless related to disease involvement
   e. Total bilirubin ≤ 1.5 x ULN, unless due to disease involvement, Gilbert's syndrome, or hemolytic anemia
   f. Estimated creatinine clearance (ie, estimated glomerular filtration rate [eGFR] using Cockcroft-Gault [Appendix 4]) ≥ 40 mL/min
8. At least one bi-dimensionally measurable nodal lesion > 1.5 cm in its longest diameter by computed tomography (CT) scan or magnetic resonance imaging (MRI) excluding lesions that meet the following criteria:
   a. Previously irradiated lesions should not be counted as target lesions
   b. Lesions that are intended to be used to collect tissue samples for biopsy should not be counted as target lesions
   c. Bone lesions should not be counted as target lesions
9. Any clinically significant toxicity related to a prior anticancer treatment (ie, chemotherapy, immunotherapy, and/or radiotherapy), except for alopecia, either resolved to ≤ Grade 1 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 or is clinically stable and no longer clinically significant
10. Negative serologic or polymerase chain reaction (PCR) test results for acute or chronic hepatitis B virus (HBV) infection (Appendix 7)

    Note: Patients whose HBV infection status could not be determined by serologic test results must be negative for HBV-DNA by PCR to be eligible for study participation. Patients seropositive for HBV with undetectable HBV-DNA by PCR are permitted with appropriate antiviral prophylaxis.
11. Negative test results for hepatitis C virus (HCV) (Appendix 8) and human immunodeficiency virus (HIV)

    Note: Patients who are positive for HCV antibody must be negative for HCV-RNA by PCR to be eligible for study participation.
12. Females of childbearing potential (FCBP) must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 mIU/mL or equivalent units of β-hCG) at screening and within 24 hours prior to the first dose of study drug. All females will be considered to be of childbearing potential unless they are naturally postmenopausal (at least 12 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause) or have been sterilized surgically (ie, total hysterectomy and/or bilateral oophorectomy, with surgery completed at least 28 days prior to the first

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dose of study drug).

13. FCBP must either practice complete abstinence or agree to use a highly effective method of contraception beginning at least 28 days prior to the first dose of study drug, during study treatment (including during dose interruptions), for 6 months after tazemetostat discontinuation, and for 12 months after rituximab discontinuation. If the contraception methods provided in Section 9.3 are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject. Examples of highly effective methods of contraception (result in a failure rate of <1% per year when used consistently and correctly) may be found in Section 9.3. Female subjects must also refrain from breastfeeding or donating oocytes during study treatment and for 12 months following the last dose of rituximab.
14. Male subjects must have had a successful vasectomy (with medically confirmed azoospermia) OR must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a FCBP from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

    NOTE: Male subjects must not donate sperm from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

Exclusion Criteria:

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2
2. Grade 3b, mixed histology, or transformed FL
3. Treatment with any of the following anticancer therapies within the indicated timeframe of a specific treatment prior to first dose of study drug:
    a) Cytotoxic chemotherapy within 21 days
    b) Noncytotoxic chemotherapy (e.g., small molecule inhibitor) within 14 days
    c) Nitrosoureas within 6 weeks
    d) Prior immunotherapy within 4 weeks
    e) Radiotherapy – within 6 weeks from prior radioisotope therapy; within 12 weeks from 50% pelvic or total body irradiation
    f) Any investigational treatment within 4 weeks or at least 5 half-lives, whichever is shorter
4. History of solid organ transplant
5. Major surgery within 4 weeks of the start of study treatment
6. Thrombocytopenia, neutropenia, or anemia of Grade > 3 (per CTCAE v5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or myeloproliferative neoplasm (MPN)
7. Prior history of T-cell lymphoblastic lymphoma (T-LBL)/T-cell acute lymphoblastic leukemia (T-ALL)
8. Unwillingness to exclude grapefruit juice, Seville oranges, and grapefruits from the diet and/ or consumed within 1 week of the first dose of study drug
9. Subjects taking medications that are known strong cytochrome P450 (CYP)3A inhibitors and strong or moderate CYP3A inducers (including St. John's wort) (See Section 9.2.5 and https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers; https://drug-interactions.medicine.iu.edu/MainTable.aspx)
10. Any uncontrolled illness including, but not limited to, significant active infection requiring systemic (IV) therapy, hypertension, angina, arrhythmias, pulmonary disease, autoimmune dysfunction, immune thrombocytopenia, or autoimmune hemolytic anemia
11. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association classification > II [Appendix 6]), myocardial infarction or stroke within 6 months of first dose of study drug
12. History of clinically significant gastrointestinal (GI) conditions, particularly:
    a. Known GI condition that would interfere with swallowing or the oral absorption or tolerance of

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Name of Investigational Product: Tazemetostat (EPZ-6438)
Name of Active Ingredient: Tazemetostat
study drug b. Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption 13. Other diagnosis of cancer that is likely to require treatment in the next 2 years, with the exception of the following: a. Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin b. Curatively treated carcinoma in situ of the cervix c. Hormonal therapy for prostate cancer 14. Females who are pregnant or lactating/breastfeeding 15. Received a live virus vaccination within 28 days of first dose of rituximab 16. Participation in a separate investigational therapeutic study 17. Psychiatric illness/social situations that would interfere with study compliance
Investigational Product, Dosage, and Mode of Administration: Subjects will receive open-label tazemetostat 800 mg twice daily starting on Cycle 1 Day 1 until the end of Cycle 24, for 24 months of therapy or until disease progression, unacceptable toxicity, or withdrawal of consent. Tazemetostat is to be supplied by Epizyme in pre-counted, appropriately labeled bottles. Subjects will also receive open-label rituximab, administered by either subcutaneous injection or IV infusion according to the regional product prescribing information, labeling, and institutional guidelines, on Days 1, 8, 15, and 22 of Cycle 1 and then on Day 1 of Cycles 3 through 6, accounting for an additional 4 doses (ie, a total of 8 doses of rituximab in 6 cycles). Rituximab will not be provided and will be procured by the clinical sites from commercial sources.
Duration of treatment: Subjects will be treated in 28-day cycles with tazemetostat in combination with rituximab through Cycle 6 then tazemetostat alone through Cycle 24, for 24 months of therapy or until disease progression, unacceptable toxicity, or withdrawal of consent.
Criteria for Evaluation: **Efficacy:** Disease response rate (ORR) at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24 for tazemetostat in combination with rituximab using the Lugano 2014 Classification (Appendix 3). Other efficacy endpoints will be PFS and DOR, with disease progression defined by 2014 Lugano Classification. **Safety:** Safety will be assessed through summaries of AEs, laboratory evaluations, vital signs, and physical examinations. Safety analyses will be based on all enrolled subjects who receive at least 1 dose or partial dose of study drugs (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all AEs is to be evaluated by the Investigator based on the CTCAE, version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA; version 23.1). The number and percentage of subjects with AEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the NCI's CTCAE, version 5.0. Laboratory shift tables of the baseline results to each of the subsequent visits will be produced.
Statistical Methods: **Primary Efficacy Endpoint – All Phase 2 Cohorts** • **ORR:** ORR is defined as the proportion of the FAS subjects with WT EZH2 status achieving a CR or PR according to the 2014 Lugano Classification (Appendix 3) as assessed by Investigator and blinded IRC at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24. Subjects with a best response of unknown/non-evaluable response will be treated as non-responders, (i.e., they will be

Name of Sponsor/Company: Epizyme, Inc.
Name of Investigational Product: Tazemetostat (EPZ-6438)
Name of Active Ingredient: Tazemetostat

included in the denominator when calculating the percentage). ORR will be presented with corresponding 2-sided 95% CIs. This analysis will be performed on a subset of the FAS that includes all subjects with WT EZH2 status.

Secondary Efficacy Endpoints:

- **PFS:** The PFS, defined as the time from the first dose of study drug to the earliest date of disease progression per the 2014 Lugano Classification (Appendix 3) or death from any cause, whichever occurs first, will be assessed by IRC. PFS will be estimated using Kaplan-Meier method and presented with corresponding 2-sided 95% CIs. PFS will be analyzed using the FAS.
- **DOR:** The DOR, defined as the time from the earliest date of CR or PR per the 2014 Lugano Classification (Appendix 3) to documented progression or death, whichever comes first, will be assessed by IRC. DOR will be estimated using Kaplan-Meier method and be presented with corresponding 2-sided 95% CIs. DOR will be analyzed using the FAS.
- **ORR:** Analysis of ORR as a secondary endpoint will be similar to analysis of the primary efficacy endpoint using the defined subgroups (MT EZH2 or rituximab refractory subjects). ORR as a secondary endpoint will be performed on the pooled group regardless of mutation status and in a subset of the FAS that includes all subjects with MT EZH2. Additionally, ORR will be analyzed in a subset of the FAS that includes rituximab refractory subjects.

Exploratory Efficacy Endpoints

- **OS:** The OS, 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 surviving at the time of OS analysis, the time of death will be censored at the date of last contact.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
^{18}FDG-PET	^{18}fluorodeoxyglucose-positron emission tomography
1L	first-line
2L	second-line
ABC	activated B-cell-like
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from zero time to 24 hours
β-hCG	beta-human chorionic gonadotropin
B-ALL	B-cell acute lymphoblastic leukemia
BID	twice daily
BP	blood pressure
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
C_{max}	maximum drug concentration
CL	total body clearance
COP	CHOP without doxorubicin
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCFR	estimated glomerular filtration rate

Abbreviation	Term
eCRF	electronic case report form
ESC	External Safety Committee
EU	European Union
EZH2	enhancer of zeste homolog 2
FCBP	females of childbearing potential
FDA	Food and Drug Administration
FE	food effect
FFPE	formalin fixed paraffin embedded
FL	follicular lymphoma
GCB	germinal-center B-cell-like
GCP	Good Clinical Practices
GELF	Groupe d'Etude des Lymphomes Folliculaires
GI	gastrointestinal
H3K27	histone H3 lysine 27
H3K27me3	trimethylated state of histone H3 lysine 27
HAT	histone acetyltransferase
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HMT	histone methyltransferase
HR	heart rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INI1	integrase interactor 1
IRB	Institutional Review Board
IRC	Independent review committee
IV	intravenous
LDH	lactate dehydrogenase
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MT	mutant
MTD	maximum tolerated dose

Abbreviation	Term
NCI	National Cancer Institute
NE	not evaluable
NHL	non-Hodgkin lymphoma
NYHA	New York Heart Association
OS	overall survival
ORR	objective response rate
PCR	polymerase chain reaction
PD	pharmacodynamic(s) or progressive disease
PET	positron-emission tomography
PFS	progression-free survival
PI	Principal Investigator
Pi3K	phosphoinositide 3-kinase
PMBCL	primary mediastinal B cell lymphoma
PR	partial response
PRC2	polycomb repressive complex 2
PT	preferred term
QSR	Quarterly Safety Review
R	accumulation ratio
R-CHOP	rituximab plus CHOP
R-DHAP	rituximab, dexamethasone, cytarabine, and cisplatin
RECIST	Response Evaluation Criteria in Solid Tumors
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide phosphate
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMARC	switch/sucrose nonfermentable-related, matrix-associated, actin-dependent regulator of chromatin
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SWI/SNF	switch/sucrose nonfermentable
$t_{1/2}$	elimination half-life
T-ALL	T-cell acute lymphoblastic leukemia
tazemetostat (EPZ-6438 and E7438)	investigational study drug: *N*-[(4,6-Dimethyl-2-oxo-1,2- dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4- yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide
TEAE	treatment-emergent adverse event

Abbreviation	Term
T-LBL	T-cell lymphoblastic lymphoma
ULN	upper limit of normal
US/USA	United States/United States of America
UTX	ubiquitously transcribed tetratricopeptide repeat, X chromosome
VP	vice president
WT	wild-type

5. INTRODUCTION

5.1. Follicular Lymphoma

In 2021, non-Hodgkin Lymphoma (NHL) represented the seventh most frequent cancer in men and the sixth in women (Siegel, 2020). Follicular lymphoma (FL) is a lymphoproliferative neoplasia of follicular center B cells and is the most common subtype of indolent NHL, representing approximately 35% of all NHLs (Freedman, 2018).

In 2016, there were an estimated 13,960 new cases of FL in the United States (US) (Teras, 2016). The average age at diagnosis is 65 years, and the disease is equally represented in males and females. The malignancy most commonly presents with insidious and painless onset of lymphadenopathy, which can be bothersome for years. While 70% of patients have bone marrow involvement, involvement of other organs is uncommon. Fewer than 20% of patients present with B symptoms or increased serum lactate dehydrogenase (LDH) (Freedman, 2018). The risk of histologic transformation of FL to a more aggressive diffuse large B-cell lymphoma (DLBCL) is ~3% per year (Montoto, 2007). Patients with low-grade FL are often asymptomatic; however, at the time of diagnosis, more than 80% of patients are at an advanced disease stage. Patients with asymptomatic, advanced-stage FL do not require immediate treatment. However, for patients with symptomatic nodal disease, extranodal disease, B symptoms, cytopenias, and/or end organ dysfunction, immediate treatment is required.

Although the past several decades have witnessed improvements in FL outcomes due to the addition of anti-CD20 antibodies, including rituximab, to chemotherapy regimens, FL remains a largely incurable disease, characterized by multiple relapses. The disease follows a highly heterogeneous course, with 10-year overall survival (OS) rates ranging from 36% for patients classified as high risk by the follicular lymphoma international prognostic index (FLIPI) to 71% for patients with few risk factors (Solal-Celigny, 2004). Despite this heterogeneity, nearly all advanced stage FL patients will relapse within 5 years of first-line (1L) treatment, regardless of the regimen (Fowler, 2016). The backbone of treatment for patients with symptomatic, advanced stage FL is an anti-CD20 antibody (rituximab or obinutuzumab) as a single agent or in combination with chemotherapy comprised of 1 or more of the following: alkylating agents, anthracyclines, antimitotic agents, or purine analogues (McNamara, 2012; Dreyling, 2014; Horwitz, 2016). The most frequently utilized 1L immunochemotherapy regimens are bendamustine and rituximab (BR) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The main goal of 1L therapy is disease control and prevention of disease-related complications. Although current 1L treatments for FL are initially effective in inducing responses, the duration of response (DOR) is variable, and most patients (~75%) eventually require second-line (2L) treatment (Dreyling, 2016; National Comprehensive Cancer Network, 2018). DLBCL and FL are the 2 most common lymphoid malignancies with annual incidences of 3.8 and 2.2/100,000, respectively, in Europe (Sant, 2010) and 6.9 and 3.7/100,000, respectively, in the US (National Cancer Institute, 2014). For both DLBCL and advanced FL, chemoimmunotherapy with rituximab has substantially improved long-term disease control (Dreyling, 2014; Tilly, 2015). There are 3 histologically indistinguishable molecular subtypes of DLBCL: the activated B-cell-like (ABC) subtype, the germinal-center B-cell-like (GCB) subtype, and the primary mediastinal B cell lymphoma (PMBCL) subtype. These subtypes differ in terms of gene expression and are believed to originate in B cells at different stages of

differentiation. In addition, the process of malignant transformation differs for each subtype, resulting in distinctive patterns of genetic abnormality. Clinical presentation and responsiveness to targeted therapies also vary across the subtypes (Foon, 2012).

The treatment landscape in patients with R/R FL in the 2L setting is not significantly different than for the 1L setting with immunochemotherapy as the main treatment choice (Dreyling, 2016; National Comprehensive Cancer Network, 2018). Following relapse to 2L therapy, US treating physicians estimate that approximately 60% of patients will receive third-line treatment. Patients who have failed ≥2 prior lines of therapy are often elderly and have a variety of co-morbid conditions, including diminished renal, cardiac, and/or hepatic function. As a result, these patients may not be able to tolerate a full course of combination immunochemotherapy. For these patients, consideration must be given to simplicity of use, benefit/risk balance, and both short as well as long-term toxicities (Sehn, 2016).

5.2. Investigational Product

5.2.1. Tazemetostat

Post-translational modifications of histones, the core proteins of chromatin, play an important role in controlling the fidelity of cellular gene transcription patterns. One of the critical transcription-controlling histone modifications is methylation of specific lysine and arginine residues, catalyzed by histone methyltransferases (HMTs) (Copeland, 2013). An HMT, enhancer of zeste homologue 2 (EZH2), is the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono-, di-, and tri-methylation of lysine 27 of histone H3 (H3K27) (Margueron, 2011). Trimethylated H3K27 (H3K27me3) catalyzed by EZH2 is a methyl mark associated with repressed transcription, known to suppress genes involved in development and cellular differentiation.

Gain of function EZH2 mutations and/or over-expression lead to an aberrant H3K27me3 state that is oncogenic (Chase, 2011). Over-expression or amplification of EZH2 has been described in numerous tumor types, including but not limited to prostate, ovarian, small cell lung cancer, bladder, breast cancer, colorectal, mesothelioma, uveal melanoma, renal carcinoma, cholangiocarcinoma, and stomach cancer (Kuroki, 2014; LaFave, 2015; Poirier, 2015; Comet, 2016). Loss of function EZH2 mutations or under-expression, on the other hand, can result in tumor suppression.

Tazemetostat is a selective, reversible, orally bioavailable, small molecule inhibitor of EZH2, an HMT (Knutson, 2013).

Tazemetostat inhibits both WT EZH2 and MT EZH2 isoforms with half-maximal inhibitory concentrations ranging from 2 to 38 nmol/L. The compound shows a 36-fold selectivity over the most closely related HMT (enhancer of zeste homologue 1), and a >4500-fold selectivity over other HMTs. It selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective in vitro killing of lymphoma cell lines and in vivo tumor growth regression in xenograft lymphoma models (Knutson, 2014; Brach, 2017). In both in vitro and in vivo settings, cell killing or tumor growth inhibition were observed in both EZH2 mutant (MT) and EZH2 wild-type (WT) models, with the median sensitivity always greater in MT over WT models (Knutson, 2014; Brach, 2017).

5.2.2. Tazemetostat Clinical Experience

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

- NHL, including DLBCL and FL
- mantle cell lymphoma
- multiple myeloma
- integrase interactor 1 (INI1) or switch/sucrose nonfermentable (SWI/SNF)-related, matrix-associated, actin-dependent regulator of chromatin (SMARC), subfamily A, member 4 (SMARCA4)-deficient tumors in both adult and pediatric populations (including synovial sarcoma, rhabdoid tumors, renal medullary carcinoma, epithelioid sarcoma, other INI1- or SMARCA4-deficient tumors)
- prostate cancer
- ovarian cancer
- mesothelioma
- small cell lung cancer

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

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

Based on the clinical experience in 779 adult subjects as of 12 April 2021, this section summarizes the anticipated safety profile for tazemetostat.

The following treatment-emergent AEs, regardless of causality, have been observed in ≥10% of adult subjects across clinical studies: nausea, fatigue, vomiting, diarrhea, cough, anemia, decreased appetite, asthenia, dyspnea, constipation, thrombocytopenia, abdominal pain, and cancer pain.

Tazemetostat treatment-emergent serious adverse events (SAEs) have been reported in 326 (42%) subjects in the adult clinical study population. Serious adverse reactions that are considered expected for tazemetostat in the adult population are nausea (27%), fatigue (22%), vomiting (19%), diarrhea (17%), anemia (16%), decreased appetite (16%), asthenia (15%), dyspnoea (14%), constipation (13%), abdominal pain (11%), thrombocytopenia (11%), back pain (9%), headache (8%), and neutropenia (7%). Refer to the tazemetostat Investigator Brochure (IB) for additional detail.

The most common TEAEs that have led to interruption of tazemetostat dosing in the adult population were thrombocytopenia (5%), neutropenia (3%), and anemia and diarrhea (each 2%).

The most common TEAEs leading to tazemetostat dose reduction in the adult population were thrombocytopenia, neutropenia and diarrhea, each reported in <1% of adult subjects.

In addition, as described in Section 12.2.2, AESIs identified for the tazemetostat development program include: T-cell lymphoblastic lymphoma (T-LBL)/ T-cell acute lymphoblastic leukemia (T-ALL), myelodysplastic syndrome (MDS), AML (acute myeloid leukemia), and other myeloid malignancies like myeloproliferative neoplasm (MPN). Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients. One event of T-LBL has occurred in pediatric subjects (n=109). The risk of T-LBL/T-ALL in adults is not known; however, the incidence of treatment-related T-LBL/T-ALL in adults is expected to be uncommon. As of 12 April 2021, over 958 subjects (adults and pediatrics) have been treated with tazemetostat as monotherapy and in combination other anti-neoplastic therapies with no other reported cases of T-LBL/T-ALL.

As of 12 April 2021, 7 myeloid malignancies have been reported in an estimated cumulative exposure of 1521 patients from both clinical and post-marketing sources. All 7 events were reported in adult clinical trial subjects. The risk of myeloid neoplasms as a result of EZH2 inhibition is considered uncertain based on available literature and Epizyme clinical data. Measures are in place to exclude potential subjects who may be predisposed to developing a myeloid neoplasia from participation in clinical studies and for early identification and monitoring of subjects who may be developing a myeloid neoplasia.

A single event of B-cell acute lymphoblastic leukemia (B-ALL) was reported in an adult subject with predisposing factors and is considered under evaluation. Refer to Section 12.2.4.2.1 for further details.

Measures are in place to exclude potential subjects who may be predisposed to developing a myeloid/lymphoid neoplasia from participation in clinical studies and for early identification and monitoring of subjects who may be developing a myeloid/lymphoid neoplasia.

Further details of study designs, tazemetostat exposure, and TEAEs regardless of causality are outlined in the current IB.

5.2.3. Rituximab

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG1 κ immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM.

5.2.4. Rituximab Clinical Experience

RITUXAN ® (rituximab) received approval for marketing in the US to treat the following:

- Adult patients with NHL
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.

  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  - Non-progressing (including stable disease), low-grade, CD20- positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone chemotherapy.
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) or other anthracycline-based chemotherapy regimens.
- Adult patients with Chronic Lymphocytic Leukemia
  - Previously untreated and previously treated CD20-positive chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide
- Rheumatoid Arthritis in combination with methotrexate in adult patients with moderately-to severely-active rheumatoid arthritis who have inadequate response to one or more tumor necrosis factor antagonist therapies
- Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis in adult and pediatric patients 2 years of age and older in combination with glucocorticoids
- Moderate to severe Pemphigus Vulgaris in adult patients

Additionally, rituximab is approved in over 100 countries for the treatment for R/R NHL.

Additional details regarding rituximab can be found in the local package insert.

5.3. Study Rationale

The proposed clinical study is a multicenter, open-label, Phase 2 study that will be initiated at a recommended dose of 800 mg twice daily in combination with rituximab. Patients with FL who fail to achieve response after front-line chemoimmunotherapy have a poor prognosis when treated with salvage chemotherapy alone or phosphoinositide 3-kinase (Pi3K) inhibitors. However, preclinical and clinical data indicate an opportunity for improved treatment response with the addition of targeted therapies that synergize with EZH2 inhibition (Knutson, 2014; Brach, 2017). The goal of this study is to examine the feasibility and efficacy of adding the EZH2 inhibitor, tazemetostat, to standard of care therapy, rituximab, as a means to improve disease response. Previous combinations of tazemetostat and standard of care therapies include tazemetostat plus R-CHOP in subjects with DLBCL (Sarkozy, 2020) and the CD20 molecule expressed on neoplastic B cells has been demonstrated to be a target for therapy of B-cell lymphomas and leukemia (Falchi, 2018). Rituximab is a human/murine, chimeric anti-CD20 monoclonal antibody. Rituximab induces killing of B cells expressing the antigen CD20 via multiple mechanisms, binds human Clq, and mediates complement-dependent cell lysis in the presence of human complement as well as antibody-dependent cellular cytotoxicity with human effector cells (Reff, 1994). In NHL cell lines, the binding of the antibody inhibits proliferation and directly induces apoptosis by increasing the Bcl-2 gene family member Bax (Mathas, 2000).

Since rituximab was first approved, over 20 years ago, it has become a standard of care treatment for FL, DLBCL, chronic lymphocytic leukemia, and mantle cell lymphoma known for prolonging survival rates and improving the clinical prognosis for patients with B-cell malignancies (Salles, 2017).

Changes to the tumor microenvironment, for instance those affecting antitumor immunity, are increasingly recognized as an important mechanism in lymphomagenesis, affecting all types of NHL (Scott, 2014). Epigenetic therapy has been suggested to release repression of molecules important for immune recognition on tumor cells (Wrangle, 2013). The anti-tumor effects of tazemetostat in B cell malignancies as well as the pleiotropic immune activating effects of tazemetostat on the tumor microenvironment make it a promising candidate for combination with rituximab. For example, EZH2 inhibition can overcome mechanisms of immune tolerance in the tumor microenvironment by diminishing the impact of regulatory T cells, increasing natural killer and natural killer T cell differentiation and function, and decreasing immunosuppressive myeloid-derived suppressor cell trafficking, while upregulating antigen presentation (Reviewed in (Kim, 2020)). In addition, EZH2 inhibition has been shown to upregulate proapoptotic Bcl-2 family members and prime mitochondria to apoptosis in models of DLBCL in vitro and in vivo (Scholze, 2020).

Follicular lymphoma is highly dependent on the tumor microenvironment; therefore, no relevant cell line models exist (Pound, 1997). Data were generated by Epizyme in a panel of DLBCL cell lines as a surrogate because of their common features including cell-of-origin and oncogenic driver mutations in EZH2, histone-lysine N methyltransferase 2D (KMT2D or MLL2), cyclic adenosine monophosphate (cAMP) responsive element binding protein 1 binding protein (CREBBP), and in components of the NF-kB and B-cell receptor signaling pathways (Morin, 2010; Pasqualucci, 2011). In studies conducted by Epizyme, long term in vitro proliferation assays showed that treatment with tazemetostat for 11 days elicited growth inhibitory activity with IC_{50} values of < 1μM in 16 of 36 DLBCL cell lines tested (Knutson, 2014; Brach, 2017). The effects are due to unsilencing of tumor suppressors and factors that mediate B cell differentiation (Knutson, 2014). Cell lines carrying mutations in EZH2 are in general more sensitive to tazemetostat than those with wild type EZH2 (Knutson, 2014; Brach, 2017). In addition, in an RNAseq study in a panel of 36 DLBCL cell lines, in vitro treatment with tazemetostat for 4 days showed an increase in CD20 mRNA expression in both mutant and wild-type EZH2 cell lines (Brach, 2017). Lastly, to investigate the potential combinatorial activity of EZH2 inhibition and anti-CD20 therapy, in vitro combination studies were performed in a panel of 13 DLBCL cell lines. Cell line cultures were cotreated for 7 days with tazemetostat and rituximab and results demonstrated synergistic antiproliferative activity in 4 of 13 DLBCL cell lines tested while an additive effect was observed in the rest of the cell lines.

Taken together these data provide a mechanistic rationale for a potential enhancement of anti-CD20 antibody therapy with EZH2 inhibition and we hypothesize that inhibition of EZH2 by tazemetostat could modulate gene expression in rituximab refractory patients to permit restoration of anti-CD20 sensitivity, and hence warrants clinical study in the population of rituximab refractory patients in the proposed study.

5.3.1. Rationale for Study Dosage Selection

Previous monotherapy and combination studies with tazemetostat [redacted] have found a safe and potentially efficacious dose level of 800 mg twice daily which will be the starting dose level in this study. Rituximab will be given per institutional guidelines and administered by either subcutaneous injection or IV infusion, according to the regional product prescribing information and labeling. Rituximab will be administered on Day 1, 8, 15, and 22 of Cycle 1, and then on Day 1 of Cycles 3 through 6, accounting for an additional 4 doses, ie, a total of 8 doses of rituximab in 6 cycles.

6. TRIAL OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

- To assess the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in combination with rituximab in subjects with R/R FL and with WT EZH2 status .

6.1.2. Secondary Objectives

- To evaluate the safety of the combination of tazemetostat and rituximab by assessing the incidence of adverse events/serious adverse events, change of vital signs, lab results, and physical exam findings from baseline
- To estimate median progression-free survival (PFS) of tazemetostat in combination with rituximab at 2 years in subjects with R/R FL and WT EZH2 status, and in the pooled group regardless of mutation status.
- To explore the response rate in a subset of subjects with MT EZH2.
- Evaluation of efficacy outcomes in rituximab refractory subjects

6.1.3. Exploratory Objective

- To estimate the OS of subjects receiving tazemetostat in combination with rituximab

6.2. Endpoints

6.2.1. Primary Endpoint

- ORR, defined as the proportion of all subjects with WT EZH2 status achieving a CR or PR according to the 2014 Lugano Classification (Appendix 3) as assessed by Investigator and blinded independent review committee (IRC) at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24

6.2.2. Secondary Endpoints

- Type, frequency, severity, timing of onset, duration, and relationship to study drug of any TEAEs or abnormalities of laboratory tests; SAEs; dose limiting toxicities (DLTs), or AEs leading to discontinuation of study treatment or death.
- PFS, defined as the time from first dose of study drug to the time of the earliest date of CR or PR per the 2014 Lugano Classification (Appendix 3) or death, whichever occurs first, as assessed by an IRC.
- Duration of response (DOR), defined as the time from the earliest date of CR or PR per the 2014 Lugano Classification (Appendix 3) to documented progression or death, whichever comes first, as assessed by an IRC.

- ORR in the pooled group regardless of mutation status and in a subset of subjects with MT EZH2 at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24 for tazemetostat in combination with rituximab using 2014 Lugano Classification (Appendix 3).
- ORR in rituximab refractory subjects at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24 for tazemetostat in combination with rituximab using 2014 Lugano Classification (Appendix 3).

6.2.3. Exploratory Endpoint

- OS, 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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

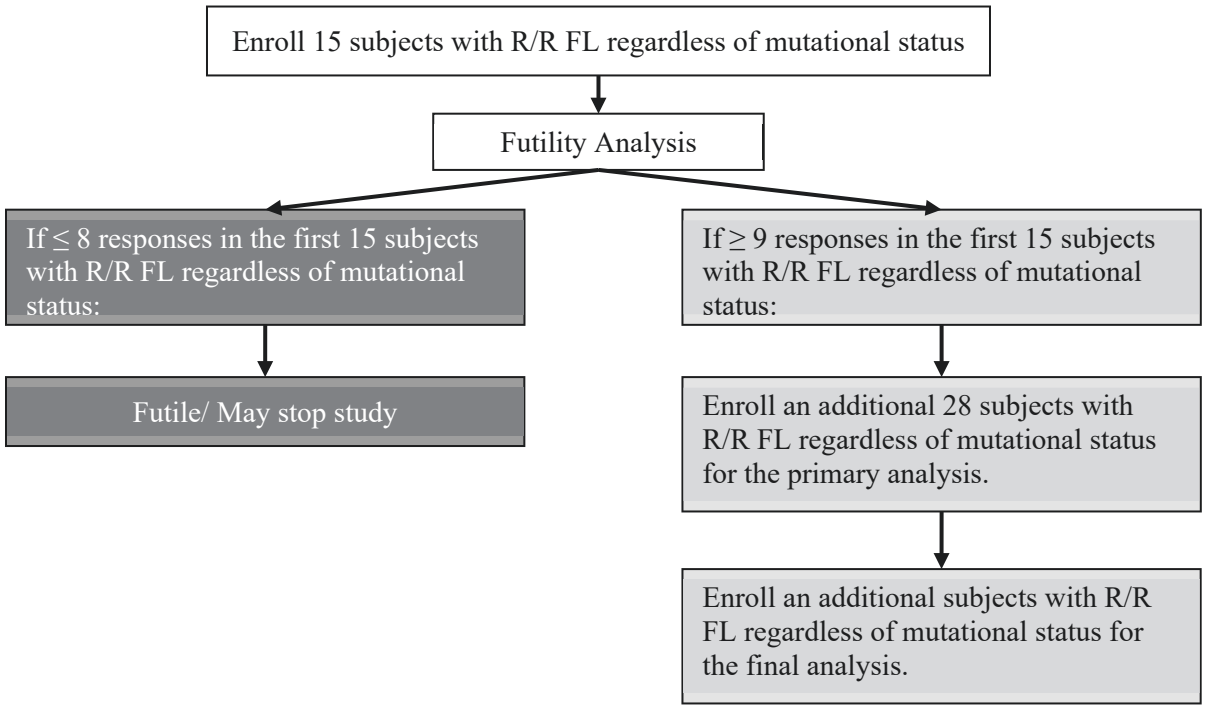
This is a phase 2, multicenter, open-label study of oral tazemetostat in combination with rituximab in subjects with R/R FL. Subjects will enroll into a single, open-label arm of the study where they will each be stratified based on EZH2 mutation status (MT or WT). Additionally, subjects will be stratified by previous experience with rituximab (rituximab refractory or rituximab-naïve). Stratification will occur during data analysis rather than at enrollment. This study is designed to evaluate the safety and efficacy of tazemetostat in combination with rituximab in subjects previously treated with at least 2 prior systemic lines of therapy for FL and features early futility stopping to maintain subject safety.

The first stage will enroll 15 subjects regardless of EZH2 mutational status. Futility analysis will be performed when the Cycle 6 Day 1 tumor assessment data are available for the first 15 subjects. If there are 8 or fewer responses in these 15 subjects, the study will be considered futile. Enrollment will continue during the interim futility analysis. If 9 responses or greater are seen in the initial 15 subjects, additional subjects will be accrued for a total of 54 evaluable subjects regardless of mutation status.

Based on Simon's 2-stage design, the primary analysis will occur after 43 evaluable subjects regardless of mutation status are available. Enrollment will continue during the primary analysis. Full set analysis will occur once data from 54 evaluable subjects regardless of mutation status are available.

This study includes a 28-day screening period, a 2-year (24-cycle) treatment period, and a follow-up period. During the treatment period, subjects will receive tazemetostat in combination with rituximab in 28-day cycles for the first 6 cycles followed by tazemetostat alone in 28-day cycles for the remaining 18 cycles, or until disease progression, unacceptable toxicity, or withdrawal of consent. Disease assessments will be performed at screening, Cycle 3 Day 1, Cycle 6 Day 1, Cycle 12 Day 1, Cycle 18 Day 1, and Cycle 24 Day 1.

Figure 1: Study Schema



Note: Enrollment will not stop during futility analysis or primary analysis.

7.2. Number of Subjects

Approximately 59 subjects (assuming a 10% early drop-out rate) will be enrolled to obtain approximately 54 evaluable subjects in the final statistical analysis:

- Approximately 43 evaluable subjects with WT EZH2 (primary study population) and
- Approximately 11 evaluable subjects with MT EZH2

7.3. Treatment Assignment

Tazemetostat 800 mg twice daily will be administered starting on Cycle 1 Day 1 (C1D1). Tazemetostat is supplied by Epizyme in pre-counted, appropriately labeled bottles. Tazemetostat will be administered from C1D1 to the end of Cycle 24, for 24 months of therapy or until disease progression, unacceptable toxicity, or withdrawal of consent.

Rituximab will be administered by either subcutaneous injection or IV infusion according to the regional product prescribing information, labeling, and institutional guidelines. For subjects receiving rituximab via IV infusion, rituximab will be administered at a dose of 375 mg/m^2 on Day 1, 8, 15, and 22 of Cycle 1, and then on Day 1 of Cycles 3 through 6, accounting for an additional 4 doses (ie, a total of 8 doses of rituximab in 6 cycles).

For subjects receiving rituximab subcutaneously, rituximab will be administered at a dose of 375 mg/m^2 via IV infusion on Cycle 1 Day 1. Subcutaneous rituximab hyaluronidase will be administered as 1,400 mg rituximab and 23,400 Units hyaluronidase per 11.7 ml total volume (120 mg/2,000 Units per mL) on Cycle 1 Days 8, 15, and 22 and Day 1 of Cycles 3 through 6,

for a total of 8 doses of rituximab in 6 cycles (7 doses of SC rituximab after the initial IV infusion). Rituximab will be procured by the clinical sites from commercial sources.

7.4. Dose Adjustment Criteria

7.4.1. Dose Adjustment for Tazemetostat

Tazemetostat dose reductions and interruptions will be allowed; however, an interruption in the administration of tazemetostat for more than 14 days must be discussed with the Medical Monitor before treatment can be resumed.

Toxicity will be managed by concomitant medication (as appropriate), treatment interruption, dose reduction, and treatment discontinuation, or a combination of these. During treatment with tazemetostat, dose interruption and reduction for subjects who experience tazemetostat-**related** toxicity will be in accordance with the Dose Modifications instructions in Table 1.

For subjects who require dose interruption due to tazemetostat-related toxicity, the treatment may restart once the toxicity has been resolved to Grade ≤ 1 or baseline, unless otherwise noted, according to the Dose Modifications instructions in Table 1. No tazemetostat dose re-escalation is permitted.

For continuation of treatment for Cycle 2 and beyond, subjects must meet the following retreatment criteria:

- Platelet count must be ≥ 50 x 10^9/L
- Absolute neutrophil count (ANC) must be ≥ 0.75 x 10^9/L, and
- Any Grade 3 or higher toxicity must have resolved to ≤Grade 1 or baseline, unless otherwise noted

Table 1: Dose Modifications for Tazemetostat Treatment-Related Toxicities

Tazemetostat-Related Toxicity[a]	During Therapy	Approximate Dose Adjustment[b]
Grade 1		
All occurrences	Continue tazemetostat	Maintain dose level
Grade 2[c,d]		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Maintain dose level
2nd occurrence (same or new toxicity)		Restart at 600 mg BID
3rd occurrence (same or new toxicity)		Restart at 400 mg BID
4th occurrence (same or new toxicity)		Discuss with Medical Monitor
Grade 3[c] (Not Including Neutropenia and Thrombocytopenia)		
1st occurrence		Restart at 600 mg BID

Tazemetostat-Related Toxicity[a]	During Therapy	Approximate Dose Adjustment[b]
2nd occurrence (same or new toxicity)	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 400 mg BID
3rd occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 Neutropenia (ANC: < 1.0 – 0.5 × 10^9/L)[e]		
ANC ≥ 0.75 × 10^9/L	Continue tazemetostat	Maintain dose level
ANC < 0.75 × 10^9/L 1st occurrence	Interrupt tazemetostat until resolved to ANC ≥ 0.75 × 10^9/L	Restart at 600 mg BID
2nd occurrence		Restart at 400 mg BID
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 3 Thrombocytopenia[f]		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 2 or baseline[b]	Restart at 600 mg BID
2nd occurrence		Restart at 400 mg BID
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 4		
Any occurrence	Interrupt tazemetostat until resolved to Grade 2 or less	Discuss with Medical Monitor

ANC = absolute neutrophil count, ASCO = American Society of Clinical Oncology; BID = twice daily
[a] Excluding alopecia and nausea, vomiting or diarrhea not receiving adequate treatment
[b] An interruption of tazemetostat for more than 14 days due to any toxicity must be discussed with the Medical Monitor before treatment can be resumed
[c] Excluding Grade 2 and 3 anemia: subjects are allowed to continue tazemetostat at their current dose level with transfusion per Investigator discretion
[d] Excluding Grade 2 neutropenia and thrombocytopenia
[e] Use of growth factors (G-CSF, GM-CSF) is permitted as per ASCO or institutional guidelines
[f] Subjects are allowed to receive platelet transfusion per Investigator discretion

7.4.2. Dose Adjustment for Rituximab

The dose of rituximab should not be reduced. Administration of rituximab may be interrupted and modified according to the clinical practice of the Investigator's institution (eg, dose splitting or dose banding), and in line with the approved prescribing information including administration, warnings, precautions, contraindications, and adverse reactions, as applicable. In case a dose of rituximab is missed during Cycle 1 because of toxicity, it will not be rescheduled. In case of delay in the start of the next cycle (Cycles 3 through 6) due to toxicity, rituximab administration will be postponed until AE has resolved, at which point the next cycle is started. If rituximab is discontinued due to toxicity, tazemetostat should be continued as per protocol and the subject should continue in the study.

7.5. Continuation of Treatment

Subjects will receive study treatment for 24 cycles across the clinical trial or until disease progression, unacceptable toxicity, or withdrawal of consent. However, if subjects experience disease progression during study treatment, they may be permitted to continue treatment on study

post-progression if they meet the 2014 Lugano Classification (Cheson, 2014; Appendix 3) criteria for disease progression as well as the following criteria:

- absence of symptoms and signs (including worsening of laboratory values, eg, new or worsening hypercalcemia) that indicate unequivocal disease progression
- no decline in ECOG performance status
- absence of tumor growth at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Subjects whose radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they have evidence of clinical benefit and continue to meet the above criteria. Investigators who note subjects with disease progression that are receiving continued clinical benefit without clinical deterioration must contact the Medical Monitor to discuss the assessment of risk/benefit of maintaining the subject on study.

7.6. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study for medical reasons or for any other reason at any time. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). Study records must be retained as noted in Section 18 .

7.7. Schedule of Procedures/Assessments

Schedule of Visits and Procedures for assessments are presented in Table 2.

Potential subjects will undergo a screening assessment within 28 days before the start of the study to evaluate their eligibility for the study. Before any procedures or assessments are performed, the nature of the study, and the potential risks associated with the study will be explained to all subject candidates and written informed consent will be obtained. Once informed consent has been obtained, study procedures and evaluations will be performed.

If Screening is done within 72 hours of Cycle 1 Day 1 (C1D1), local laboratory tests and physical exam do not need to be repeated.

Efforts should be made to conduct study visits on the day scheduled. Whenever possible, subjects should be evaluated at approximately the same time of the day (eg, morning or afternoon) at each visit, and reasonable efforts should be made to conduct all evaluations in the same test order at each visit.

Table 2: Schedule of Visits and Procedures

Procedures/ Assessments[a]	**Screen-ing**[b]	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycles 9, 12, 15, 18, 21, & 24**[c]	**EOT**[d]	**Safety Follow-up**[e]	**Survival Follow up**[f]
Cycle Day	**Day (-28 to -1)**	**Day 1 (± 1 Days)**	**Day 8 (± 1 Days)**	**Day 15 (± 1 Days)**	**Day 22 (± 1 Days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 7 days)**	**Within 7 Days After Last Dose**	**30 Days After Last Dose (+5 Days)**	**Every 90 Days (± 30 Days)**
Site visit	X	X	X	X	X	X	X	X	X	X	X	X	X		
Phone call														X	X
Informed consent	X														
Inclusion/exclusion criteria	X	X[b]													
Demographics, medical and surgical history, and prior and current medications	X														
Viral serology/virology[g]	X														
Pregnancy test[h]	X	X[h]				X		X	X	X	X	X[h]	X	X	
Height	X														
Body weight	X	X	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive physical examination	X												X		
Symptom-directed physical examination		X				X		X	X	X	X	X			

Procedures/ Assessments[a]	**Screen-ing**[b]	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycles 9, 12, 15, 18, 21, & 24**[c]	**EOT**[d]	**Safety Follow-up**[e]	**Survival Follow up**[f]
Cycle Day	**Day (-28 to -1)**	**Day 1 (± 1 Days)**	**Day 8 (± 1 Days)**	**Day 15 (± 1 Days)**	**Day 22 (± 1 Days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 7 days)**	**Within 7 Days After Last Dose**	**30 Days After Last Dose (+5 Days)**	**Every 90 Days (± 30 Days)**
ECOG performance status	X	X				X		X	X	X	X	X	X		
Vital sign measurements[i]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests[j]															
Comprehensive metabolic (chemistry) panel	X[b]	X				X		X	X	X	X	X	X		
LDH	X[b]	X						X				X (Cycle 24 only)	X		
Hematology	X[b]	X	X	X	X	X	X	X	X	X	X	X	X		
Peripheral blood smear[k]	X[b]	X	X	X	X	X	X	X	X	X	X	X	X		
Bone marrow aspirate/biopsy for AESI[k]	Dependent upon peripheral blood smear morphology results														
CT (neck, chest, abdomen, pelvis)[l, m]	X							X			X	X[m] (Cycles 12, 18, & 24 only)	X[l]		X[m]

Procedures/ Assessments[a]	**Screen-ing**[b]	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycles 9, 12, 15, 18, 21, & 24**[c]	**EOT**[d]	**Safety Follow-up**[e]	**Survival Follow up**[f]
Cycle Day	**Day (-28 to -1)**	**Day 1 (± 1 Days)**	**Day 8 (± 1 Days)**	**Day 15 (± 1 Days)**	**Day 22 (± 1 Days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 7 days)**	**Within 7 Days After Last Dose**	**30 Days After Last Dose (+5 Days)**	**Every 90 Days (± 30 Days)**
^{18}FDG-PET [l, n]	X							X			X^{n}	X^{n} (Cycles 12, 18, & 24 only)	X^{l}		X^{n}
Bone marrow biopsy (with IHC) for disease assessment[o]	X^{o}	At first notation of possible CR if bone marrow involvement at screening and when clinically indicated[m]													
AE[p]	Collected from time of signing informed consent form to either 30 days after discontinuation of study treatment or until initiation of subsequent anticancer therapy													X	
Concomitant medications/ procedures	X	Continuous from the first dose of study drug to either 30 days after discontinuation of study treatment or until initiation of subsequent anticancer therapy												X	
Tissue for EZH2 mutation testing[q]	X														
Dispense and administer continuous 28-day cycles of tazemetostat, 800 mg BID, PO		X				X		X	X	X	X	X			
Administer rituximab, IV or SC		X^{r}	X^{s}	X^{s}	X^{s}			X^{s}	X^{s}	X^{s}	X^{s}				
Survival status and														X	X

Procedures/ Assessments[a]	**Screen-ing**[b]	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycles 9, 12, 15, 18, 21, & 24**[c]	**EOT**[d]	**Safety Follow-up**[e]	**Survival Follow up**[f]
Cycle Day	**Day (-28 to -1)**	**Day 1 (± 1 Days)**	**Day 8 (± 1 Days)**	**Day 15 (± 1 Days)**	**Day 22 (± 1 Days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 3 days)**	**Day 1 (± 7 days)**	**Within 7 Days After Last Dose**	**30 Days After Last Dose (+5 Days)**	**Every 90 Days (± 30 Days)**
subsequent anticancer therapy															

[a] All **assessments** must be performed pre-dose and within the visit specified windows, unless otherwise described. Additional unscheduled safety and efficacy assessments may be performed at any time as clinically indicated to determine the relevance of specific findings and/or the duration of events.

[b] **Screening period** extends from Day -28 to Day -1. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment; however, subjects must continue to meet eligibility criteria prior to first dose of tazemetostat on Cycle 1 Day 1. All site visits in Cycle 1 have a ± 1-day window. All site visits in Cycles 2, 3, 4, 5, and 6 have a ± 3-day window. All site visits starting in Cycle 9 have a ± 7-day window.

[c] Subjects may continue treatment with tazemetostat beyond 24 cycles until disease progression, unacceptable toxicity or withdrawal of consent. Procedures/Assessments required every 3 months (ie, C27D1, C30D1, etc), unless otherwise described, until EOT.

[d] The **end-of-treatment assessments** must occur within 7 days after treatment discontinuation (eg, at the visit at which the decision to discontinue treatment occurs).

[e] **Safety follow-up** will be performed 30 days (+5 days) after the last dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of a new anticancer therapy, whichever occurs first.

[f] **Survival follow-up** will be conducted approximately every 90 days on all subjects, unless consent is withdrawn. Information on all anticancer therapies will be collected (the Sponsor may choose to stop the collection of therapies after the first anticancer treatment following tazemetostat). This may be done by telephone contact. Once the study has achieved the number of events necessary for the final analysis, subjects may no longer be contacted for this information.

[g] **Viral serology/virology testing**: If infection status is unknown, testing should include viral serologies for HBV (Appendix 7) and HCV (Appendix 8), and virology testing for HBV and HCV (as indicated), and HIV as per institutional standard. Additional HBV-DNA testing by PCR may be required if subject is HBsAg negative, anti-HBs positive and/or anti-HBc positive. Hepatitis C virus testing by HCV antibody and if positive (reactive), further HCV-RNA testing by PCR must be performed.

[h] **Pregnancy testing:** Serum pregnancy test (β-hCG) must be performed at Screening and within 24 hours prior to the first dose of study drug on Cycle 1 Day 1 for all FCBP. A urine or serum pregnancy test will be performed pre-dose on Day 1 of each cycle beginning with Cycle 2 and at the End-of-Treatment visit. Pregnancy tests will have a minimum sensitivity of 25 mIU/mL. Any positive urine pregnancy test must be confirmed by a serum test.

[i] **Vital signs** include blood pressure, heart rate, and body temperature. Blood pressure and heart rate will be collected after the subject has been sitting for 5 minutes.

[j] **Clinical laboratory tests** will be performed by Investigators per standard of care. Unscheduled visits may be performed at any time for additional clinical laboratory assessments (samples collected at clinic visit or site's local laboratory) as clinically indicated. See Table 7 for additional information.

[k] At screening and during the study, a **peripheral blood smear** will be performed manually or automated along with routine hematology testing and assessed for abnormal morphology. If results are abnormal and suggestive of MDS/AML or MPN, the subject will undergo a bone marrow aspirate/biopsy procedure. The

bone marrow aspirate/biopsy sample will then be analyzed by cytogenetic testing at the local laboratory to closely monitor subjects for abnormalities known to be associated with MDS (eg, del 5q, chr 7, abn) and MPN (eg, JAK2 V617F). Additional local laboratory testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted next generation sequencing (NGS) of known disease genes, as necessary. If local testing is unavailable or if results are inconclusive/indeterminate, the site will be required to ship samples for central laboratory testing. If the cytogenetic testing and, if conducted, DNA sequencing by NGS results are abnormal and associated with myeloid malignancies, tazemetostat will be discontinued.

[l] **Tumor response assessments** by disease-appropriate standard criteria (2014 Lugano Classification [Appendix 3]) using ^{18}FDG-PET and CT, or combined as PET-CT, of known sites or newly suspected sites of disease (neck, chest, abdomen, and pelvis required at all time points). MRI instead of CT if clinically indicated. Additional imaging of brain or bone by MRI or CT if clinically indicated at screening and during the study for CNS signs/symptoms or bone marrow involvement. Radiologic tumor assessments will be performed at screening between day -28 and day -1 and at specified time points (±7 days) during study treatment beginning from start of treatment (C1D1), irrespective of treatment delays, until loss of clinical benefit or disease progression (i.e., C3D1, C6D1, C12D1, C18D1, C24D1, etc). CT imaging (as PET-CT or CT alone) must include diagnostic quality CT scan AND should preferably be contrast enhanced; FDG-avid disease should report PET-CT based response, non FDG-avid disease should report CT based response. Tumor assessment at EOT required if no disease progression previously documented. Subjects who discontinue study treatment for any reason other than disease progression will continue to undergo tumor response assessments at timepoints (±7 days) as scheduled until disease progression. A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will be performed at screening and with tumor assessments (See Section 11).

[m] **CT of neck, chest, abdomen, and pelvis** required at screening then during study treatment (±7 days) at C3D1, C6D1, C12D1, C18D1, and C24D1, as well as EOT. If no disease progression previously documented and subject continues treatment with tazemetostat beyond 24 cycles, CT will be required every 6 months (±7 days) at C30D1, C36D1, etc. During Survival Follow-up, CT performed every 6 months (±30 days) for 2 years then every 12 months (±30 days) thereafter, or until disease progression (See Section 11).

[n] **^{18}FDG-PET** required at screening then during study treatment at C3D1 (±7 days). ^{18}FDG-PET also required at the first notation of possible CR and thereafter (C6D1, C12D1, C18D1, and C24D1) may be performed as clinically indicated, except required at EOT. If no disease progression previously documented and subject continues treatment with tazemetostat beyond 24 cycles, ^{18}FDG-PET as clinically indicated every 6 months (±7 days) at C30D1, C36D1, etc. During Survival Follow-up, ^{18}FDG-PET may be performed as clinically indicated, in addition to CT, every 6 months (±30 days) for 2 years then every 12 months (±30 days) thereafter, or until disease progression (See Section 11).

[o] For purposes of disease assessment, a **bone marrow biopsy (including IHC)** will be performed during screening for those subjects with a history of lymphoma involvement of the bone marrow if a bone marrow biopsy with IHC has not been performed within 42 days of C1D1. A written approval from the Medical Monitor is needed if the bone marrow biopsy with IHC has been performed outside of this time window. At the first notation of possible CR and when clinically indicated, a repeat bone marrow biopsy should be performed if lymphoma involvement of the bone marrow was reported at screening. If bone marrow biopsy is not performed at CR, ^{18}FDG-PET will be used to confirm CR (Perry, 2016; Rutherford, 2017).

[p] **AEs** will be collected from the time the subject signs the informed consent form until the end of the safety reporting period (or until screen failure). The safety reporting period ends at the time of the safety follow-up visit, 30 days after the last dose of study drug, or initiation of an investigational agent or anticancer therapy, whichever occurs first.

[q] All enrolled subjects will be required to submit tissue for assessment of EZH2 mutation status. If archival formalin fixed paraffin embedded (FFPE) tumor tissue is not available or will be more than 15 months old at C1D1, subjects will provide a fresh biopsy.

[r] Dose to be administered: rituximab 375 mg/m^2 IV. Note: On days when both drugs are administered, tazemetostat should be taken prior to the dosing of rituximab.

[s] Dose to be administered: rituximab 375 mg/m^2 IV **or** rituximab hyaluronidase SC as 1,400 mg rituximab and 23,400 units hyaluronidase per 11.7 ml total volume (120 mg/2,000 units per mL). Note: On days when both drugs are administered, tazemetostat should be taken prior to the dosing of rituximab.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all of the inclusion criteria to be included in this study and any subjects meeting any of the exclusion criteria will be excluded from this study.

8.1. Study Population

8.1.1. Inclusion Criteria

1. Men and women of 18 years of age and older
2. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol
3. Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 (Appendix 1)
4. Life expectancy (in the opinion of the Investigator) of ≥3 months before enrollment
5. Have histologically confirmed FL, Grade 1 to 3a. Subjects may have R/Rdisease following at least 2 standard prior systemic treatment regimens where at least 1 anti-CD20-based regimen was used
6. Treatment recommended in accordance with the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria due to the presence of at least one of the following:
    a. Any nodal or extranodal tumor mass >7 cm diameter
    b. Involvement of at least 3 nodal sites, each with diameter >3 cm
    c. Presence of any systemic or B symptoms
    d. Splenic enlargement with inferior margin below the umbilical line
    e. Compression syndrome (ureteral, orbital, gastrointestinal)
    f. Pleural or peritoneal serous effusion (irrespective of cell content)
    g. Leukemic phase (>5.0 x 10^9/L circulating malignant cells)
    h. Cytopenias (granulocyte count <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
7. Meet the following laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥ 750 cells/µL (0.75 x 10^9/L), or ≥ 500 cells/µL (0.50 x 10^9/L) in subjects with documented bone marrow involvement
    b. Platelet count ≥ 50,000 cells/µL (50 x 10^9/L), or ≥ 30,000 cells/µL (30 x 10^9/L) in subjects with documented bone marrow involvement, and without transfusion dependence
    c. Hemoglobin ≥ 8 g/dL
    d. Serum alanine aminotransferase (AST) and aspartate aminotransferase (ALT) ≤ 3.0 x ULN, unless related to disease involvement
    e. Total bilirubin ≤ 1.5 x ULN, unless due to disease involvement, Gilbert's syndrome, or hemolytic anemia

f. Estimated creatinine clearance (ie, estimated glomerular filtration rate [eGFR] using Cockcroft-Gault [Appendix 4]) ≥ 40 mL/min

8. At least one bi-dimensionally measurable nodal lesion > 1.5 cm in its longest diameter by computed tomography (CT) scan or magnetic resonance imaging (MRI) excluding lesions that meet the following criteria:

   a. Previously irradiated lesions should not be counted as target lesions
   b. Lesions that are intended to be used to collect tissue samples for biopsy should not be counted as target lesions
   c. Bone lesions should not be counted as target lesions

9. Any clinically significant toxicity related to a prior anticancer treatment (ie, chemotherapy, immunotherapy, and/or radiotherapy), except for alopecia, either resolved to ≤ Grade 1 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 or is clinically stable and no longer clinically significant

10. Negative serologic or polymerase chain reaction (PCR) test results for acute or chronic hepatitis B virus (HBV) infection (Appendix 7)

    Note: Patients whose HBV infection status could not be determined by serologic test results must be negative for HBV-DNA by PCR to be eligible for study participation. Patients seropositive for HBV with undetectable HBV-DNA by PCR are permitted with appropriate antiviral prophylaxis.

11. Negative test results for hepatitis C virus (HCV) (Appendix 8) and human immunodeficiency virus (HIV)

    Note: Patients who are positive for HCV antibody must be negative for HCV-RNA by PCR to be eligible for study participation.

12. Females of childbearing potential (FCBP) must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 mIU/mL or equivalent units of β-hCG) at screening and within 24 hours prior to the first dose of study drug. All females will be considered to be of childbearing potential unless they are naturally postmenopausal (at least 12 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause) or have been sterilized surgically (ie, total hysterectomy and/or bilateral oophorectomy, with surgery completed at least 28 days prior to the first dose of study drug).

13. FCBP must either practice complete abstinence or agree to use a highly effective method of contraception beginning at least 28 days prior to the first dose of study drug, during study treatment (including during dose interruptions), for 6 months after tazemetostat discontinuation, and for 12 months after rituximab discontinuation. If the contraception methods provided in Section 9.3 are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject. Examples of highly effective methods of contraception (result in a failure rate of <1% per year when used consistently and correctly) may be found in Section 9.3 . Female subjects must also refrain from

breastfeeding or donating oocytes during study treatment and for 12 months following the last dose of rituximab.

14. Male subjects must have had a successful vasectomy (with medically confirmed azoospermia) OR must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a FCBP from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

    NOTE: Male subjects must not donate sperm from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

8.1.2. Exclusion Criteria

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2
2. Grade 3b, mixed histology, or transformed FL
3. Treatment with any of the following anticancer therapies within the indicated timeframe of a specific treatment prior to first dose of study drug:
    a. Cytotoxic chemotherapy within 21 days
    b. Noncytotoxic chemotherapy (e.g., small molecule inhibitor) within 14 days
    c. Nitrosoureas within 6 weeks
    d. Prior immunotherapy within 4 weeks
    e. Radiotherapy – within 6 weeks from prior radioisotope therapy; within 12 weeks from 50% pelvic or total body irradiation
    f. Any investigational treatment within 4 weeks or at least 5 half-lives, whichever is shorter
4. History of solid organ transplant
5. Major surgery within 4 weeks of the start of study treatment
6. Thrombocytopenia, neutropenia, or anemia of Grade > 3 (per CTCAE v5.0 criteria) or any prior history of myeloid malignancies, including MDS/AML or MPN
7. Prior history of T-LBL/T-ALL
8. Unwillingness to exclude grapefruit juice-containing products, Seville oranges, and grapefruits from the diet and/ or consumed within 1 week of the first dose of study drug
9. Subjects taking medications that are known strong cytochrome P450 (CYP)3A inhibitors and strong or moderate CYP3A inducers (including St. John's wort) (See Section 9.2.5 and https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers; https://drug-interactions.medicine.iu.edu/MainTable.aspx)
10. Any uncontrolled illness including, but not limited to, significant active infection requiring systemic (IV) therapy, hypertension, angina, arrhythmias, pulmonary disease, autoimmune dysfunction, immune thrombocytopenia, or autoimmune hemolytic anemia

11. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association classification > II [Appendix 6]), myocardial infarction or stroke within 6 months of first dose of study drug
12. History of clinically significant gastrointestinal (GI) conditions, particularly:
    a. Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug
    b. Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption
13. Other diagnosis of cancer that is likely to require treatment in the next 2 years, with the exception of the following:
    a. Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin
    b. Curatively treated carcinoma in situ of the cervix
    c. Hormonal therapy for prostate cancer
14. Females who are pregnant or lactating/breastfeeding
15. Received a live virus vaccination within 28 days of first dose of rituximab
16. Concurrent participation in a separate investigational therapeutic study
17. Psychiatric illness/social situations that would interfere with study compliance

8.2. Subject Withdrawal Criteria

Subjects will be treated for 6 cycles of combination therapy followed by 18 cycles of tazemetostat monotherapy across the trial or until disease progression or unacceptable toxicity or withdrawal of consent.

A subject removed from the study for any reason may not be replaced.

8.2.1. Withdrawal of Subjects from Study Treatment/Procedures

Subjects have the right to withdraw from the study at any time and for any reason without penalty or prejudice to future medical care by the physician or institution. The Investigator is also free to terminate a subject's study drug treatment at any time if the subject's clinical condition warrants it. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent (eg, death records).

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

The primary reasons for discontinuation or withdrawal of a subject from protocol-required treatment or procedures must be determined using the following categories:

- Confirmed disease progression by Investigator
- Confirmed disease progression by independent radiologic review
- Death
- Subject request to end study treatment and/or procedures
- Withdrawal of consent
- AE
- Pregnancy
- Noncompliance with study drug
- Lost to follow-up
- Physician decision
- Termination of study by Sponsor
- Any other reason that, in the opinion of the Investigator, would justify removing the subject from the study drug, based on the interest of the subject

8.2.2. Subsequent Therapy After Discontinuation of Study Treatment

Once a subject has permanently discontinued study treatment, every effort should be made to have the subject complete the End-of-Treatment and Survival Follow-up visits prior to initiating any subsequent anticancer therapy (approved or investigational). Post-study anticancer therapy will not be provided as part of this study. The subject may receive subsequent anticancer therapy at the discretion of the treating physician. The subsequent anticancer therapy should be documented on the electronic case report form (eCRF). The subject will continue to be monitored until disease progression.

9. TREATMENT OF SUBJECTS

All subjects will receive tazemetostat in combination with rituximab as described in following sections.

9.1. Description of Study Drug

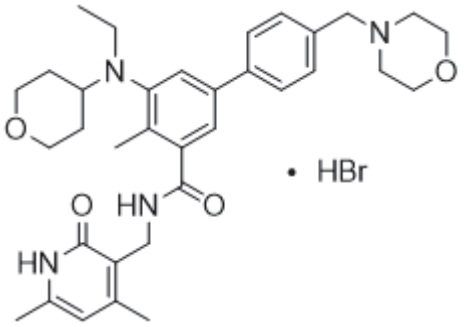
In June 2020, the US FDA granted accelerated approval of TAZVERIK (tazemetostat) in the US for the treatment of adult patients with R/R FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for the treatment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

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

Tazemetostat (EPZ-6438) is an Epizyme IP and is defined as an Investigational Medicinal Product (IMP) under the European Union Clinical Trials Directive (EU CT Dir). The contents of the package label will be in accordance with all applicable regulatory requirements. The expiry date will be printed on the label.

Tazemetostat is available as tablets in 200 mg strength and supplied in white HDPE bottles. Additional details on tazemetostat can be found in Table 3 and Section 10.1.

Table 3: Chemical Name, Structural Formula of Tazemetostat

Test drug code:	EPZ-6438
International non-proprietary name:	Tazemetostat
Chemical name:	[1,1'-Biphenyl]-3-carboxamide, *N*-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(4-morpholinylmethyl)-, hydrobromide (1:1)
Molecular formula:	$C_{34}H_{44}N_4O_4 \cdot HBr$ (Hydrobromide salt) $C_{34}H_{44}N_4O_4$ (Free base)
Molecular weight:	653.66 (Hydrobromide salt) 572.75 (Free base)
Structural formula:	

9.2. Concomitant Medication

9.2.1. Prior and Concomitant Medications

Prior and concomitant medications include all prescription and nonprescription medications, vitamins, herbals (including medical marijuana), and transfusions.

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug will be recorded. Any concomitant therapy administered to the subject during the course of the study (starting at the date of first dose of informed consent) until 30 days after the final dose of study drug or until initiation of subsequent anticancer therapy will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded.

9.2.2. Permitted Concomitant Medications

Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with tazemetostat may be continued during the study.

Subjects enrolled may receive prophylaxis treatment for *Pneumocystis jirovecii* at the discretion of the Investigator.

Subjects may receive prednisone (or equivalent corticosteroid) for systemic or local symptom control prior to and while on study. However, starting at Cycle 1 Day 1, subjects may receive no more than 10 mg of prednisone (or equivalent corticosteroid) daily when used for treatment of lymphoma related symptoms, with the intent to taper by the end of Cycle 1.

Treatment of complications, AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, antidiarrheal drugs, etc.) may be given at the discretion of the Investigator, unless it is expected to interfere with the evaluation of (or to interact with) tazemetostat. The Investigator will record any AE on the AE eCRF for which the concomitant medication/therapy was administered.

Over-the-counter medications, nutritional supplements, vitamins, and herbal preparations are permitted under physician recommendation only. Aspirin, nonsteroidal anti-inflammatory drugs, and low-molecular-weight heparin or prophylactic doses of heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor (G-CSF), or equivalent, may be used in accordance with American Society of Clinical Oncology (ASCO) (Smith, 2015), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines.

9.2.3. Premedication for Rituximab

Premedication with an antihistamine and acetaminophen is required for all rituximab administration, including both IV infusion and subcutaneous injection. Additional premedication for subjects receiving rituximab may be given according to institutional practice and current product prescribing information.

9.2.4. Permitted Radiation Therapy

Palliative radiotherapy may be given for the control of pain or for other reasons (ie, bronchial obstruction, ulcerating skin lesions, etc) with no curative intent. The irradiated area should be as small as possible and should never involve more than 10% of the bone marrow in any given 4-week period for distribution of active bone marrow. The irradiated area cannot be used as a parameter for response assessment. Treatment with tazemetostat should be delayed in subjects receiving palliative radiotherapy after discussion with the Medical Monitor. In addition, other palliative procedures intended for symptom control and concurrent dose interruptions may be permitted after discussion with the Medical Monitor.

9.2.5. Prohibited Concomitant Therapies and Drugs

Subjects must not receive other antitumor therapies while on study. Prohibited antitumor medications during this study are any other investigational or unapproved drugs, and other anticancer therapies unless otherwise stated. If a subject receives any prohibited antitumor medications, this will be judged as evidence of disease progression, and study drug will be discontinued. In this case, the subject should complete all off-treatment assessments and be followed for survival in the Survival Follow-up period.

Known strong CYP3A inhibitors and strong or moderate CYP3A inducers (including St. John's wort) are prohibited within 14 days prior to the first dose of study drug (tazemetostat) and for the duration of the study. Coadministration of tazemetostat with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations, which may increase the frequency or severity of adverse reactions.

Coadministration of tazemetostat with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations, which may decrease the efficacy of tazemetostat. Because there is a potential for interaction of tazemetostat with other concomitantly administered drugs through the cytochrome P450 system, all over-the-counter medications, and alternative therapies, in addition to prescribed medications, must be recorded in the eCRF. The Investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Medications that are strong CYP3A inhibitors and strong or moderate CYP3A inducers include, but are not limited to, those listed in Table 4 (refer to product information and the source websites in Table 4 for the most up-to-date information).

Table 4: Examples of Strong and Moderate Clinical CYP3A Inhibitors and Inducers and Clinical CYP3A Sensitive Substrates for P450-Mediated Metabolisms

Strong Inhibitors	Moderate Inhibitors	Strong Inducers	Moderate Inducers	Sensitive Substrates
boceprevir clarithromycin[a] cobicistat[a] danoprevir and ritonavir[b] elvitegravir and ritonavir[b] grapefruit juice[c]	aprepitant ciprofloxacin conivaptan[d] crizotinib cyclosporine diltiazem[e] dronedarone[a] erythromycin	apalutamide carbamazepine enzalutamide[f] mitotane phenytoin rifampin St. John's wort[g]	bosentan efavirenz etravirine phenobarbital primidone	alfentanil avanafil budesonide buspirone conivaptan darifenacin darunavir[h] dasatinib

Strong Inhibitors	Moderate Inhibitors	Strong Inducers	Moderate Inducers	Sensitive Substrates
idelalisib indinavir and ritonavir[b] itraconazole[a] ketoconazole lopinavir and ritonavir[a,b] nefazodone nelfinavir[a] paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[b] posaconazole ritonavir[a,b] saquinavir and ritonavir[a,b] telaprevir[a] telithromycin tipranavir and ritonavir[a,b] troleandomycin voriconazole	fluconazole fluvoxamine imatinib tofisopam verapamil[a]			dronedarone ebastine eletriptan eplerenone everolimus felodipine ibrutinib indinavir[h] lomitapide lovastatin[i] lurasidone maraviroc midazolam naloxegol nisoldipine quetiapine saquinavir[h] sildenafil simvastatin[i] sirolimus tacrolimus ticagrelor tipranavir[h] tolvaptan triazolam vardenafil

Source: US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers. March 2020; https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. 2020; https://drug-interactions.medicine.iu.edu/MainTable.aspx
Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome p450; OATP1B1 = organic anion transporting polypeptide 1B1; P-gp = P-glycoprotein.
[a] Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).
[b] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
[c] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
[d] The classification is based on studies conducted with intravenously administered conivaptan.
[e] Diltiazem increased AUC of certain sensitive CYP3A substrates (eg, buspirone) more than 5-fold.
[f] Except as prescribed in this study.
[g] The effect of St. John's wort varies widely and is preparation-dependent.
[h] Usually administered to subjects in combination with ritonavir, a strong CYP3A inhibitor.
[i] Acid form is an OATP1B1 substrate.
Note: These lists of example medications are not exhaustive; refer to specific product information and the source websites in this table for current information.

Use of live vaccines is prohibited 4 weeks (28 days) prior to initiation of study treatment and during study treatment with rituximab.

9.2.6. Concomitant Medications to be used with Caution

The following medications are to be used with caution:

- CYP3A sensitive substrates
- Moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the dose of tazemetostat as shown in Table 5. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the tazemetostat dose that was being taken prior to initiating the inhibitor.

Table 5: Tazemetostat Dose Reduction for Coadministration with Moderate CYP3A Inhibitors

Current Dosage	Adjusted Dosage
800 mg twice daily	400 mg twice daily
600 mg twice daily	400 mg for first dose and 200 mg for second dose
400 mg twice daily	200 mg twice daily

Examples of CYP3A sensitive substrates and moderate CYP3A inhibitors include, but are not limited to, those listed in Table 4. This list of medications is not exhaustive; refer to product information and the source websites in Table 4 for the most up-to-date information.

Refer to product information for rituximab for guidance regarding concomitant medications use and cautions related to interaction with other medications.

9.2.7. Prohibitions and Restrictions During Study Period

Grapefruit, grapefruit juice-containing products, and Seville oranges are not permitted 1 week prior to the first dose of study drug and for the duration the study.

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

9.3. Contraception and Pregnancy

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

9.3.1. Definition of Childbearing Potential: Female Subjects

A female subject is considered of childbearing potential if she:

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

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

- Is naturally postmenopausal (at least 12 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause).
- Is surgically sterilized (i.e., total hysterectomy and/or bilateral oophorectomy) with surgery completed at least 1 month before the first dose of study drug.
- Has a documented congenital or acquired disorder that is incompatible with pregnancy.

9.3.2. Definition of Child-fathering Potential: Male Subjects

A male subject is considered of child-fathering potential if he:

- Is anatomically and physiologically capable of causing a pregnancy in a female partner,

and

- Will be or could possibly be sexually active with a female (who is or may become pregnant) while undergoing study treatment.

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

- Has a documented successful vasectomy (with medically confirmed azoospermia) or male subjects must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a pregnant female or FCBP from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

9.3.3. Pregnancy Prevention

9.3.3.1. Female Subjects

FCBP must either practice complete abstinence or agree to use a highly effective method of contraception beginning at least 28 days prior to the first dose of study drug, during study treatment (including during dose interruptions), for 6 months after tazemetostat discontinuation, and for 12 months after rituximab discontinuation. Female subjects must also not breastfeed or donate oocytes during study treatment and for 12 months following the last dose of rituximab. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject. The following are examples of highly effective methods of contraception (result in a failure rate of <1% per year when used consistently and correctly):

- Intrauterine device (IUD)

- Intrauterine hormone-releasing system (IUS)
- Hormonal (ovulation inhibitory combined [estrogen and progesterone]: oral, intravaginal, or transdermal; ovulation inhibitory progesterone-only: oral, injectable, or implantable)

  NOTE: Due to the potential of enzyme induction with tazemetostat, hormonal contraception methods must be supplemented with a barrier method of contraception (preferably male condom)
- Bilateral tubal ligation
- Partner's vasectomy (if medically confirmed [azoospermia] and sole sexual partner)

NOTE: Female subjects of childbearing potential exempt from these contraception requirements are subjects who practice complete abstinence from heterosexual sexual contact. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

9.3.3.2. Male Subjects

Male subjects must have had a successful vasectomy (with medically confirmed azoospermia) OR must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a female of childbearing potential (FCBP) from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

NOTE: Male subjects must not donate sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation

9.4. Treatment Compliance

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

9.5. Randomization and Blinding

This is a one-arm, open-label study, and therefore does not utilize randomization or blinding.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Rituximab in combination with tazemetostat is under investigation as a treatment for subjects with R/R FL.

A description of the study drugs is provided in Table 6.

Table 6: Study Drugs

Product name	**Study Drug (Tazemetostat)**	**Rituximab**	**Rituximab**
Dosage form:	tablet	solution	solution
Unit dose:	200 mg	100 mg/10 mL or 500 mg/50 mL	1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) per 11.7 mL (120 mg/2,000 Units per mL)
Route of administration:	oral	intravenous	subcutaneous
Physical description:	red, round, and biconvex film-coated tablets packaged in white high-density polyethylene bottle with a child resistant, tamper-evident polypropylene screw cap	Refer to current manufacturer's prescribing information	Refer to current manufacturer's prescribing information
Manufacturer:	Manufactured for Epizyme by Patheon	Refer to current manufacturer's prescribing information	Refer to current manufacturer's prescribing information

Biosimilar formulations for rituximab will be allowed during the study.

10.2. Study Drug Packaging and Labeling

Tazemetostat will be supplied in white high-density polyethylene (HDPE) bottles, labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. Additional labeling can be added per institutional requirements. Additional labels must not obscure any information on the tazemetostat label.

Rituximab is available as single-dose vials of 100 mg/10 mL (10 mg/mL) and single-dose vials of 500 mg/50 mL (10 mg/mL) for IV, or single-dose vials of 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) for SC.

The label(s) for IP will include Sponsor name, address, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

10.3. Study Drug Storage

Tazemetostat must be stored in a secure area, in compliance with the storage requirements listed on the label, with access limited to the Investigator and authorized site staff only. Tazemetostat tablets will be stored at temperatures below 25°C (77°F) in accordance with the labeled storage conditions. Refer to the pharmacy manual for details.

Rituximab will be refrigerated at 2°C to 8°C (36°F to 46°F). Rituximab vials should be protected from direct sunlight. Do not freeze or shake. Refer to the package label for further details and the current manufacturer's prescribing information.

10.4. Study Drug Preparation

No preparation is needed for tazemetostat.

For rituximab preparation, refer to the current manufacturer's prescribing information.

10.5. Administration

Subjects will be administered 800 mg of tazemetostat orally twice daily (approximately 12 hours apart), with or without food, at approximately the same time each day.

Tazemetostat will be administered in continuous 28-day cycles beginning on Cycle 1 Day 1 through the end of Cycle 24, for 24 months of therapy or until disease progression, unacceptable toxicity, or withdrawal of consent.

Missed or vomited dose: If a dose of tazemetostat is missed (ie, not taken within 4 hours of the scheduled dosing time), do not take the dose. Resume dose administration at the next scheduled dose. If a subject vomits after tazemetostat administration, do not take an additional dose. Resume dose administration at the next scheduled dose.

Rituximab will be administered by either subcutaneous injection or IV infusion according to the regional product prescribing information, labeling, and institutional guidelines.

For subjects receiving IV rituximab, rituximab via IV infusion will be administered at a dose of 375 mg/m^2 on Day 1, 8, 15, and 22 of Cycle 1, and then on Day 1 of Cycles 3 through 6, accounting for an additional 4 doses (ie, a total of 8 doses of rituximab in 6 cycles).

For subjects planning to receive subcutaneous rituximab hyaluronidase, the initial dose (Cycle 1 Day 1) of rituximab will be administered as 375mg/m^2 via IV infusion. Subsequent doses of rituximab may be administered via IV infusion or subcutaneously (SC) per Investigator choice. For SC rituximab hyaluronidase, administer 1,400 mg rituximab and 23,400 Units hyaluronidase (11.7 ml total volume) over approximately 5 minutes on Cycle 1 Days 8, 15, and 22 then Day 1 of Cycles 3-6, for a total of 8 doses of rituximab in 6 cycles (an initial IV rituximab dose followed by 7 doses of SC rituximab).

On days when both drugs are administered, tazemetostat should be taken prior to the dosing of rituximab.

All doses of study drugs administered, missed, and vomited (as applicable) are to be recorded.

10.6. Study Drug Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the Investigator until the following documentation has been received by the Sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page signed and dated by the Investigator
- Written proof of approval of the protocol, the informed consent form(s) (ICFs), and any other information provided to the subjects by the Institutional Review Board or Independent Ethics Committee (IRB/IEC) for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required) and the import license (if required)
- An Investigator-signed and dated Form Food and Drug Administration (FDA) 1572, a signed and dated curriculum vitae for the Principal Investigator (PI) including a copy of the PI's current medical license (required in the US) or medical registration number on curriculum vitae
- Financial Disclosure Form for the PI listed on Form FDA 1572
- A signed and dated clinical trials agreement.

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local and regional requirements.

Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study. An accurate and timely record of the receipt of all clinical supplies, dispensing of study drug to the subject, collection and reconciliation of used and unused supplies that are either returned by the subject or shipped to the site but not used, subsequent return of unused study drug to the Sponsor or designated central or local depot, and (where applicable) destruction of study drug at the site must be maintained. This includes but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study drug dispensing/return reconciliation log, (c) study drug accountability log, (d) all shipping service receipts, (e) documentation of drug returned to the Sponsor, and (f) certificates of destruction for any destruction that occurs at site. All forms will be provided by the Sponsor. Any comparable forms that the investigational site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor or a representative of any health authority. All used and

unused study drugs, including empty containers, are to be returned to the Investigator by the subject and ultimately to the Sponsor's designated contractor or depot by the conclusion of the study, unless approval is given by the Sponsor for destruction of supplies and containers at the investigational site. Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by the Sponsor's personnel, study drug that is to be returned to the Sponsor's approved contract vendor must be boxed and sealed and shipped back to the Sponsor's approved contract vendor following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the Sponsor's specified location by sponsor representatives.

Drug accountability will be reviewed during site monitoring visits and at the completion of the study.

10.7. Study Drug Handling and Disposal

All drug supplies are to be used only for this protocol and not for any other purpose. The Investigator (or a designated pharmacist) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by Epizyme. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or a designated pharmacist) will either return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Epizyme designated contractor or, where approval is given by Epizyme, will destroy supplies and containers at the investigational site.

11. ASSESSMENT OF EFFICACY

11.1. Tumor Assessments

Tumor response assessments will be performed (Cheson, 2014;Appendix 3) at each assessment time point and entered onto the appropriate eCRF. Investigator determined response assessments at each assessment time point will be entered onto the appropriate eCRF. All baseline local tumor assessments are to be performed within 28 days prior to the start of study treatment.

For additional details, see the Schedule of Visits and Procedures (Table 2).

Tumor response assessments at screening and during the study will include ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) and computed tomography (CT), or combined as PET-CT when both imaging modalities are required, of the neck, chest, abdomen and pelvis, and other applicable sites of disease. Magnetic resonance imaging (MRI) instead of CT may be performed if clinically indicated. Additional imaging of brain or bone by MRI or CT, as appropriate, to be performed if metastases are present or suspected. All CT scans (including PET-CT and CT) must be of diagnostic quality AND preferably contrast enhanced; FDG-avid disease should report PET-CT based response, non FDG-avid disease (low or variable FDG avidity) should report CT based response. ^{18}FDG-PET required at screening then during study treatment at 3 months (±7 days). ^{18}FDG-PET also required at the first notation of possible CR and thereafter may be performed as clinically indicated at tumor assessment timepoints. CT required at screening then during study treatment (±7 days) at 3 months, 6 months, 12 months, 18 months, and 24 months. If no disease progression previously documented and subject continues treatment with tazemetostat beyond 24 cycles; CT, with additional ^{18}FDG-PET as clinically indicated, required every 6 months (±7 days). At End-of-Treatment, CT with additional ^{18}FDG-PET required if no disease progression previously documented. During Survival Follow-up, tumor assessments will be performed by CT, with additional ^{18}FDG-PET as clinically indicated, every 6 months (±30 days) for 2 years then every 12 months (±30 days) thereafter, or until disease progression.

CT (or MRI if clinically indicated) scans are considered the primary and preferred method of response assessment, with ^{18}FDG-PET additionally required at certain time points.

A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will be performed at screening and with tumor assessments. A bone marrow biopsy (including immunohistochemistry [IHC]) will be performed for those subjects at screening with a history of lymphoma involvement of the bone marrow if a bone marrow biopsy with IHC has not been performed within 42 days of cycle 1 day 1. A written approval from the Medical Monitor is required if the bone marrow biopsy with IHC is performed outside of the allowed protocol-specified window. At the first notation of possible CR and when clinically indicated, a repeat bone marrow biopsy should be performed if lymphoma involvement of the bone marrow was reported at screening. If bone marrow biopsy is not performed at CR, ^{18}FDG-PET will be used to confirm CR (Perry, 2016; Rutherford, 2017).

All subjects will be followed until disease progression as indicated in the Schedule of Assessments (Table 2). Subjects who discontinue study treatments for any reason other than withdrawal of consent or disease progression without documented evidence of disease progression, i.e., if a subject withdraws consent but agrees to continue collection of follow-up

data, will continue to be assessed as scheduled until disease progression. For equivocal progression, the Investigator is strongly encouraged to contact the Medical Monitor for evaluation in a real-time manner.

11.2. Techniques

The CT scan should be a diagnostic quality spiral or multidetector CT with oral and iodinated intravenous (IV) contrast, and the MRI scan should be performed with IV gadolinium chelate. Scans of the neck, abdomen, pelvis, and other areas of the body may be performed with MRI instead of CT, but evaluation of the chest must be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with non-contrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). Spiral/multidetector CT should be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.

The same imaging modality and image-acquisition protocol (including use or nonuse of IV contrast) should be used consistently across all time points to allow consistent comparison of lesions. Low-dose noncontrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable, unless they are of diagnostic quality. Ultrasound should not be used for radiographic tumor assessment.

Brain scans should be performed by MRI pre- and post-contrast enhancement or CT with contrast enhancement, with 5-mm contiguous slices recommended (maximum inter-slice gap of 1 mm on MRI).

Whole body ^{18}FDG-PET scans should be performed using institutional guidelines.

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT or MRI) technique should be used for the assessment of target and nontarget lesions.

Assessments are to be performed at the site by appropriately qualified personnel and results of the site interpretation are to be recorded on the appropriate eCRFs.

11.3. Independent Review Committee

An IRC review will be used, if the data are promising and warrants label expansion for tazemetostat, to decrease any potential bias of Investigator assessments of radiologic response. The IRC will be chartered to evaluate response assessment for analysis independently per 2014 Lugano Classification (Appendix 3). Blinded reviewers will be radiologists experienced in oncology. The independent review will not be used for treatment decisions. Investigators will review for standard of care.

11.4. Survival Follow-up

Survival follow-up will be conducted approximately every 90 days on all subjects, unless subject withdraws consent. Information on all anticancer therapies will be collected (the Sponsor may choose to stop the collection of therapies after the first anticancer treatment following tazemetostat). This may be done by telephone contact. Once the study has achieved the number of events necessary for the final analysis, subjects may no longer be contacted for this information.

12. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording of all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE V5.0).

For details, refer to the Schedule of Visits and Procedures (Table 2).

12.1. Safety Parameters

12.1.1. Demographic/Medical History

Demographic information will be collected at the Screening Visit. Standard demography parameters include age, gender, and race/ethnicity (recorded in accordance with prevailing regulations). The Screening Visit will occur within 28 days prior to the first dose of study drug to confirm that the subjects meet the selection criteria for the study. The assessments to be conducted at screening are provided in Table 2 (Schedule of Visits and Procedures). Medical and surgical histories will be obtained at the Screening Visit, along with a record of prior concomitant medications and/or procedures. Significant findings before the start of study drug will be recorded on the Medical History and Current Medical Conditions eCRF. A standard of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed at the Screening Visit and at all disease assessments.

12.1.2. Vital Signs

Vital signs will be collected at the visits designated in the Schedule of Visits and Procedures (Table 2) by a validated method. Vital sign measurements will include systolic and diastolic blood pressure, heart rate (beats per minute), and body temperature (°C). Blood pressure and heart rate will be collected after subjects have been sitting for 5 minutes.

When vital signs are to be obtained concurrently with blood samples, the vital sign measurements will be performed before blood samples are collected in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood collection on other safety assessments.

12.1.3. Weight and Height

Body weight (kg) is required to be measured at the visits designated in the Schedule of Visits and Procedures (Table 2). Height measurement is required at the Screening Visit only.

12.1.4. Eastern Cooperative Oncology Group Performance Status

An ECOG performance status assessment will be completed at the visits designated in the Schedule of Visits and Procedures (Table 2). The ECOG performance scale will be used (Appendix 1).

12.1.5. Physical Examinations

12.1.5.1. Comprehensive Physical Examination

A comprehensive physical examination of all body systems must be performed by a qualified licensed individual at the visits designated in the Schedule of Visits and Procedures (Table 2). A review of body systems will include the following:

- General appearance
- Skin
- Head, ears, eyes, nose, throat
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Neurological examination with sensory testing and seizure status, if applicable
- Musculoskeletal

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

12.1.5.2. Symptom-Directed Physical Examination

A symptom-directed physical examination must be performed by a qualified licensed individual at visits where a comprehensive PE is not required for that visit (Table 2). This will consist of a focused review of systems and physical examination addressing any new symptoms, AEs, or complaints.

12.1.6. Laboratory Assessments

Clinical laboratory samples will be collected at the visits designated in the Schedule of Visits and Procedures (Table 2). The clinical laboratory parameters that will be measured are detailed in Table 7.

All routine, scheduled clinical laboratory assessments and screening laboratory assessments (see below) will be conducted locally only (these samples should not be sent to central laboratory for testing unless local testing is not available):

- Hematology
- Comprehensive chemistry panel
- Lactate dehydrogenase(LDH)
- Peripheral blood smear (Section 12.1.8)

- Cytogenetic testing and, if necessary, DNA sequencing by NGS of bone marrow aspirate/biopsy for subjects with abnormal morphology in peripheral blood smear suggestive of MDS/AML or MPN (performed by local laboratory, please refer to Lab Manual for details. Please see below if local laboratory is not equipped.)
- Viral serology/virology (Section 12.1.7)
- Pregnancy testing (serum or urine as indicated) (Section 12.1.9)

- The below samples/assessments may be conducted at the appropriate central laboratory:

  - If local laboratory is unable to perform cytogenetic testing and, if necessary, DNA sequencing of prespecified disease-related genes by NGS, or if results are inconclusive/indeterminate: bone marrow aspirate/biopsy for subjects with abnormal morphology in peripheral blood smear suggestive of MDS/AML or MPN can be sent to central laboratory for testing as backup.

NOTE: In the future, any of the blood and tissue samples that were not completely used may be used for additional research.

A Laboratory Manual will be provided to detail handling, processing, and shipping procedures.

All hematology and serum chemistry (including pregnancy testing, where applicable) samples are to be obtained before study drug administration and results reviewed before administration/dispensing of study drugs. For the management of clinically significant laboratory abnormalities, refer to the dose adjustment criteria for tazemetostat in Section 7.4.1.

A laboratory abnormality may meet the criteria of an AE as described in this protocol (Section 12.2.1.1) and the eCRF completion guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For a laboratory abnormality meeting the criteria for an SAE (Section 12.2.1.2), the study site must send the SAE reporting form and the laboratory report to the Sponsor or Sponsor's designee at the fax number or email address indicated in the Investigator file.

Table 7: Clinical Laboratory Tests

Category	Parameters
Hematology	• hematocrit, hemoglobin • red blood cell count • platelet count • white blood cell count with differential and ANC (neutrophils, bands [optional], basophils, eosinophils, lymphocytes, and monocytes,) • peripheral blood smear morphology assessment (if peripheral blood smear morphology is abnormal and suggestive of MDS/AML or MPN, then conduct bone marrow aspirate/biopsy with cytogenetic testing to closely monitor subjects for cytogenic abnormalities known to be associated with myelodysplastic syndrome [MDS; eg, del 5q, chr 7, abn] and myeloproliferative neoplasm [MPN; eg, JAK2 V617F]. Additional testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted next generation sequencing (NGS) of known disease genes, as necessary.) • Complete blood count with peripheral blood smear will be performed at least once every 3 months while a subject is receiving tazemetostat.
Chemistry	
Comprehensive Metabolic (Chemistry) Panel	• bicarbonate • chloride • potassium • sodium • alkaline phosphatase (ALP), • alanine aminotransferase (ALT), • aspartate aminotransferase (AST), • total bilirubin, • albumin • calcium, • glucose, • total protein, • blood urea or blood urea nitrogen, • creatinine
Other	• lactate dehydrogenase(LDH)

12.1.7. Viral Serology/Virology

If infection status is unknown at screening, testing should include viral serologies for HBV (Appendix 7) and HCV (Appendix 8), and virology testing for HBV and HCV (as indicated), and HIV as per institutional standard. Additional HBV-DNA testing by PCR may be required if subject is HBsAg negative, anti-HBs positive and/or anti-HBc positive. Hepatitis C virus testing by HCV antibody and if positive (reactive), further HCV-RNA testing by PCR must be performed.

12.1.8. Bone Marrow Aspirate/Biopsy Pertaining to AESI

At screening and during the study, a peripheral blood smear will be performed manually or automated along with routine hematology testing and assessed for abnormal morphology. If results are abnormal and suggestive of MDS/AML or MPN, the subject will undergo a bone

marrow aspirate/biopsy procedure. The bone marrow aspirate/biopsy sample will then be analyzed by cytogenetic testing at the local laboratory to closely monitor subjects for abnormalities known to be associated with MDS (e.g., del 5q, chr 7, abn) and MPN (e.g., JAK2 V617F). Additional local laboratory testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted next generation sequencing (NGS) of known disease genes, as necessary. If local testing is unavailable or if results are inconclusive/indeterminate, the site will be required to ship samples for central laboratory testing. If the cytogenetic testing and, if conducted, DNA sequencing by NGS results are abnormal and associated with myeloid malignancies, tazemetostat will be discontinued.

12.1.9. Pregnancy Testing

A serum pregnancy test (β-hCG) must be performed at Screening and within 24 hours prior to the first dose of study drug for all FCBP. Subsequent pregnancy testing will be performed pre-dose on Day 1 of each cycle beginning with Cycle 2 and at the End-of-Treatment visit by urine or serum. Pregnancy tests will have a minimum sensitivity of 25 mIU/mL. Any positive urine pregnancy test must be confirmed by a serum test. Blood (or urine) will be collected for pregnancy testing at designated time points on the Schedule of Visits and Procedures (Table 2).

Refer to Section 12.4.2 for reporting of pregnancy.

12.2. Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Events

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

Laboratory values that are deemed not clinically significant or related to underlying disease do not need to be captured as AEs. Laboratory values that warrant treatment change or result and an SAE do need to be captured as applicable.

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

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

All AEs will be collected from time of signing informed consent to 30 days after the final dose of study drug, or until the start of subsequent anticancer therapy, whichever happens first. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone.

12.2.1.2. Serious Adverse Events

A SAE is any adverse event (untoward medical occurrence) that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization, but when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of an SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry
- An emergency room visit lasting longer than 24 hours but not resulting in hospitalization

Note: Disease progression is a study endpoint and should not be reported as an SAE term. However, AEs (eg, dyspnea) that meet seriousness criteria, although associated with disease progression, should be reported as an SAE. Refer to Section 12.2.3.

12.2.2. Adverse Events of Special Interest (AESIs)

The following AESIs have been identified as requiring mitigation steps and monitoring to minimize the risk for the occurrence of these events. All potential and identified AESIs must also be discussed with the Medical Monitor and reported following the procedures for reporting SAEs (Section 12.4).

12.2.2.1. T-Cell Lymphoblastic Lymphoma/T-Cell Acute Lymphoblastic Leukemia

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

CCI [redacted]

This event was reported to regulatory authorities as a 7-day suspected unexpected serious adverse reaction (SUSAR) on 13 April 2018 (PPD).

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

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

Based on this evaluation, we continue to believe that tazemetostat is a clinically active drug and has the potential to benefit both adult and pediatric subjects across different tumor types where there are unmet medical needs. We also conclude that the risk assessment identifies a possible direct association between tazemetostat and T-LBL/T-ALL. Epizyme considers the risk for T-LBL/ T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric subjects based on 1) higher area under the concentration-time curve from zero time to 24 hours (AUC_{0-24}) exposures in pediatric subjects 2) increases over time in age-related thymic involution, and 3) the known epidemiology / pathophysiology of T-LBL/ALL. The risk of T-LBL/T-ALL in adults is not known, however the incidence of treatment-related T-LBL/T-ALL in adults is expected to be uncommon. To date, there have been no observed cases of T-LBL/T-ALL in adults. Refer to the tazemetostat IB for further details.

12.2.2.2. Myelodysplastic Syndrome/Acute Myeloid Leukemia/Myeloproliferative Neoplasm

Five myeloid AESI in the adult population have been reported in the adult population. The three AML cases were reported in one subject each with rhabdoid sarcoma and FL and DLBCL. The DLBCL subject experienced MDS which then transformed into AML. Two cases of MDS were reported in one subject each with FL and DLBCL.

In the event of suspicion of these malignancies or related concerns, please contact the Medical Monitor for evaluation and consideration of dose adjustments. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any MDS/AML and other myeloid malignancies like MPN. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be discontinued.

12.2.3. Disease-Related Events

Events that meet the criteria for serious but are thought to be due to the underlying malignancy or associated with progression of disease under study should be reported as SAE if untoward.

Note: Disease progression per se should not be reported as an SAE term in and of itself.

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be reported to Epizyme, Inc.

12.2.4. Other Risks

Refer to the respective package inserts or IB and established treatment guidelines and dose modified according to approved product labeling or IB for additional risks.

12.2.4.1. Identified Risks

12.2.4.1.1. Associated with Tazemetostat

- Events of thrombocytopenia, neutropenia, or anemia (Grade 3 or Grade 4).
- AEs associated with treatment overdose, misuse, abuse, or medication error; and any treatment-emergent significant laboratory abnormality.

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

12.2.4.1.2. Associated with Rituximab

Other identified risks for rituximab include:

- Tumor lysis syndrome
- Infections
- Cardiac adverse reactions
- Renal toxicity

- Bowel obstruction and perforation
- Immunizations: Live virus vaccinations prior to or during rituximab treatment is not recommended
- Embryo-fetal toxicity: Can cause neonatal harm

For rituximab, refer to the current manufacturer's prescribing information.

12.2.4.2. Events Under Evaluation

12.2.4.2.1. B-cell Acute Lymphoblastic Leukemia (B-ALL)

CCI

Total exposure (study CCI and CCI) to tazemetostat is approximately 46 months. Other possible etiologies/risk factors include genetic predisposition to lymphoid malignancies leading to the event as an evolution of the underlying lymphoma and possibly induced by previous aggressive chemotherapy.

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

Based upon medical review of the biology, nonclinical data and literature of this isolated case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure. However, Epizyme will continue to monitor patient safety with regard to secondary malignancy and all hematological secondary malignancies and all hematological secondary malignancies will be assessed by the tazemetostat QSR and ESC as detailed in Section 12.5.

12.2.5. Special Situations: Overdose, Misuse, Abuse and Medication Error

Definitions, reporting, and management of overdose, misuse, abuse, and medication errors are presented below and refer to tazemetostat.

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

These occurrences must be reported on the dosing administration eCRF. Adverse events associated with these occurrences are to be captured on the AE eCRF.

All instances of special situations are to be reported using the paper special situations form regardless of presence or absence of an associated AE. Refer to Section 12.4.3 for detailed instructions on how to handle the reporting of special situations.

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

12.3. Relationship to Study Drug

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

Items to be considered when assessing the relationship of an AE to the study drug are:

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

Classification of Causality

- Not Related: A causal relationship between the study drug and the AE is not a reasonable possibility.
- Related: A causal relationship between the study drug and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty as "possible" or "probable."

12.3.1. Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE V5.0 (Appendix 2). Investigators will collect all CTCAE grades for AEs (for both increasing and decreasing severity). All AEs reported using CTCAE classification and graded as 4 or 5 are to be considered serious. Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study drug. In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guidelines.

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

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event (as in "mild," "moderate," or "severe"). See Section 12.2.1.2 for the definition of an SAE.

12.3.2. Outcome Categorization

The outcome of AEs may be classified as resolved, resolved with sequelae, unresolved or fatal.

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

12.4. Reporting Adverse Events

All AEs will be recorded from the signing of consent form until 30 days following the last study drug administration. All SAEs must be reported to Sponsor within one business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to Sponsor. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should also be reported.

A copy of all additional follow-up information, if required or available, should be sent to Sponsor within one business day of receipt and this should be completed on a follow-up SAE form, placed with the original SAE information, kept with the appropriate section of the eCRF and Investigator Study File.

Epizyme is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site in accordance with IRB/ IEC guidelines. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial or at other trials using the same study drug. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

12.4.1. Reporting of Adverse Events of Special Interest

All potential and identified AESIs, irrespective of their relationship to study drug, must be reported as soon as possible, but no later than 24 hours from when the Investigator becomes aware of the event.

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

12.4.2. Reporting of Pregnancy

Any pregnancy where the estimated date of conception occurs either before the last visit or within 30 days of the last dose of study drug or any exposure to study drug through breastfeeding during study drug or within 30 days of last dose of study drug must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study drug.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Adverse Events Section 12.4).

Pregnancies or exposure to study drug through breastfeeding must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy.

The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File.

A subject who becomes pregnant must be withdrawn from the study.

12.4.3. Reporting of Special Situations

Report the special situation(s) of overdose, misuse, abuse, and/or medication error (described in Section 12.2.5) using one of the following sets of instructions according to whether the special situation occurred without any associated AEs, with an associated non-serious AE, or with an associated SAE:

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

- Report to Epizyme using a paper Special Situations Form following the procedures for reporting AE (Section 12.4).

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

- Enter the non-serious event on the AE eCRF and mark the SAE field, "no". SAE related narrative fields should not be completed.
- Report to Epizyme using a paper Special Situations Form following the procedures for reporting AE (Section 12.4).

Special situation(s) with an associated SAE:

- Complete the AE eCRF per protocol for the associated SAE term ONLY (Special situations are not adverse event terms in and of themselves); complete CRF SAE fields.
- Report to Epizyme using both a paper Special Situations Form and a paper Serious Adverse Event Form following the procedures for reporting AE (Section 12.4).

12.5. Quarterly and External Safety Review: The Tazemetostat Safety Committees

Monitoring of second primary malignancies is a pharmacovigilance function. All AESIs will be fully evaluated in Quarterly Safety Review (QSR) meetings and in the External Safety Committee (ESC).

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

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

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

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

The purpose of the ESC is to provide independent review of clinical data for the purposes of identifying and evaluating secondary malignancy safety signals from Epizyme sponsored clinical trials. The ESC also monitors the data of those study subjects who have experienced the

tazemetostat AESIs, namely T-LBL/T-ALL, MDS, AML, and other myeloproliferative malignancies such as MPN.

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

13. BIOMARKER ASSESSMENTS

CCI

[redacted]

14. STATISTICS

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. A statistical analysis plan (SAP) will be finalized prior to final database lock. Should the SAP and the protocol be inconsistent with respect to any further planned analyses, the language of the SAP is governing.

All statistical analyses will be performed by the Sponsor or designee. Sample and power calculations are based on nQuery 8.0.

Definitions of Analysis Sets

The analysis sets will be defined as follows:

- **Futility Analysis Set** will comprise of the first 15 subjects regardless of EZH2 status who received at least 1 dose of study drug and had tumor assessment at both baseline and Cycle 6.
- **Primary Analysis Set** will comprise of the first 43 subjects regardless of EZH2 status who received at least 1 dose of study drug and had tumor assessment at both baseline and at least one post-baseline timepoint (Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24).
- **Full Analysis Set** (FAS) will include all subjects who received at least 1 dose of study drug and had tumor assessment at baseline and at least one post-baseline timepoint (Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24). This will be the overall analysis set for efficacy evaluations.
- **Safety Population** will include all subjects who received at least 1 dose of the study drug and have at least 1 post-baseline safety evaluation, regardless of mutation status. This will be the analysis set for all safety evaluations.

14.1. Futility Analysis

Futility analysis (FA) will be performed when the Cycle 6 tumor assessment data are available for the first 15 evaluable subjects regardless of EZH2 status. ORR, defined as the proportion of the subjects achieving a CR or PR according to the 2014 Lugano Classification (Appendix 3), will be calculated. Subjects with the best response of unknown/non-evaluable response will be treated as non-responders, (i.e., they will be included in the denominator only when calculating ORR).

14.2. Primary Efficacy Analyses

ORR is defined as the proportion of subjects achieving a CR or PR according to the 2014 Lugano Classification (Appendix 3) as assessed by Investigator and blinded IRC at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24.

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 only when calculating the percentage). ORR will be presented with corresponding 2-sided 95% confidence intervals (CIs). This analysis will be performed on a subset of the FAS that includes all subjects with WT EZH2 status.

14.3. Secondary Efficacy Analyses

PFS is defined as the time from the first dose of study drug to the earliest date of documented disease progression per the 2014 Lugano Classification (Appendix 3) or death from any cause, whichever occurs first. Disease progression will be assessed by a blinded IRC. Cases without a reported PFS event will be censored at the time of the last tumor assessment. Median PFS, first and third quartiles will be estimated using Kaplan-Meier method on the FAS, if there are a sufficient number of PFS events (ie, relapses, progressions or deaths), and 2-sided 95% CIs will be estimated. Figures and listings of PFS will also be provided.

For each subject with a CR or PR, DOR is defined as time from the earliest date of CR or PR per the 2014 Lugano Classification (Appendix 3) to documented disease progression or death, whichever occurs first. DOR will be assessed by a blinded IRC If there are a sufficient number of responders who subsequently progress or die due to any cause. The median DOR, first and third quartiles, will be calculated from the Kaplan-Meier estimates using the FAS. The associated 2-sided 95% CIs will be estimated. A listing of DOR will be provided.

Analysis of ORR as a secondary endpoint will be similar to analysis of the primary efficacy endpoint but performed on FAS regardless of mutation status and the defined subgroups (MT EZH2 or rituximab refractory subjects).

14.4. Exploratory Analyses

Overall survival (OS) is defined as the interval of time between the date of the first dose of study drug and the date of death due to any cause. For subjects surviving at the time of OS analysis, the time of death will be censored at the date of last contact. The reason for death may be included in the summary.

14.5. Safety Analyses

All safety analyses, unless otherwise specified, will be performed on the Safety Population. The incidence of AEs and SAEs will be summarized. Laboratory test results, vital signs, and their changes from baseline, will be summarized using descriptive statistics. Abnormal values will be flagged.

14.6. Determination of Sample Size and Criteria for Early Stopping Due to Futility

The primary objective of this study is to evaluate the ORR obtained in subjects with R/R FL and WT EZH2 status, treated with the combination of rituximab and tazemetostat. Given the historical data with single agent rituximab (McLaughlin, 1998; Leonard, 2019), the Sponsor would consider the combined regimen to be of no further interest if the ORR were 50% or less, but of considerable interest if the ORR were at least 70%.

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 50% will be tested against the one-sided alternative. In the first stage, 15 subjects will be accrued. If there are 8 or fewer responses in these 15 subjects, the regimen will be considered as futile.

Subject enrollment will continue during futility analysis. If 9 responses or greater (CR + PR) are seen in the initial 15 subjects, additional subjects will be accrued for a total of 54 evaluable subjects. The Sponsor expects 80% of enrolled subjects to have WT EZH2 status. Consequently, the study will enroll approximately 43 WT subjects as well as approximately 11 MT subjects. With an estimated early dropout rate of 10%, this study estimates a total accrual of 59 subjects.

For the primary analysis, the null hypothesis will be rejected if 27 or more responses (CR + PR) are observed in the first 43 evaluable subjects regardless of mutation status. This design yields a one-sided type I error rate of 0.05 and power of 0.801 when the true response rate is 70%.

If the primary analysis is successful, full analysis will be conducted once 54 evaluable subjects are available regardless of mutation status. Subjects in the FAS will be stratified to 2 subgroups depending on their EZH2 mutation status (WT vs MT).

With an estimated 54 eligible subjects in the combined FAS, rates of individual AEs can be estimated to within at most ± 14% (95% confidence interval). Any AE with a true rate of at least 5% is likely to be observed at least once (93% chance).

Assuming accrual takes place over 24 months, with at least an additional 12 months of follow-up for progression, there would be approximately 65% power to rule out a benchmark median PFS of 12 months against the alternative of a true PFS of 18 months (one-sided, 0.05 level test) in the primary analysis subset of 43 subjects with at least 26 PFS events. If PFS is similar in both subsets regardless of EZH2 status, then there would be 80% power for the same analysis in the combined FAS of 54 subjects with at least 33 PFS events.

The reporting of response rate in the MT EZH2 subset (anticipated to be 11 subjects) will have very little precision and is exploratory only. Note, the subjects with MT EZH2 status will be included in all primary safety analyses.

14.7. Criteria for Early Stopping Due to Unacceptable Rates of Adverse Events

Criteria will be in place for halting enrollment and treatment due to safety findings:

- Any fatality that is at least possibly related to treatment calls for immediately stopping accrual and treatment. If attribution is in doubt, the study should be halted until attribution is definitively determined and a decision is made by the study team.
- Two or more observations of a secondary myelodysplastic syndrome or AML or secondary malignancy attributed to tazemetostat will result in stopping accrual and treatment. (Note: observations may not occur during the study period and may occur later, after it is too late to stop accrual.)
- Continuous monitoring with Pocock-like boundaries using the method of Ivanova (Ivanova, 2005) will be utilized for other categories of adverse events, with following rates applied to the continuous stopping rules:
- Combined rate of reportable SAE or SUSAR: 10%
  - Any single category of grade > 3 AE: 50%
  - Grade >3 non-hematologic AE overall: 30%

A table of stopping boundaries for these criteria are provided in Appendix 5 . These criteria are independent of the futility analysis for efficacy and will be applied to all subjects that receive any treatment with tazemetostat, regardless of mutation status. See Appendix 2 for details. The stopping rules assume a full accrual of 54 subjects in order to retain statistical properties.

However, if the study stops early due to futility, any bias introduced in the stopping rules due to a change in total accrual should no longer be a concern.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Epizyme will visit the investigational study site or conduct a remote visit, if necessary, to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Epizyme or its representatives. This will be documented in a Clinical Study Agreement between Epizyme and the Investigator.

During the study, a monitor from Epizyme or representative will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator, Sub-Investigator(s) and study staff
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Epizyme.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Epizyme and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Epizyme, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an Epizyme audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Epizyme immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. DATA QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Epizyme may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Epizyme before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Epizyme will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by GCP as described in the current ICH Tripartite Guideline E6: GCP: Consolidated Guideline. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with all applicable country and local legal and regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

18. DATA HANDLING AND RECORD KEEPING

18.1. Inspection of Records

Epizyme will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Epizyme or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Data Management

Data required by the protocol will be collected on a CRF and entered into an Electronic Data Capture clinical database that is compliant with all regulatory requirements.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF. The Investigator or designee as identified on Form FDA 1572 must sign the CRF casebook to attest to its accuracy, authenticity, and completeness.

The completed eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

18.4. Recording of Data

A CRF is required for each subject and must be completed by qualified and authorized personnel. Only data required by the protocol for the purposes of the study should be reported on the CRF. All data on the CRF must reflect the corresponding source document. Any corrections to entries made on the CRF must be documented in a valid audit trail.

18.5. Identification of Source Data

The following items in the CRF will be handled as source data:

- Study drug compliance (eg, the reason for dose increase/reduction)
- Discontinuation information
- Sampling date and time for the drug concentration
- Sampling date and time for the clinical laboratory test
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

18.6. Handling of Study Drug

All tazemetostat will be supplied to the PI (or a designated pharmacist) by Epizyme. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug label. The Investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. Once study drug has been received by the investigational site, the assigned review personnel may request the records for reviewing these documents along with all other study conduct documents at appropriate intervals during investigational site visits.

All drug supplies are to be used only for this protocol and not for any other purpose. The Investigator (or a designated pharmacist) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by Epizyme. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or a designated pharmacist) will either return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Epizyme designated contractor or, where approval is given by Epizyme, will destroy supplies and containers at the investigational site.

18.7. Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the coordinating center. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of the coordinating center. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and the coordinating center.

19. PUBLICATION POLICY

A summary of the study results will be made publicly available within 12 months of reaching the end of the study, defined as the date of the last subject last visit. Clinical study results will be made publicly available in compliance with local legislation and guidelines.

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

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

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Electronic Record and Signature Disclosure: Accepted: 6/30/2020 11:05:15 AM ID: CCI [redacted]		
PPD Epizyme Inc. Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: CCI [redacted] Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/22/2021 9:48:43 AM Viewed: 10/24/2021 10:22:11 AM Signed: 10/24/2021 10:22:28 AM
Electronic Record and Signature Disclosure: Accepted: 6/3/2020 4:04:37 PM ID: CCI [redacted]		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

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	10/22/2021 9:48:43 AM
Certified Delivered	Security Checked	10/24/2021 10:22:11 AM
Signing Complete	Security Checked	10/24/2021 10:22:28 AM
Completed	Security Checked	10/24/2021 10:22:28 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Epizyme Inc. (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Use of 21 CFR Part 11 Electronic Signatures

As an Epizyme DocuSign user, you understand and agree that by adopting and applying your electronic signature to documents, the signature is the legally binding equivalent of your traditional handwritten signature. Additionally, you affirm that the electronic signature is unique to you and may only be used by you to sign documents.

Please refer to the free available DocuSign training for applying your electronic signature at CCI

Acknowledging your access and consent to receive and sign documents electronically

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- You understand that your electronic signature is a legally binding equivalent to your handwritten signature.