Protocol Number: EZH-105

Protocol Title: An Open-Label, Multicenter, Two-Part, Phase 1 Study to Characterize the Effects of a Moderate CYP3A Inhibitor on the Pharmacokinetics of Tazemetostat (EPZ-6438) (Part A), the Effects of Tazemetostat on the Pharmacokinetics of CYP2C8 and CYP2C19 Substrates, and the Effect of Increased Gastric pH on the Pharmacokinetics of Tazemetostat (Part B) in Subjects with B-cell Lymphomas or Advanced Solid Tumors

NCT Number: NCT03028103

Protocol Amendment 4 Final: 28 September 2018

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: An Open-Label, Multicenter, Two-Part, Phase 1 Study to Characterize the Effects of a Moderate CYP3A Inhibitor on the Pharmacokinetics of Tazemetostat (EPZ-6438) (Part A), the Effects of Tazemetostat on the Pharmacokinetics of CYP2C8 and CYP2C19 Substrates, and the Effect of Increased Gastric pH on the Pharmacokinetics of Tazemetostat (Part B) in Subjects with B-cell Lymphomas or Advanced Solid Tumors

Protocol Number: EZH-105

Approved by:

Responsible Sponsor Medical Officer:

Signature: _____ **Date:** 5-OCT-2018

Shefali Agarwal, MBBS, MPH, MIS
Chief Medical Officer
Epizyme, Inc.

Responsible Sponsor Medical Monitor:

Signature: _____ **Date:** 5 OCT 2018

Deyaa Adib, MD
NHL Medical Director
Clinical Development
Epizyme, Inc.

Date: Original, Version 2, 03 October 2016
Amendment 1, 07 February 2017
Amendment 2, 07 July 2017
Amendment 3, 06 March 2018
Amendment 4.0, 28 September 2018

INVESTIGATOR AGREEMENT PAGE

Protocol Title: An Open-Label, Multicenter, Two-Part, Phase 1 Study to Characterize the Effects of a Moderate CYP3A Inhibitor on the Pharmacokinetics of Tazemetostat (EPZ-6438) (Part A), the Effects of Tazemetostat on the Pharmacokinetics of CYP2C8 and CYP2C19 Substrates, and the Effect of Increased Gastric pH on the Pharmacokinetics of Tazemetostat (Part B) in Subjects with B-cell Lymphomas or Advanced Solid Tumors

Protocol Number: EZH-105

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

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

I have read and agree to the following Confidentiality Statement:

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

Principal Investigator:

Name: _____

Title: _____

Signature: _____ **Date:** _____

Name/Address of Institution: _____

_____

CLINICAL STUDY PROTOCOL

Protocol Title:	An Open-Label, Multicenter, Two-Part, Phase 1 Study to Characterize the Effects of a Moderate CYP3A Inhibitor on the Pharmacokinetics of Tazemetostat (EPZ-6438) (Part A), the Effects of Tazemetostat on the Pharmacokinetics of CYP2C8 and CYP2C19 Substrates, and the Effect of Increased Gastric pH on the Pharmacokinetics of Tazemetostat (Part B) in Subjects with B-cell Lymphomas or Advanced Solid Tumors
Compound Name (Number):	Tazemetostat (EPZ-6438)
Protocol Number:	EZH-105
Effective Date:	03-Oct. 2016
IND Number:	124025
Sponsor:	Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA
Sponsor Medical Monitor:	Deyaa Adib, MD Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA Phone: (617) 674-1795 Mobile: (617) 908-246-2899

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

1. SYNOPSIS

Study title	An Open-Label, Multicenter, Two-Part, Phase 1 Study to Characterize the Effects of a Moderate CYP3A Inhibitor on the Pharmacokinetics of Tazemetostat (EPZ-6438) (Part A), the Effects of Tazemetostat on the Pharmacokinetics of CYP2C8 and CYP2C19 Substrates, and the Effect of Increased Gastric pH on the Pharmacokinetics of Tazemetostat (Part B) in Subjects with B-cell Lymphomas or Advanced Solid Tumors
Protocol number:	EZH-105
Clinical phase	1
Number of study centers	3 centers in the US
Investigational product	Tazemetostat (EPZ-6438)
Study objectives	**Primary objectives** **Part A:** • To determine the effect of CYP3A inhibition by fluconazole on the pharmacokinetics (PK) of tazemetostat **Part B:** • To investigate the potential of tazemetostat to inhibit or induce CYP2C8 using repaglinide as a probe substrate • To investigate the potential of tazemetostat to inhibit or induce CYP2C19 using omeprazole as a probe substrate • To investigate the effect of increased gastric pH by omeprazole on the PK of tazemetostat **Secondary objectives** **Part A** • To investigate the safety profile of tazemetostat 400 mg twice daily (BID) after co-administration with fluconazole • To determine the PK of tazemetostat and its metabolites after administration alone and with fluconazole • To determine the systemic exposure of fluconazole after administration of 400 mg once daily for 4 days **Part B:** • To investigate the safety profile of tazemetostat, repaglinide, and omeprazole after co-administration • To determine the PK of repaglinide and its metabolites after administration with omeprazole and administration with omeprazole and tazemetostat • To determine the PK of omeprazole and its metabolites after administration with repaglinide and administration with repaglinide and tazemetostat • To determine the PK of tazemetostat and its metabolites after repeated dose of tazemetostat alone and with fluconazole **Parts A and B:** • To assess antitumor activity of tazemetostat in subjects with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), follicular lymphoma (FL), or advanced solid tumors

	Exploratory objectives • To investigate the effects of variations in genes encoding for CYP enzymes and transporters on the potential drug-drug interaction profile of tazemetostat • To explore the effect of tazemetostat on overall survival (OS)
Study design	Phase 1, open-label, 2-part, pharmacokinetic, safety, and activity study
Methodology	This 2-part study is designed to characterize the drug-drug interaction (DDI) potential of tazemetostat. Upon initiation of tazemetostat treatment, eligible subjects will receive tazemetostat BID continuously in 28-day cycles in both parts of the study. **Part A.** Subjects enrolled in Part A will receive treatment with oral tazemetostat tablets 400 mg BID for 24 days beginning on Day 1. Blood samples for the analysis of plasma tazemetostat and its metabolites concentrations will be collected predose and over 8 hours after the morning dose of tazemetostat on Day 15. Subjects will receive fluconazole 400 mg once daily for 4 days starting on Day 16. On Day 19, blood samples for the analysis of plasma tazemetostat, its metabolites, and fluconazole will be collected predose and over 8 hours after the morning tazemetostat dose. Tazemetostat 400 mg BID will continue through Day 24. Subjects will then receive tazemetostat 800 mg BID starting on Day 25. **Part B**. Subjects enrolled in Part B will receive single oral doses of repaglinide 0.25 mg and omeprazole 20 mg on Day 1. Administration of tazemetostat 800 mg BID will begin on Day 2. On Day 16, subjects again will receive single oral doses of repaglinide 0.25 mg and omeprazole 20 mg approximately 1 hour after the morning dose of tazemetostat. Subjects also will receive omeprazole 20 mg once daily in the morning on Days 16 through 19. Blood samples for analysis of plasma repaglinide, repaglinide metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone will be collected predose and over 7 hours after administration on Day 1 and Day 16. Blood samples for analysis of plasma tazemetostat and metabolites will be collected over 8 hours after administration of the morning dose on Day 16 and Day 19. Upon initiation of tazemetostat treatment, all subjects enrolled in this study will receive oral tazemetostat for up to 6 months (24 weeks) until they have an unacceptable toxicity, disease progression, or withdraw consent. Subjects continuing to receive benefit from tazemetostat treatment can be transitioned to Study EZH-501 (a rollover study) upon completion of Study EZH-105, at the investigator's discretion, and after completing all study assessments and receiving at least 6 months of treatment with tazemetostat. Subjects who are enrolled in the study and do not complete all study assessments, or who do not transition to Study EZH-501 must have a post-treatment follow-up visit within 30 days of the last dose of tazemetostat. Subjects who permanently discontinue treatment with tazemetostat and do not transition to the EZH-501 study, will be followed for OS.
Number of subjects	Approximately 32 subjects will be enrolled to achieve 12 subjects who complete each part of the study (total of 24 completed subjects). Subjects will complete either Part A or Part B. Subjects (both parts of study) who require a dose reduction during the first 19 days of treatment may be replaced. Subjects who miss 2 or more consecutive tazemetostat doses during the first 19 days of treatment or miss more than 3 tazemetostat doses during the first 19 days of treatment may be replaced. Subjects who miss 2 or more PK blood sample collections may be replaced.

Diagnosis and criteria for inclusion	Subjects must meet all criteria to be eligible for enrollment in this study. **Inclusion criteria** 1. Male or female ≥ 18 years of age at time of consent 2. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Appendix 3) 3. Has the ability to understand informed consent and provided signed written informed consent **Must meet one of the following criteria:** 4. Has histologically confirmed diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), marginal zone lymphoma (MZL), or mantle cell lymphoma (MCL) and have relapsed or refractory disease following at least 2 standard lines of systemic therapy, including alkylator/anthracycline (unless anthracycline–based chemotherapy is contraindicated)/anti-CD20-based therapy (R-CHOP: rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisolone or prednisone, or equivalent) AND must be considered unable to benefit from intensification treatment with autologous hematopoietic stem cell transplantation (ASCT), as defined by meeting at least 1 of the following criteria : a. Relapsed following, or refractory to, previous ASCT b. Did not achieve at least a partial response (PR) to a standard salvage regimen (e.g., R-ICE; rituximab, ifosfamide, carboplatin, etoposide, or R-DHAP; rituximab, dexamethasone, cytarabine, cisplatin) c. Ineligible for intensification treatment due to age or significant comorbidity d. Ineligible for intensification treatment due to failure to mobilize an acceptable number of hematopoietic stem cells e. Refused intensification treatment and/or ASCT Note: Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen **OR** Has histologically confirmed FL, all grades. Subjects must have relapsed/refractory disease following at least 2 standard lines of systemic therapy, including at least 1 anti-CD20-based regimen (eg, rituximab), as well as alkalating agents (eg, cyclophosphamide or bendamustine), and have no curative option with other available therapies OR have a contra-indication to their use. Subjects with prior ASCT may be included. Transformed disease is permitted. **NOTE:** Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen **OR**

5. Has histologically and/or cytologically confirmed advanced or metastatic solid tumor that has progressed after treatment with approved therapies or for which there are no standard therapies available.
6. Must have evaluable or measurable disease
7. Has all prior treatment (i.e., chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per NCI CTCAE, Version 4.03 or are clinically stable and not clinically significant, at time of consent

8. Time required between the last dose of the latest therapy and the first dose of study drug:

Prior Therapy	**Time from Last Prior Therapy**
Chemotherapy: cytotoxic	At least 21 days
Chemotherapy: nitrosoureas	At least 6 weeks
Chemotherapy: non-cytotoxic (e.g., small molecule inhibitor)	At least 14 days
Monoclonal antibody (ies)	At least 28 days
Non-antibody immunotherapy (e.g., tumor vaccine)	At least 42 days
Radiotherapy (RT)	At least 14 days for stereotactic radiosurgery At least 12 weeks for craniospinal, ≥50% radiation of pelvis, or total body irradiation prior to first dose of study drug
Autologous hematopoietic cell infusion after high dose therapy	At least 60 days
Hematopoietic growth factor	At least 14 days

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

System	**Laboratory Value**
Hematologic (BM Function)	
Hemoglobin[a]	≥9 g/dL
Platelets[b]	≥75,000/mm^3 (≥75 × 10^9/L)
ANC[c]	Lymphoma subjects: ≥750/mm^3 (≥0.75 × 10^9/L) Solid tumor subjects: ≥1,000/mm^3 (≥1.0 x 10^9/L)
Hematologic (Coagulation Factors)	
PT	<1.5 ULN
PTT	<1.5 ULN
Renal Function	
eGFR[d]	≥ 50 mL/min/1.73 m^2

Hepatic Function	
Conjugated bilirubin	<1.5 × ULN
AST[e]	<3 × ULN
ALT[e]	<3 × ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BM = bone marrow; eGFR = estimated glomerular filtration rate; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

a. May receive transfusion
b. Should be evaluated after at least 7 days since last platelet transfusion
c. Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
d. Calculate eGFR per institutional standard formula
e. If attributed to tumor involvement, AST and ALT <5×ULN

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

10. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec
11. Subjects with a history of Hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion No. 10 and are hepatitis B surface antigen negative and/or have undetectable HCV RNA.
12. Male subjects must refrain from donating sperm starting at the planned first dose of investigational product (IP) until 30 days following the last dose of IP
13. Male subjects with a female partner of childbearing potential must:
    a. Be vasectomized, **or**
    b. Remain abstinent or use a condom as defined in Section 8.3.10.4.2, starting at the planned first dose of IP until 30 days following the last dose of IP. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
14. Female partners of male subjects who are of childbearing potential must also adhere to one of the following:
    a. Placement of an intrauterine device or intrauterine system.
    b. Established use of oral, injected, or implanted hormonal methods of contraception plus an additional barrier method.
    c. Progesterone-only oral contraception, where inhibition of ovulation is not the primary mode of action.
15. Women of childbearing potential:
    a. A woman is considered to be of childbearing potential if she is post menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    b. Must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year starting at the planned first dose of IP until 30 days following the last dose of IP.

	c. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. d. Due to the potential of enzyme induction with tazemetostat, female subjects who use hormonal contraceptives should use an additional barrier method of birth control while on study treatment and for 30 days after discontinuation of study treatment. e. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. f. Barrier methods must always be supplemented with the use of a spermicide.
	Exclusion criteria 1. Is pregnant or nursing 2. Has active central nervous system (CNS) or leptomeningeal metastasis 3. Has had a prior malignancy other than the malignancies under study **Exception:** Subject who has been disease-free for 3 years, or a subject with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible. 4. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) and any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS). **NOTE:** Bone marrow aspirate/biopsy will be conducted following abnormal peripheral blood smear morphology assessment conducted by the local laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy. 5. Has a prior history of T-LBL/T-ALL 6. Has had major surgery within 3 weeks prior to enrollment **NOTE**: Minor surgery (e.g., minor biopsy, central venous catheter placement) is permitted within 3 weeks prior to enrollment. 7. Is unwilling to exclude grapefruit juice, Seville oranges, and grapefruit from the diet and all foods that contain those fruits from time of enrollment to the last dose of tazemetostat 8. Has cardiovascular impairment, history of congestive heart failure greater than NYHA Class II (see Appendix 4), uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of tazemetostat; or ventricular cardiac arrhythmia requiring medical treatment 9. Subjects taking medications that are known potent or moderate inducers/ inhibitors of CYP3A4 (including St. John's Wort) 10. Has an active infection or recent history (<30 days before study drug administration) requiring systemic treatment 11. Is immunocompromised, including subjects with known human immunodeficiency virus (HIV) infection 12. Has known hypersensitivity to any of the components of IP. 13. Is unable to take oral medications, has a history of surgery that would interfere with the administration or absorption of oral medication, has malabsorption syndrome or any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea or vomiting) that might impair the bioavailability of IP

<table>
<tr><td></td><td>
14. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements.
15. Is unwilling to adhere to contraception criteria from time of enrollment in study to at least 30 days after last dose of IP.
16. A history of bleeding (i.e., hemoptysis, hematuria, gastrointestinal blood loss, epistaxis, or others with greater than Grade 1 according to NCI CTCAE Version 4.03) within 1 month prior to beginning therapy or any clinical indications of current active bleeding.
17. Clinical history, current alcohol (ethanol), or illicit drug use which, in the judgment of the investigator, will interfere with the subject's ability to comply with the dosing schedule and protocol-specified evaluations.
18. Regular alcohol consumption averaging more than 7 drinks/week for women and 14 drinks/week for men within 6 months of screening. A drink is defined as follows:
<table>
<tr><th>Alcohol</th><th>1 Drink
(12 g alcohol)</th><th>7 Drinks/week
(84 g alcohol)</th><th>14 Drinks/week
(168 g alcohol)</th></tr>
<tr><td>Wine</td><td>150 mL (5 ounces)</td><td>1050 mL (35 ounces)</td><td>2100 mL (70 ounces)</td></tr>
<tr><td>Beer</td><td>360 mL (12 ounces)</td><td>2520 mL (84 ounces)</td><td>5040 mL (168 ounces)</td></tr>
<tr><td>Distilled spirits
80 proof</td><td>45 mL (1.5 ounces)</td><td>315 mL (10.5 ounces)</td><td>630 mL (21 ounces)</td></tr>
</table>
</td></tr>
<tr><td>Test article</td><td>Tazemetostat will be provided as oral tablets.
Epizyme will provide each investigator with adequate supplies of tazemetostat.</td></tr>
<tr><td>Dosage and administration</td><td>Part A: Subjects in Part A will receive tazemetostat 400 mg orally BID for 24 days starting on Day 1. Tazemetostat dose will be increased to 800 mg BID starting on Day 25.
Part B: Subjects in Part B will receive tazemetostat 800 mg BID starting on Day 2.
Treatment with tazemetostat for both parts in this study may continue for up to 6 months (24 weeks) or until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study by the sponsor.</td></tr>
<tr><td>Other medications</td><td>Fluconazole, Repaglinide, and Omeprazole
Part A: Subjects in Part A will receive fluconazole 400 mg once daily for 4 days on Days 16 through 19, inclusive
Part B: Subjects in Part B will receive single doses of repaglinide 0.25 mg orally in the morning on Day 1 and Day 16. Subjects in Part B also will receive omeprazole 20 mg in the morning on Day 1 and Days 16 through 19, inclusive.</td></tr>
<tr><td>Duration of subject participation and duration of study:</td><td>Up to 30 weeks: Up to 4 weeks screening; 24 weeks dosing; and 2 weeks follow-up. Subjects who discontinue treatment will be followed for survival via email, mail, phone contact, or clinic visit for up to 2 years after end of treatment.</td></tr>
<tr><td>Concomitant medications</td><td>Documentation of all concomitant medication administered during study treatment will be recorded in the eCRF at each visit.
Because there is a potential for interaction of tazemetostat with other concomitantly administered drugs through the cytochrome P450 system, over-the-counter medications, or alternative therapies must be recorded in the eCRF. The investigator should be alerted</td></tr>
</table>

	if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. See Section 9 for additional information.
Safety assessments	Safety assessments will include adverse events (AEs), serious adverse events (SAEs), physical examinations (PEs), vital sign measurements, clinical safety laboratory evaluations, electrocardiograms (ECGs), ECOG performance status, and reasons for treatment discontinuation due to toxicity. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading clinical and laboratory AEs. The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and continues through 14 days after the last dose of study drug. All AEs that occur in enrolled subjects during the AE reporting period must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as possibly related to study drug also should be recorded.
Pharmacokinetics	Serial blood samples will be collected throughout the study. For PK analysis, approximately 24 mL of blood will be obtained in Part A and 56 mL of blood will be obtained in Part B. See Section 8.3.6 for specific collection timepoints for each part of the study. All PK blood samples may be drawn from either a central venous catheter or a peripherally placed intravenous catheter. Plasma concentrations of all analytes will be determined by validated bioanalytical methods. Plasma concentrations of all analytes will be listed for each subject and summarized by study part, treatment, day, and nominal time. Standard summary statistics will be calculated (i.e., arithmetic mean, standard deviation (STD), median, minimum, and maximum) for each endpoint.
Activity	Antitumor activity will be assessed using the Lugano Classification (Cheson 2014, Appendix 1) for subjects with lymphoma, or RECIST v1.1 (Appendix 2) for subjects with solid tumors. Overall response rate (ORR: complete response [CR] or partial response [PR]) and disease control rate (DCR: any CR or PR, or stable disease [SD] lasting 24 weeks or longer from start of treatment with tazemetostat) will be determined.
Study endpoints	**Primary endpoints** **Part A** • AUC_{0-t}, AUC_{0-8}, AUC_{0-12}, and C_{max} of tazemetostat on Day 15 and Day 19. **Part B** • AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of repaglinide on Day 1 and Day 16. • AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of omeprazole on Day 1 and Day 16. • AUC_{0-t}, AUC_{0-8}, AUC_{0-12}, and C_{max} of tazemetostat on Day 16 and Day 19 **Secondary endpoints** **Part A** • T_{max}, and $t_{1/2}$ of tazemetostat and AUC_{0-t}, AUC_{0-8}, C_{max}, T_{max}, and $t_{1/2}$ of tazemetostat metabolites on Day 15 and Day 19. • Safety and tolerability parameters including AEs, clinical laboratory assessments, and vital signs. • Plasma fluconazole AUC_{0-8}, C_{max}, and T_{max} on Day 19 **Part B**

	• T_{max}, and $t_{1/2}$ of repaglinide and AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$ of repaglinide metabolites on Day 1 and Day 16. The metabolite to repaglinide ratio for $AUC_{0-\infty}$ and AUC_{0-t} on Day 1 and Day 16. The plasma metabolite to repaglinide concentration ratios at 1, 2, 3, 5, and 7 hours after administration of repaglinide on Day 1 and Day 16. • T_{max}, and $t_{1/2}$ of omeprazole on Day 1 and Day 16. AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$ of 5-hydroxyomeprazole (5-OH-omeprazole) and omeprazole sulfone. The 5-OH-omeprazole to omeprazole and the omeprazole sulfone to omeprazole ratios for $AUC_{0-\infty}$ and AUC_{0-t} on Day 1 and Day 16. The plasma 5-OH-omeprazole to omeprazole and omeprazole sulfone to omeprazole concentration ratios at 1, 2, 3, 5, and 7 hours after administration of omeprazole on Day 1 and Day 16. • T_{max}, and $t_{1/2}$ of tazemetostat on Day 16 and Day 19. AUC_{0-t}, AUC_{0-8}, C_{max}, T_{max}, and $t_{1/2}$ of tazemetostat metabolites on Day 16 and Day 19 • Safety and tolerability parameters including AEs, clinical laboratory assessments, and vital signs. **Parts A and B** • Overall response rate (ORR: CR or PR) and disease control rate (DCR: CR or PR, or SD lasting 24 weeks or longer from start of treatment with tazemetostat) using Lugano Classification (Cheson 2014, Appendix 1) for subjects with lymphoma, or RECIST v1.1 for subjects with solid tumors (Appendix 2). **Exploratory endpoints** • Genotyping data for genes encoding CYP enzymes and transporters • Overall survival (OS)
Statistical methods	Four populations will be employed in the analyses of the study data: • The Intent-to-Treat (ITT) population will consist of all subjects who receive at least one dose of tazemetostat. The ITT population will be used for summaries and analyses of the efficacy endpoints. • The Safety population will consist of all subjects who receive at least one dose of IP who have at least one post dose safety observation recorded. The Safety population will be used for summaries and analyses of the safety and tolerability. • Pharmacokinetic (PK) population will include all subjects in the Safety population who have sufficient postdose samples collected to allow estimation of the PK parameters. The PK population will be used for PK summaries and analyses. • The Pharmacogenomic (PGx) population will include all subjects in the PK population from whom PGx results are available. The PGx population will be used for summary of PK parameters by presence or absence of polymorphic genetic markers. Log-transformed PK parameters will be analyzed by an analysis of variance (ANOVA). The geometric least squares (adjusted) mean and associated 90% confidence interval (CI) for the test treatment to reference treatment ratio of adjusted geometric means will be provided after transformation of the results from the log-transformed analysis back to the original scale. **Part A** Descriptive statistics will be calculated for plasma concentrations and PK parameters of tazemetostat and its metabolites and fluconazole. To evaluate the effect of fluconazole on the PK of tazemetostat, the ratio of adjusted geometric means and 90% CI for the test treatment (tazemetostat administered in combination with fluconazole) to the reference treatment (tazemetostat alone) for tazemetostat PK parameters will be calculated. **Part B**

	Descriptive statistics will be calculated for plasma concentrations and PK parameters for repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, omeprazole sulfone, and tazemetostat and its metabolites. To evaluate the effect of tazemetostat on the PK of repaglinide and omeprazole, the ratio of adjusted geometric means and 90% CI for the test treatment (repaglinide administered with omeprazole and steady-state tazemetostat) to the reference treatment (repaglinide administered with omeprazole) for repaglinide and omeprazole PK parameters will be calculated. To evaluate the effect of increased gastric pH on the PK of tazemetostat, the ratio of adjusted geometric means and 90% CI for the test treatment (tazemetostat administered after 4 days of treatment with omeprazole) to the reference treatment (tazemetostat administered 1 hour before administration of repaglinide and omeprazole) for tazemetostat PK parameters will be calculated. Treatment-emergent adverse events (TEAE) will be summarized. Summaries of TEAEs will consist of the number and percentage of subjects reporting the AE by System Organ Class (SOC) and by preferred term. TEAEs which occur more than once for a subject will be counted only once in the subject frequencies. TEAEs with different CTCAE grades for a subject will be counted at the worst (highest) grade for the same SOC (likewise for preferred term). TEAEs with different drug relationship for a subject will be counted at strongest relationship for the same SOC (likewise for preferred term. TEAEs with missing relationship to study treatment will be counted as "related". TEAEs with missing CTCAE grade will be counted as Grade 3 ("severe"). TEAEs, SAEs, related TEAEs, related SAEs, ≥ Grade 3 AEs, TEAEs leading to withdrawal or treatment discontinuation, and TEAEs of special interest will be summarized overall and by study part according to SOC and preferred terms. TEAEs will also be summarized in listings. Shifts from baseline in low, normal, and high classification and clinically significant findings for each parameter will be summarized by study part and overall at each planned post-baseline visit. Physical examination, vital signs, ECG, and ECOG performance status will be summarized by study part and overall. Response will be based on Lugano Classification (Cheson 2014) for subjects with lymphoma, or RECIST v1.1 for subjects with solid tumors. ORR (CR or PR) will be summarized along with an exact 90% CI. DCR (CR or PR, or SD lasting 24 weeks or longer since start of treatment) will be summarized similarly. OS will be calculated using the Kaplan-Meier method. If there are a sufficient number of deaths at the time of the analysis, median OS, first and third quartiles, and 90% CI (Brookmeyer-Crowley method) will be summarized.

Table 1: Schedule of Assessments and Procedures: Part A

Visit Description / Study Period	**Screening[a,b]**	**Cycle 1[c]**						**Cycle 2, Day 1**	**Cycles 2 – 6[c]**	**End-of-Study[d]**
Study Days	-28 to -1	1	2 - 14	15	16 - 18	19	25		1	
Procedures/Assessments										
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographics[e]	X									
Medical History/Current Medical Conditions[f]	X									X
Prior & concomitant medications		Throughout the study								
Complete PE	X								X	X
Symptom-directed PE		X		X		X				
Weight	X								X	X
Height	X									
Vital signs[g]	X	X		X		X			X	X
ECOG performance status	X	X		X		X			X	X
12-lead ECGs[h]	X			X		X			X	X
Safety laboratory tests[i,j,t]	X			X		X			X	X
Coagulation profile[k]	X	If clinically indicated								X
Pregnancy testing[l]	X								X	X
PGx blood sample[m]	X									
PK blood samples[n]				X		X				X
Archival tumor tissue[o]	X									
Optional tumor tissue biopsy[p]	X							X		
Optional chest ultrasound[s]	X								X	X
Tumor assessments: PET, CT, bone marrow, or other[q,t]	X								X	
AEs/SAEs		Throughout the study								
Tazemetostat 400 mg BID		X	X	X	X	X[q]				
Fluconazole 400 mg					X	X[q]				
Tazemetostat 800 mg BID[r]							X		X	
Survival status and subsequent anti-cancer therapy[s]										X

Abbreviations: AE = adverse event; BID = twice daily; CT = computed tomography; ECG = electrocardiograms; ECOG = Eastern Cooperative Oncology Group; h = hour; HR = heart rate; PGx = pharmacogenomics; PE = physical examination; PET = positron emission tomography; PK = pharmacokinetic; SAE = serious adverse event

a. **Screening**: Screening Period extends from Day -28 to Day -1.
b. **Pre-Study Procedures** and tumor assessment must be performed within 28 days before first dose of study treatment.
c. Each **cycle** is 28 days in length.
d. **End of Study:** An End-of-Study visit will be conducted within 30 days (±3 days) after last dose of IP, prior to enrollment in Study EZH-501, or prior to the start of a new treatment or therapy, whichever occurs first. The post-treatment assessments will be required and, in the event of a continuing AE, the subject will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely. End of study assessments will be conducted including safety, PK and response. A 3 mL blood sample will be required for end of study PK assessments.
e. **Demographics:** Date of birth, gender, ethnicity, and race must be recorded.
f. **Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions, full history of the course of the subject's malignancy including primary diagnosis. Stage and date, and information on prior antitumor therapies including response to prior therapies must be recorded at Screening.
g. **Vital Signs:** Blood pressure (BP), heart rate (HR), and temperature (T) must be measured after the subject has been sitting for 5 minutes at screening and at regular intervals during treatment.
h. **ECG:** 12-lead ECG reading must be performed at Screening and Days 15 and 19, Day 1 of Cycles 2 – 6, and End of Study. A single ECG will be recorded unless there is an abnormality. If an abnormality is detected, then ECGs will be recorded in triplicate at least 2 minutes apart.
i. **Safety Laboratory Tests** to include hematology and serum chemistry**:** Hematology includes complete blood count with differential and absolute neutrophil count (differential values should be recorded as absolute counts whenever possible) and assessment of peripheral blood smear morphology. If peripheral blood smear morphology is abnormal, then conduct bone marrow aspirate with cytogenic testing to closely monitor patients with cytogenic abnormalities known to be associated with MDS (9del 5q, chr 7, abn, etc.) and MPN (e.g. JAK2 V617F, etc.) as observed with cytogenetic testing and DNA sequencing. Bone marrow aspirate/biopsy will be conducted following an abnormal peripheral blood smear morphology assessment conducted by the local laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy. See Section 8.3.9 for further details.
j. **Chemistries include:** alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, and total bilirubin, electrolytes, Blood urea/blood urea nitrogen, creatinine, albumin, calcium, magnesium, glucose, phosphorus, triglycerides, and total protein.
k. **Coagulation Profile:** Coagulations tests include: prothrombin time (PT), partial thromboplastin time (PTT).
l. **Pregnancy Testing:** The screening test can be either urine or serum and must have been completed within 28 days of the first dose of study drug. Subsequent testing on the first day of each cycle (Cycles 2 – 6) and at the End-of-Study visit can be either urine or serum. Any positive urine pregnancy test must be confirmed with a serum test.
m. **PGx:** A single 10 mL whole blood will be collected at any time during the screening period.
n. **PK:** Blood samples (1 mL) for analysis of tazemetostat and its metabolites will be collected at the following time points on Day 15: predose (within 30 minutes prior to dose), 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. Blood samples (2 mL) for analysis of tazemetostat and its metabolites and fluconazole will be collected at the following time points on Day 19: predose (within 30 minutes prior to dose), 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. All PK blood samples may be drawn from either a central venous catheter or a peripherally placed intravenous catheter. Allowable windows for collection of PK blood samples are ± 5 minutes for sample timepoints ≥ 0.5 and ≤ 4 and ± 30 minutes for sample timepoints > 5 hours. Subjects will check into the clinic on the morning of each PK sampling day and will be required to stay until the final sample is obtained and either tazemetostat and/or fluconazole have been dispensed.
o. **Archival tumor tissue** (block or slides) is requested for molecular characterization, e.g., detection of somatic mutations and/or candidate biomarkers of response.

p. **Optional tumor tissue biopsies** may be obtained prior to and after initiation of treatment with tazemetostat. An optional lymph node, core-needle biopsy, or bone marrow biopsy will be performed during the screening period and on Day 1 of Cycle 2,+ or - 14 days (must be done between Day 14 of Cycle 1 and Day 14 of Cycle 2).

q. **Disease (Tumor) Assessment:** Tumor assessments by disease-appropriate standard criteria (Lugano Classification [Cheson 2014, Appendix 1] for lymphoma or RECIST v1.1 [Appendix 2] for solid tumors) using PET (lymphoma only), CT, MRI of known sites of disease as clinically indicated. Assessments should be completed within 28 days of Study Day 1 and at the end of Cycle 2 (8 weeks), Cycle 4 (16 weeks), and Cycle 6 (24 weeks) (± 7 days).

r. **Tazemetostat Administration:** On the morning of Day 19, tazemetostat and fluconazole will be taken together and no more than 5 minutes apart. The tazemetostat dose will be increased to 800 mg BID administered continuously in 28-day cycles starting on Day 25, following sufficient wash-out of fluconazole. An adequate supply of tazemetostat should be dispensed to subjects to take at home until the next scheduled clinic day.

s. **OS** is to be assessed every 3 months following the end-of-treatment visit for up to 2 years (may be completed via phone, mail, email, or clinic visit). All anti-cancer therapies will be collected.

t. An optional chest ultrasound may be performed every 8 weeks at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL.

Table 2: Schedule of Assessments and Procedures: Part B

Visit Description / Study Weeks	**Screening[a,b]**	**Cycle 1[c]**						**Cycle 2, Day 1**	**Cycles 2 – 6[c]**	**End-of-Study[d]**
Study Days	-28 to -1	1	2 -15	16	17 & 18	19	20 - 28		1	
Procedures/Assessments										
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographics[e]	X									
Medical History/Current Medical Conditions[f]	X									X
Prior and concomitant medications		Throughout the study								
Complete PE	X								X	X
Symptom-directed PE		X		X		X				
Weight	X								X	X
Height	X									
Vital signs[g]	X	X		X		X			X	X
ECOG performance status	X	X		X		X			X	X
12-lead ECGs[h]	X			X		X			X	X
Safety Laboratory tests[i]	X			X		X			X	X
Coagulation profile[j]	X	If clinically indicated								X
Pregnancy testing[k]	X								X	X
PGx blood sample[l]		X								
PK blood samples[m,d]		X		X		X				X
Archival tumor tissue[n]	X									
Optional tumor tissue biopsy[o]	X							X		
Optional chest ultrasound[t]	X								X	X
Tumor assessments: PET, CT, bone marrow, or other[p,d]	X								X	
AEs/SAEs		Throughout the study								
Tazemetostat 800 mg BID[r]			X	X	X	X	X		X	
Repaglinide 0.25 mg		X[q]		X[q]						
Omeprazole 20 mg		X[q]		X[q]	X	X				

Visit Description / Study Weeks	Screening[a,b]	Cycle 1[c]						Cycle 2, Day 1	Cycles 2 – 6[c]	End-of-Study[d]
Study Days	-28 to -1	1	2 -15	16	17 & 18	19	20 - 28		1	
Procedures/Assessments										
Survival status and subsequent anti-cancer therapy[s]										X

Abbreviations: AE = adverse event; BID = twice daily; CT = computed tomography; ECG = electrocardiograms; ECOG = Eastern Cooperative Oncology Group; h = hour; PGx = pharmacogenomics; PE = physical examination; PET = positron emission tomography; PK = pharmacokinetic; SAE = serious adverse event

a. **Screening:** Screening Period extends from Day -28 to Day -1.
b. **Pre-Study procedures** and tumor assessment must be performed within 28 days before first dose of study treatment.
c. Each cycle is 28 days in length
d. **End of Study:** An End-of-Study visit will be conducted within 30 days (±3 days) after last dose of IP, prior to enrollment in Study EZH-501, or prior to the start of a new treatment or therapy, whichever occurs first. The post-treatment assessments will be required and, in the event of a continuing AE, the subject will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely. End of study assessments will be conducted including safety, PK and response. A 3 mL blood sample will be required for end of study PK assessments.
e. **Demographics:** Date of birth, gender, ethnicity, and race must be recorded.
f. **Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions, full history of the course of the subject's malignancy including primary diagnosis. Stage and date, and information on prior antitumor therapies including response to prior therapies must be recorded at Screening.
g. **Vital Signs:** Blood pressure (BP), heart rate (HR), and temperature (T) must be measured after the subject has been sitting for 5 minutes at screening and at regular intervals during treatment.
h. **ECG:** 12-lead ECG reading must be performed at Screening and Days 16 and 19, Day 1 of Cycles 2 – 6, and End of Study. A single ECG will be recorded unless there is an abnormality. If an abnormality is detected then ECGs will be recorded in triplicate at least 2 minutes apart.
i. **Safety Laboratory Tests:** Hematology includes complete blood count with differential and absolute neutrophil count (differential values should be recorded as absolute counts whenever possible) and assessment of peripheral blood smear morphology. If peripheral blood smear morphology is abnormal, then conduct bone marrow aspirate with cytogenic testing to closely monitor patients with cytogenic abnormalities known to be associated with MDS (9del 5q, chr 7, abn, etc.) and MPN (e.g. JAK2 V617F, etc.) observed with cytogenetic testing and DNA sequencing. Chemistries include: alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, and total bilirubin, electrolytes, Blood urea/blood urea nitrogen, creatinine, albumin, calcium, magnesium, glucose, phosphorus, triglycerides, and total protein.
j. **Coagulation Profile:** Coagulations tests include: prothrombin time (PT), partial thromboplastin time (PTT).
k. **Pregnancy Testing:** The screening test can be either urine or serum and must have been completed within 28 days of the first dose of study drug. Subsequent testing on the first day of each cycle (Cycles 2 – 6) and at the End-of-Study visit can be either urine or serum. Any positive urine pregnancy test must be confirmed with a serum test.
l. **PGx:** A single 10 mL whole blood will be collected at any time during the screening period.

m. **PK: Day 1:** Blood samples (2 mL) for analysis of plasma repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone will be collected at the following time points on Day 1: predose (within 90 minutes prior to dose) and 0.25, 0.5, 1, 2, 3, 5, and 7 hours postdose. **Day 16:** Blood samples (1 mL) for analysis of plasma tazemetostat and metabolites will be collected predose (within 30 minutes prior to dose) and 0.5, and 1 h after administration of tazemetostat. Blood samples (2 mL) for analysis of repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone will be collected predose (within 30 minutes prior to tazemetostat) and 1.25 and 1.5 h after tazemetostat administration (0.25 and 0.5 h after repaglinide and omeprazole administration). Blood samples (3 mL) for analysis of tazemetostat and its metabolites, repaglinide and its metabolite, omeprazole, 5-OH-omeprazole, and omeprazole sulfone will be collected 2, 3, 4, 6, and 8 hours after tazemetostat administration (1, 2, 3, 5, and 7 hours after repaglinide and omeprazole administration). **Day 19:** Blood samples (1 mL) for analysis of tazemetostat and its metabolites will be collected predose (within 30 minutes prior to dose) and 0.5, 1, 2, 3, 4, 6, and 8 hour postdose. All PK blood samples may be drawn from either a central venous catheter or a peripherally placed intravenous catheter. Allowable windows for collection of PK blood samples are ± 5 minutes for sample timepoints ≥ 0.25 and ≤ 4 and ± 30 minutes for sample timepoints > 5 hours.

n. **Archival tumor tissue** (block or slides) is requested for molecular characterization, e.g., detection of somatic mutations and/or candidate biomarkers of response.

o. **Optional tumor tissue biopsies** may be obtained before and after initiation of treatment with tazemetostat. An optional lymph node, core-needle biopsy, or bone marrow biopsy will be performed during the screening period and on Day 1 of Cycle 2, + or – 14 days (must be done between Day 14 of Cycle 1 and Day 14 of Cycle 2).

p. **Disease (Tumor) Assessment:** Tumor assessments by disease-appropriate standard criteria (Lugano Classification [Cheson 2014, Appendix 1] for lymphoma or RECIST v1.1 (Appendix 2) for solid tumors) using PET (lymphoma only), CT, MRI of known sites of disease as clinically indicated. Assessments should be completed within 28 days of study Day 1 and at the end of Cycle 2 (8 weeks), Cycle 4 (16 weeks), and Cycle 6 (24 weeks) (± 7 days).

q. **Repaglinide and omeprazole administration:** repaglinide and omeprazole will be taken together, no more than 5 minutes apart.

r. **Tazemetostat**: An adequate supply of tazemetostat should be dispensed to the subject to take at home until the next scheduled clinic day.

s. **OS** is to be assessed every 3 months following the End-of-Treatment visit for up to 2 years (may be completed via phone, mail, email, or clinic visit). All anti-cancer therapies will be collected.

t. An optional chest ultrasound may be performed every 8 weeks at the investigator's discretion to monitor for early signs of T-LBL/T-ALL.

Table 3: Timing Allowance Windows for Vital Sign and ECG Measurements

Vital Signs	
Timepoint	**Tolerance Window**
0 hour	-60 min to 0 hour

Pharmacokinetic Sampling	
Timepoint	**Tolerance Window**
0 hour	-90, 60, or 30 min to 0 hour (depending on Part A or Part B and day of sampling)
>0 hour – 4 hour	-5 minutes/+ 5 minutes
5 hour – 8 hour	-30 minutes/+ 30 minutes

ECG	
Timepoint	**Tolerance Window**
0 hour	-60 min to 0 hour

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
ASCT	autologous hematopoietic stem cell transplantation
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the concentration-time curve
AUC_{0-8}	Area under the concentration-time curve from time 0 to 8 hours after administration
AUC_{0-12}	Area under the concentration-time curve from time 0 to 12 hours after administration
AUC0-t	Area under the concentration-time curve from time 0 to the last quantifiable concentration
AUC0-∞	Area under the concentration-time curve from time 0 extrapolated to infinity
BAP1	BRCA1 associated protein 1
BID	Twice daily
BM	Bone marrow
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
CYP	Cytochrome
DCR	Disease control rate
DDI	Drug-drug interaction
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Glomerular filtration rate
E_{max}	Maximum effect
EPZ-6438, E7438	Tazemetostat
EPZ-6930, ER-897387	Desethyl metabolite of tazemetostat
EU CT Dir	European Union Clinical Trial Directive
EZH-2	Enhancer of zeste homolog
FDA	Food and Drug Administration
FL	Follicular lymphoma
GCP	Good Clinical Practice
H3K27	Lysine 27 of histone H3
H3K27me3	H3K27 trimethylation
HATs	Histone acetyl transferases
HbA_{1c}	Hemoglobin A_{1c}
H2AK119	Histone H2A lysine 119

Abbreviation	Definition
HMT	Histone methyl transferases
hr	Hour
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INI1	Integrase interactor 1
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
LNH	Low, normal, high
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome
MLL2	Mixed lineage leukemia protein 2
MPN	Myeloproliferative disorder
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic or progressive disease
PE	Physical exam
PET	Positron emission tomography
PgP	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetics
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
PRC2	Polycomb repressive complex 2
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
QTc	Corrected QT interval
R-CHOP	Rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisolone or prednisone
R-DHAP	Rituximab, dexamethasone, cytarabine, cisplatin
RECIST	Response Evaluation Criteria in Solid Tumors
R-ICE	Rituximab, ifosfamide, carboplatin, etoposide
RP2D	Recommended Phase II dose
RNA	Ribonucleic acid
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCID	Severe combined immunodeficiency
SD	Stable disease
SI	International System of Units
SOC	System Organ Class

Abbreviation	Definition
STD	Standard deviation
$t_{1/2}$	Apparent elimination half-life
TEAE	Treatment-emergent adverse event
T-LBL/T-ALL	T-cell lymphoblastic leukemia/ T-cell acute lymphoblastic leukemia
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
US	United States
UTX	Ubiquitously transcribed tetratricopeptide repeat, X chromosome
UV	Ultraviolet
WBC	White blood cell
WHO	World Health Organization

2. BACKGROUND AND RATIONALE

This document is a protocol for a human research study. This study is to be conducted according to United States (US) and international standards of Good Clinical Practice (GCP; Food and Drug Administration [FDA] Title 21 Part 312 and International Conference on Harmonization [ICH] guidelines), applicable government regulations, and institutional research policies and procedures.

2.1. Background

Post-translational modifications of histones, the core proteins of chromatin, play an important role in controlling the fidelity of cellular gene transcription patterns. One of the critical transcription-controlling histone modifications is methylation of specific lysine and arginine residues, catalyzed by histone methyl transferases (HMTs) which all use S-adenosyl methionine (SAM) as a co-factor for the methylation reaction [Copeland, 2013]. Genetic alterations in a number of HMTs or associated regulatory proteins have been identified in several human cancers where they are purported to be oncogenic. Enhancer of Zeste homolog 2 (EZH2) is the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono-, di-, and trimethylation of lysine 27 of histone H3 (H3K27) [Margueron, 2011]. EZH2 mutation and/or over-expression has been observed in several cancer types, leading to an aberrant H3K27 trimethylation (H3K27me3) state which is oncogenic [Chase, 2011]. For instance, somatic gain of function mutations within EZH2, found within subsets of non-Hodgkin lymphoma (NHL), result in an oncogenic dependency on EZH2 production of abnormally high H3K27me3 levels, and resultant transcriptional reprogramming of the cell. [Morin 2010]

2.2. Lymphoma

Somatic mutations within the EZH2 gene on 3 hotspots (Y646. A682, and A692 [NM_001203247]) are present in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) and lead to high levels of H3K27 trimethylation (H3K27me3) in these lymphomas. Those mutations of EZH2, therefore, have been proposed to be required for the development and maintenance of the mutation-bearing lymphomas. Inhibition of EZH2 leads to reduction in H3K27me3 and cell death in lymphoma cell lines bearing the mutation. In addition, loss of function of mixed lineage leukemia protein 2 (MLL2) and histone acetyl transferases (HATs) may generate abnormal methylation states of H3K27, potentially leading to a dependency on EZH2. In nonclinical models, inhibition of EZH2 leads to reduction in H3K27me3 in all lymphoma cell lines irrespective of their EZH2 mutation status. While cells with wild-type

EZH2 are growth inhibited with EZH2 inhibition in vitro, only mutant bearing cells undergo cell death in culture [Béguelin 2013; Knutson 2014].

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], and EZH2 inhibition may induce similar effects. In addition, loss of EZH2 has been described as affecting T helper cell plasticity [Tumes 2013] and is proposed to inhibit the function of regulatory T cells [Arvey 2014; DuPage 2015; Yang 2015], suggesting that EZH2 inhibition may contribute to enhancing antitumor immunity.

In summary, the available nonclinical data suggest that EZH2 mutant lymphomas should show the highest sensitivity to EZH2 inhibition, but wild-type cases could also be affected through tumor cell autonomous mechanisms (mutations in MLL2, HATs, ubiquitously transcribed tetratricopeptide repeat, X chromosome [UTX], etc.) and/or effects of EZH2 inhibitors on the tumor microenvironment.

2.3. Solid Tumors

In addition to the EZH2 gain of function activation mutations described above, overexpression or amplification of EZH2 has been described in numerous tumor types, including not but limited to bladder, breast cancer, colorectal, lung, pancreatic, ovarian, prostate, mesothelioma, uveal melanoma, renal carcinoma, cholangiocarcinoma and stomach cancer [LaFave 2015, Comet 2016, Kuroki 2014]. This is partially explained by the regulation of EZH2 gene expression by the pRB-E2F pathway, which is dysregulated in many tumor types [Bracken 2003]. In many of these tumors, EZH2 has been demonstrated to function as an oncogene [Comet 2016]. For instance, EZH2 overexpression promotes anchorage-independent growth and cell invasion in breast cancer [Kleer 2003], proliferation and epithelial-mesenchymal transition in lung cancer [Takawa 2011, Tiwari 2013], and tumorigenesis and metastasis in prostate cancer [Min 2010]. These data suggest that inhibition of EZH2 might also be beneficial in solid tumors that overexpress EZH2 or contain amplifications of the EZH2 gene.

Genetic changes in other proteins in addition to genetic alterations in EZH2 itself, can lead to an oncogenic dependency on EZH2 activity, specifically those affecting proteins of the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex. At many gene loci, polycomb repressive complex (PRC2) and SWI/SNF antagonize each other and loss of the

SWI/SNF component, integrase interactor 1 (INI1), has been demonstrated to generate over-activation of the PRC2 pathway and tumor cell proliferation [Wilson, 2010]. Genetic loss of INI1 has been described in many human malignancies, e.g., rhabdoid tumors, epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumor, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma, and renal medullary carcinoma [Margol, 2014]. Inhibition of EZH2 activity by either knock-down or small molecule inhibition induces tumor cell killing and durable tumor regressions in pre-clinical models of rhabdoid tumors [Alimova 2013; Knutson 2013]. Genetic alterations in synovial sarcomas can create a state of INI1 deficiency and result in aberrant SWI/SNF complex chromatin remodeling activity at various genes [Kadoch, 2013], sensitizing these tumors to EZH2 inhibition [Kawano, 2016]. Loss of SMARCA2 and SMARCA4 protein, the redundant catalytic subunits of the SWI/SNF chromatin remodeling complex, have been described in small cell carcinoma of the ovary, hypercalcemic type [Jellinic 2014; Ramos 2014; Witkowski 2014], and inhibition of EZH2 activity in in vivo preclinical models by a small molecule inhibitor results in dose dependent tumor growth inhibition and regressions [Penebre 2017]. It has additionally been postulated that additional tumor types with loss or mutation of SWI/SNF subunits, such as ovarian cancer with loss of ARID1A, would also be sensitive to EZH2 inhibition [Bitler 2015; Kim 2015]. Given that approximately 20% of tumors contain a mutation in one or more subunit of the SWI/SNF complex, this suggests that EZH2 inhibition might have therapeutic value in a diverse number of solid tumor types [Kadoch 2016].

Finally, genetic and/or protein loss of chromatin remodelers other than SWI/SNF have been associated with sensitivity to EZH2 inhibition. For instance, BRACA1 associated protein 1 (BAP1) can also lead to an oncogenic dependency on EZH2 activity [LaFave 2015]. This is clinically relevant as genetic and/or protein loss of BAP1 has also been described in multiple human malignancies including mesothelioma, uveal melanoma, renal carcinoma, and cholangiocarcinoma [Testa 2011; Harbour 2010; Pena-Llopis 2012; Jiao 2013].

2.4. Tazemetostat

2.4.1 Preclinical Pharmacology

Tazemetostat (EPZ-6438) is a selective oral small molecule inhibitor of EZH2. Tazemetostat inhibits both wild-type EZH2 and mutant bearingEZH2 residues with Y641, A667G and A687 with half maximal inhibitory concentrations (IC50) ranging from 2-38 nmol/L. The compound shows a 35-fold selectivity over the most closely related HMT, EZH1, and greater than a 4500-fold selectively over other HMTs. It selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective cell killing of cell lines.

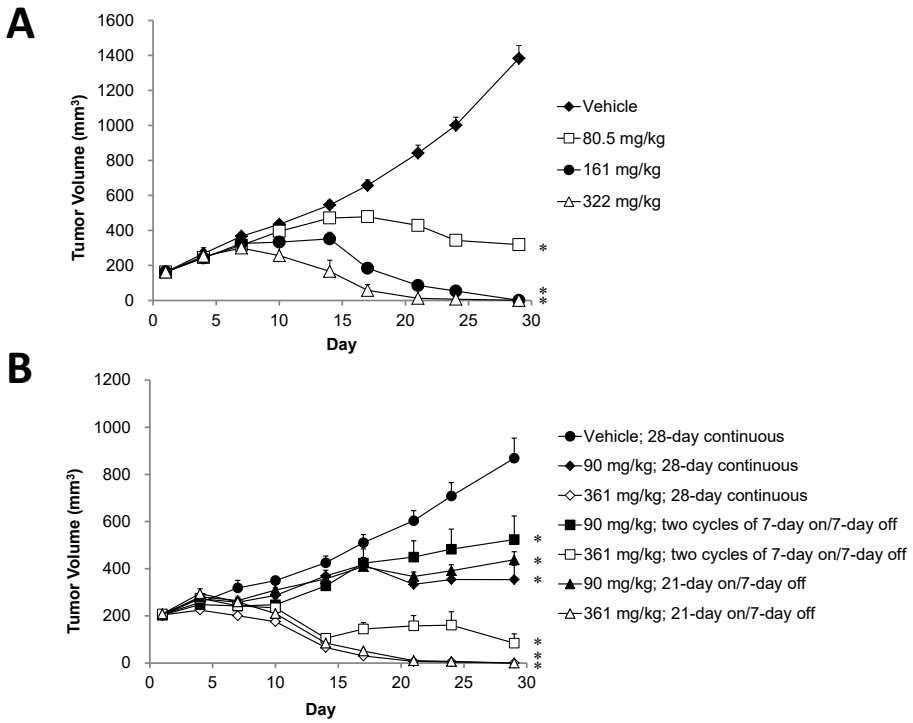
Tazemetostat specifically inhibits human lymphoma cell lines bearing EZH2 point mutations and integrase interactor 1 (INI1) unit deficient (also known as SNF5, SMARCB1, or BAFT47) MRT cell lines with IC50 in the nanomolar range. Additionally, tazemetostat administered orally has demonstrated antitumor activity in vivo against several EZH2 mutant human lymphoma xenograft murine models [Knutson, 2014].

2.4.2 Lymphomas

Antitumor effects of oral tazemetostat dosing were evaluated in 3 *EZH2* mutant DLBCL xenograft models; WSU-DLCL2 *EZH2* Y646F, KARPAS-422 *EZH2* Y646N, and Pfeiffer *EZH2* A682G. In severe combined immunodeficiency (SCID) mice bearing WSU-DLCL2 *EZH2* Y646F mutant xenograft tumors, tazemetostat induced dose-dependent tumor growth inhibition, showing a maximum of 58% at the highest dose of 160 mg/kg 3 times daily. A dose-dependent increase in plasma and tumor tissue exposure was observed. ELISA analysis of histones from tumors collected on Day 28 indicated dose-dependent reduction in H3K27Me3 levels.

In KARPAS-422 *EZH2* Y646N mutant xenografts, 28-day dosing of tazemetostat on a twice daily (BID) schedule induced tumor growth inhibition at doses as low as 80.5 mg/kg BID, but all higher doses induced complete xenograft tumor regression (Figure 1A). When investigating intermittent dosing schedules in this model, tazemetostat showed significant dose-dependent antitumor effects with 2 cycles of 7-day on/7-day off and 21 day on/7 day off schedules (Figure 1B). For all dosing schedules, tumor growth inhibition and complete regressions were observed at 90 and 361 mg/kg BID, respectively. In a parallel study, the inhibition of H3K27Me3 by tazemetostat was evaluated in KARPAS-422 human DLBCL xenografts in athymic mice. Tazemetostat induced a dose-dependent reduction of tumor H3K27Me3 levels with both regimens (Figure 2).

Figure 1 Antitumor Effects of Tazemetostat in KARPAS 422 Human DLBCL Xenograft Model in Athymic Mice

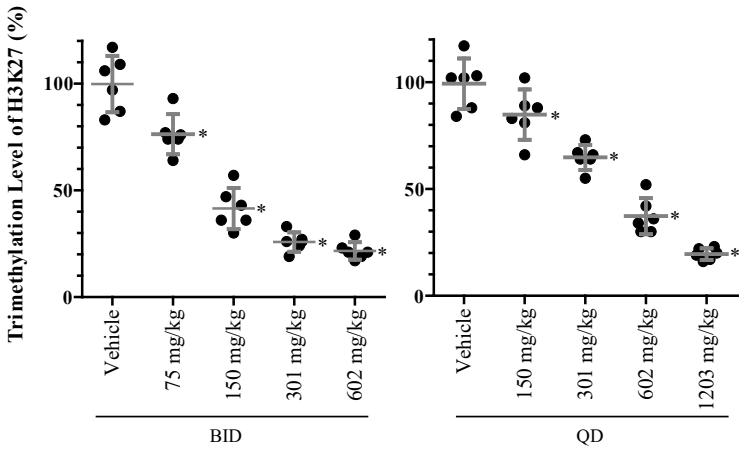


Abbreviations: DLBCL = diffuse large B-cell lymphoma, STD = standard deviation.

A: Change of tumor volume from mice dosed BID at the indicated doses of tazemetostat. Data represent the mean ± STD (n = 9). A dosage of 644 mg/kg was not plotted because it exceeded the maximum tolerated dose in the study. * $P < 0.05$ versus vehicle control on Day 29 (repeated measures analysis of variance followed by Dunnett's multiple comparison test). Source: Study M11024.

B: Change of tumor volume at 3 different dosing schedules of tazemetostat administered BID. Data represent the mean ± STD (n = 8 – 9). * $P < 0.05$ versus vehicle 28-day continuous dosing group on Day 29 (repeated measures analysis of variance followed by Dunnett's multiple comparison test). Source: Study M12002.

Figure 2 H3K27Me3 Inhibition in KARPAS-422 Human DLBCL Xenografts in Athymic Mice Administered Tazemetostat EPZ-6438 for 7 Days



Source: Study W-20120483.

Abbreviations: BID = twice daily, DLBCL = diffuse large B-cell lymphoma, H3K27 = lysine 27 of histone H3, H3K27Me3 = trimethylated form of H3K27, STD = standard deviation, QD = once daily.

Note: Each bar represents a mean ± STD (n = 6) of H3K27Me3 level in each group.

* $P < 0.05$ versus vehicle control (one-way analysis of variance followed by the Dunnett's multiple comparison test).

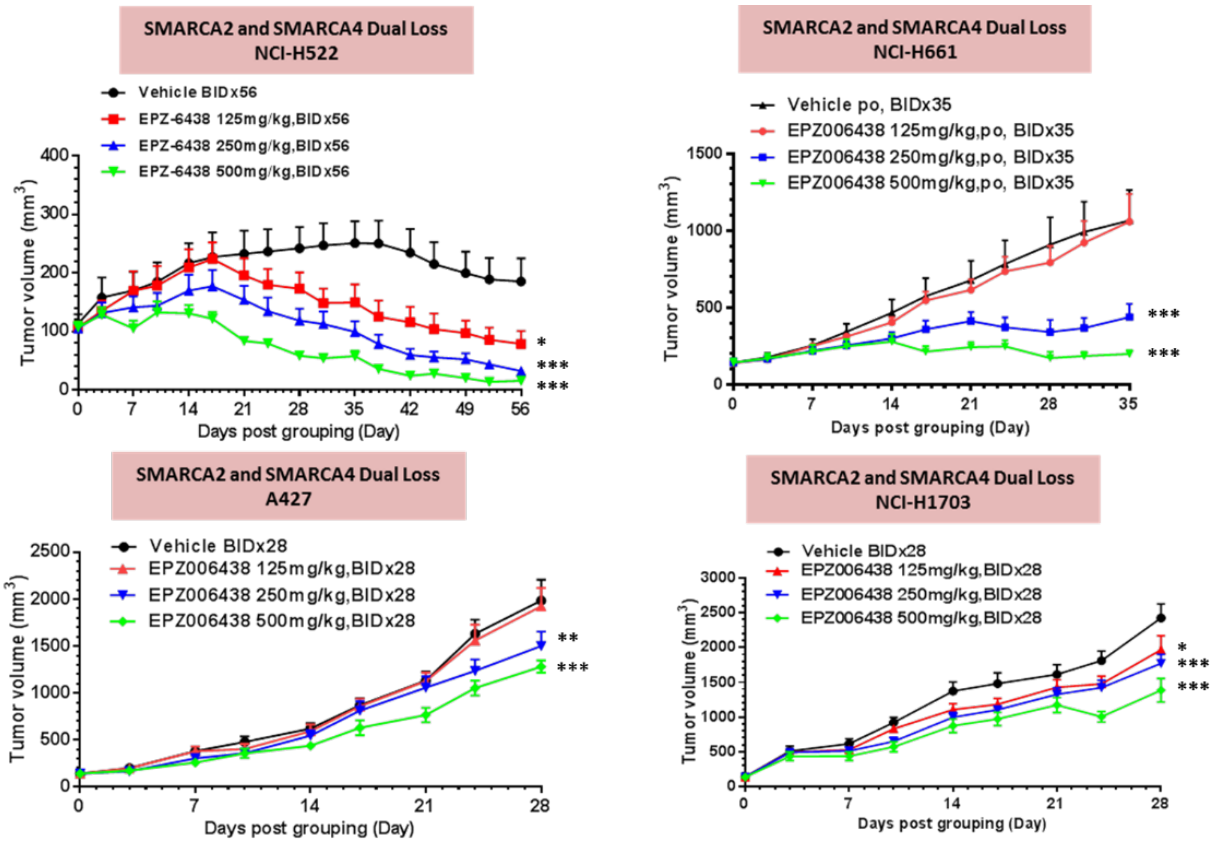
The Pfeiffer *EZH2* A682G mutant xenograft model was the most sensitive DLBCL tumor model. Complete tumor regressions were observed in all animals in the 114 mg/kg tazemetostat once daily and 342 mg/kg once daily dose groups. Tumor regrowth was not observed up to the end of the study (36 days after stopping tazemetostat administration).

2.4.3 Solid Tumors

Oral administration of tazemetostat in 4 NSCLC cell line xenografts with dual *SMARCA2/A4* loss demonstrated inhibition of tumor growth or tumor regressions. As shown in Figure 3, tumor regression was observed in the NCI H522 and NCI-H661 NSCLC xenograft models at ≥ 125 mg/kg and ≥ 250 mg/kg, respectively. Significant tumor growth inhibition but not tumor regressions was seen in the A427 and NCI-H1703 NSCLC xenografts at ≥ 250 mg/kg. In addition, antitumor activity was observed in xenograft models of INI-1 deficient tumors. The most robust antitumor activity was demonstrated in the G401 INI1-negative human malignant rhabdoid tumor (MRT) xenograft model following oral dosing with tazemetostat. Figure 4A and B shows significant and dose-dependent antitumor effects with tumor stasis and growth delay at 143 mg/kg and tumor regression at 285 mg/kg and 571 mg/kg with no regrowth at study end. A dose-dependent increase in plasma and tumor tazemetostat concentration and strong inhibition of H3K27Me3, which correlated with antitumor activity, are demonstrated in Figure 4C and D,

respectively. Changes in expression of INI1-regulated genes are shown in Figure 4E (Study E7438-PD001).

Figure 3: Antitumor Effect of Tazemetostat Against 4 Human NSCLC Xenografts Models with SMARCA2/SMARCA4 Loss

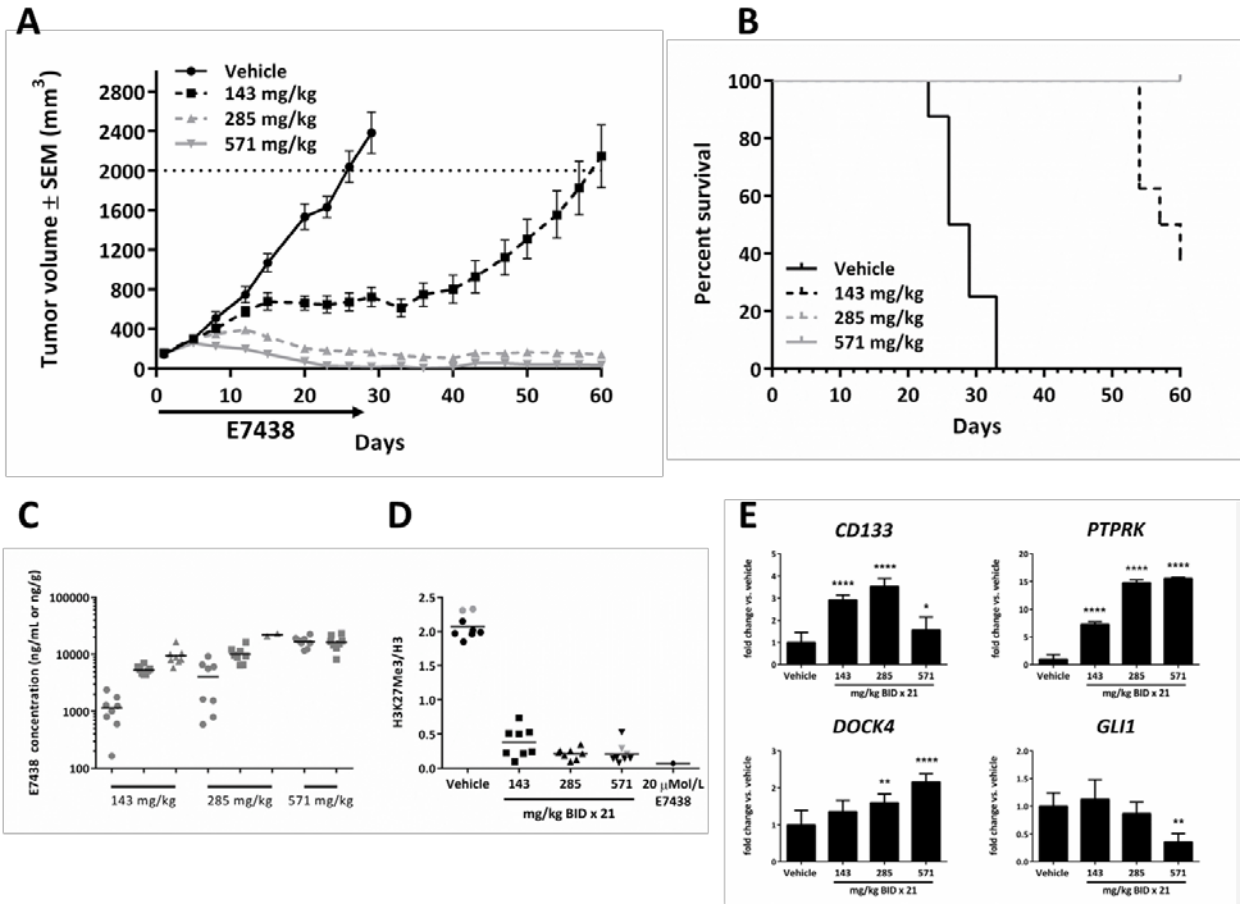


Source: Chan-Penebre *et al.*, AACR 2017.

Abbreviations: BID= twice daily, EPZ006438= tazemetostat, SMARCA2= SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, PO= by mouth.

Tumor volume (in mm^3) in mice dosed BID with vehicle or tazemetostat (noted as EPZ-6438). SMARCA2/A4-negative NSCLC cell lines were implanted in Nude (NCI-H522), NOD-SCID (NCI-H661 and NCI-H1703) or SCID (A427) mice and dosed with 125, 250, and 500 mg/kg tazemetostat. Data are displayed as mean ± SEM (n=10 per group). Statistics were calculated for the last data point with two-way ANOVA followed by Bonferroni post-test; * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

Figure 4 Antitumor Effect of Tazemetostat (E7438) Against the G401 Human MRT Xenograft Model in SCID Mice



Abbreviations: BID = twice daily, ELISA = enzyme-linked immunosorbent assay, H3 = histone H3, H3K27Me3 = trimethylated form of histone H3 lysine 27, MRT = malignant rhabdoid tumor, SCID = severe combined immunodeficiency, SEM = standard error of the mean.

A: Change of tumor volume from mice dosed BID at the indicated doses for 28 days. Each point represents the mean ± SEM (n = 7 – 8, tumor growth delay cohort). * $P < 0.05$, ** $P < 0.01$ versus vehicle control on Day 21 (repeated measures analysis of variance and Dunnett's posttest versus vehicle).

B: Kaplan-Meier survival curve for the mice in the tumor growth delay cohort (n = 7 – 8). The tumor volume endpoint was 2000 mm^3.

C: Tazemetostat concentration in plasma (closed circle: 5 minutes before dosing, closed square: 3 hours after dosing) or tumor (closed triangle) in mice on Day 21. Symbols represent values for the individual animals; horizontal lines represent group mean values.

D: H3K27Me3/total H3 ratio in tumors on Day 21. Symbols represent values for the individual animals; horizontal lines represent group mean values. Symbols represented in gray are values that fell outside of the ELISA standard curve.

E: Changes in gene expression in tumors on Day 21. Data are presented as fold change compared with vehicle ± SEM (n = 6, except for 571 mg/kg group [n = 4]). * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$, versus vehicle (2-tailed t test).

2.4.4 In Vitro Aqueous Solubility

The solubility of tazemetostat was investigated in buffer systems of pH 1.0, 2.0, 3.0, 4.0, 5.5, and 6.8. Mean solubility of tazemetostat was approximately 7 mg/mL at pH values of 1.0 to 4.0. However, mean aqueous solubility of tazemetostat decreased to 0.508 mg/mL and 0.0333 mg/mL at pH 5.5 and pH 6.8, respectively. The pH values at which the aqueous solubility changes are similar to the pKa values for tazemetostat of 5.3 and 6.9.

2.4.5 Nonclinical Pharmacokinetics

Sixteen metabolites of tazemetostat were identified from incubations of liver microsomes and hepatocytes from mouse, rat, dog, monkey, and human. The major metabolites in liver microsomal incubations were the result of N-deethylation (M5, EPZ-6930), oxidation of the pyridone (M7), and dual oxidation (M12). The major metabolites in hepatocyte incubations were the results of oxidation and dehydrogenation (M11), and N-dealkylation of the pyridone (M13). EPZ-6930 appeared to be the major metabolite formed in liver microsomes and hepatocytes from monkey and human. There was no metabolite observed that was considered to be unique to humans.

Results from in vitro studies with human liver microsomes suggested that CYP3A, CYP2C8, and CYP2D6 were involved in the metabolism of tazemetostat. In experiments using recombinant human CYPs (Supersomes^{TM}), CYP3A4 was the only isoform which caused detectable turnover of tazemetostat. Taken together, these results suggest that CYP3A4 is the predominant enzyme involved in tazemetostat metabolism with potentially lesser contributions from CYP2C8 and CYP2D6.

Tazemetostat inhibited CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (testosterone 6β-hydroxylation) activities in vitro with Ki values of 1.3, 15.0, 6.7, 9.2, and 3.1 μmol/L, respectively. The IC_{50} values for tazemetostat inhibition of CYP3A-mediated midazolam 1' hydroxylation and nifedipine dehydrogenation in vitro were 12.7 and 19.4 μmol/L, respectively. Tazemetostat demonstrated time-dependent inhibition of CYP3A with a half-maximum inactivation of 6.4 μmol/L and maximum rate constant of inactivation of 0.077 min^{-1}. Tazemetostat induced CYP3A4 in human hepatocytes in vitro with concentration that achieved 50% of the maximal effect values of 2.18 to 2.96 μmol/L, and maximum effect values of 15.62- to 103.5-fold increase in mRNA. Tazemetostat may induce other CYP isoforms, such as CYP1A, CYP2B6, and CYP2C9, but the effect is expected to be much weaker than that observed for induction of CYP3A4.

A physiologically-based pharmacokinetic (PBPK) model was developed based on in vitro and in vivo data to simulate the effect of tazemetostat on CYP probe substrates. The model was used to predict the magnitude of interaction of tazemetostat with probe substrates for CYP2C8 (repaglinide and rosiglitazone), CYP2C9 (S-warfarin), and CYP2C19 (omeprazole and S-mephenytoin) based upon the in vitro Ki and protein binding values. Simulations also were conducted to predict the magnitude of interaction of tazemetostat given a worst-case scenario with Ki values 10-fold lower than the observed in vitro values and a fraction unbound of 0.2. Results of the analysis indicated that interactions between tazemetostat and substrates for CYP2C8, CYP2C9, and CYP2C19 likely will be negligible based on observed in vitro estimates of K_i for tazemetostat. However, the worst-case scenario for tazemetostat is to cause a 1.30- to 1.55-fold and 1.39- to 2.40-fold increase in the exposure of CYP2C8 and CYP2C19 substrates, respectively, at tazemetostat doses ranging from 400 to 1600 mg BID.

2.4.6 Clinical Pharmacokinetics

The PK of tazemetostat and the desethyl metabolite, EPZ-6930, have been characterized following single (Day 1) and multiple (Day 15) dose administration to subjects with advanced solid tumors or B-cell lymphoma (n=36). Doses administered were 100 mg BID as a suspension (n=3) or tablet (n=3) formulation and 200, 400, 800, and 1600 mg BID as a tablet formulation. Tazemetostat was absorbed rapidly with a time to the maximum plasma concentration (T_{max}) of approximately 1-2 hours postdose. Plasma concentrations declined in a mono-exponential manner with a mean $t_{1/2}$ of approximately 3-5 hours, and quantifiable plasma concentrations of both tazemetostat and its metabolite, EPZ-6930, were observed up to 12 hours postdose. The tazemetostat maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased in a greater than dose-proportional fashion after a single dose and in an approximately a dose-proportional fashion at steady-state.

After multiple dosing, there was a dose-dependent decrease in tazemetostat exposure between Days 1 and 15. Accumulation ratios ($R_{ac} = AUC_{D15}/AUC_{D1}$) evaluated at Day 15 of dosing were 0.89 at 100 mg BID (suspension) and 0.48 at 1600 mg BID. The R_{ac} at the RP2D of 800 mg BID was 0.58. Further reduction in systemic exposure at steady-state was not observed beyond Day 15 as evidenced by predose C_{trough} (observed concentration at the end of a dosing interval, immediately before the next administration) levels from Days 15 to 29. There was negligible change in T_{max} or $t_{1/2}$ on multiple dosing across the dose range.

The T_{max} for the tazemetostat metabolite EPZ-6930 was observed at 1 to 2 hours after tazemetostat administration and its elimination paralleled that of tazemetostat ($t_{1/2}$ = 3 – 5 hours).

In contrast to the parent compound, C_{max} and AUC of the metabolite increased after multiple dosing. Metabolite-to-parent AUC ratios (EPZ-6930 relative to tazemetostat) ranged from approximately 0.57 to 1.3 on Day 1 and from 1.1 to 2.1 on Day 15. EPZ-6930 T_{max} was observed at 1-2 hours postdose and its elimination paralleled that of tazemetostat ($t_{½}$ =3-5 hours). The time-dependency in kinetics of both parent and the desethyl metabolite are consistent with induction of CYP3A-mediated metabolism by tazemetostat.

The effect of food on the PK of tazemetostat was investigated as part of Study E7438-G000-101. Subjects with advanced solid tumors or B-cell lymphomas received 200 mg tazemetostat in either the fasted state or immediately after consuming a high-fat breakfast in a randomized, crossover fashion. Serial blood samples for the analysis of plasma tazemetostat concentrations were collected over 24 hours after dosing. A summary of the preliminary PK parameters from the food effect portion of Study E7438-G000-101 is displayed in Table 4.

Table 4: Summary of Tazemetostat Pharmacokinetic Parameters After Administration Fasted or Immediately After a High-Fat Breakfast in Study E7438-G000-101 (n=12)

Meal State	C_{max} ng/mL	AUC_{0-t} ng•h/mL	$AUC_{0-\infty}$ ng•h/mL	T_{max}[a] h	$t_{1/2}$ h
Fed	170 (232) (5.62 – 752)	755 (207) (25 – 2890)	803 (191) (32 – 3100)	4.0 (1.0 – 6.0)	4.24 (28.1) (2.63 – 6.22)
Fasted	276 (151) (50.4 – 1470)	944 (155) (167 – 5990)	1140 (135) (179 – 6250)	1.0 (0.6 – 6.0)	41.0 (37.2) (1.80 – 7.18)

[a] Data are presented as geometric mean [(%CV) (range)]
[b] T_{max} presented as median (range)

The fed: fasted geometric mean ratios and 90% confidence intervals (CI) for log-transformed C_{max} and $AUC_{0-\infty}$ were determined with a linear mixed-effects model. Results are displayed in Table 5.

Table 5: Fed: Fasted Geometric Mean Ratio and 90% Confidence Interval for Tazemetostat C_{max} and $AUC_{0-\infty}$ in Study E7438-G000-101

Parameter	Fed: Fasted Ratio	90% CI
C_{max} (ng/mL)	0.62	0.41, 0.93
$AUC_{0-\infty}$ (ng•h/mL)	0.82	0.56, 1.90

Abbreviations: AUC= area under concentration-time curve, C_{max}= Maximum plasma concentration, CI= Confidence interval.

Administration of tazemetostat with a high-fat meal decreased geometric mean $AUC_{0-\infty}$ and C_{max} values approximately 18% and 38%, respectively, relative to administration in the fasted state. However, the 90% CI for the fed: fasted geometric mean ratio for both C_{max} and $AUC_{0-\infty}$ contained 1. Administration of tazemetostat with a high-fat meal also resulted in a 4-fold increase in median T_{max} relative to administration in the fasted state. Geometric mean $t_{1/2}$ values were nearly identical after administration in the fed and fasted state (4.24 h and 4.10 h, respectively). These results indicate that administration of tazemetostat with a high-fat breakfast results in slower absorption into the systemic circulation with no effect on the systemic disposition or overall exposure to tazemetostat as measured by AUC. The decrease in systemic exposure is not clinically significant, and therefore tazemetostat can be taken without regards to meals.

The effect of tazemetostat on the PK of midazolam also was investigated as part of Study E7438-G000-101. Subjects with solid tumors (n=13) received a single oral dose of 2 mg midazolam on Day -1 and on Day 15. Tazemetostat 800 mg BID was administered continuously starting on Day 1. Serial blood samples for the analysis of plasma midazolam and metabolites were collected over 24 h on Day -1 (midazolam alone) and Day 15 (midazolam plus tazemetostat).

A summary of preliminary midazolam PK parameters after administration alone (Day -1) and with tazemetostat 800 mg BID (Day 15) in subjects with solid tumors is presented in Table 6.

Table 6: Summary of Midazolam Pharmacokinetic Parameters After Administration Alone (Day -1) or with Tazemetostat 800 mg BID for 15 Days (Day 15) in Study E7438-G000-101 (n=12)

Parameter	Day -1[a]	Day 15[a]	GLSMR (90% CI)
$AUC_{0-\infty}$ ng•h/mL	52.4 (86.9)	31.1 (48.1)	0.59 (0.45, 0.78)
C_{max} ng/mL	15.5 (94.1)	12.3 (50.5)[c]	0.79 (0.59, 1.06)
$t_{1/2}$ h	5.69 (34.6)	4.12 (33.8)	NC

Abbreviations: AUC= area under concentration-time curve, CI= confidence interval, GLSMR = geometric least squares mean ratio, NC = not calculated T_{max} = time to maximum concentration
[a]Data presented as geometric mean (%CV)

[c]n=13

Plasma midazolam $AUC_{0-\infty}$ and C_{max} decreased approximately 40% and 20%, respectively, after

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

2.4.7 Clinical Experience

In 2013, Study E7438-G000-101, a single-agent, Phase 1/2 study of tazemetostat in adult subjects with advanced B-cell lymphomas or advanced solid tumors for which there was no known effective therapy was initiated. Enrollment in Phase 2 is continuing. Three additional studies have also been initiated and are currently recruiting subjects:

- EZH-102, A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma
- EZH-202 A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma
- EZH-203, A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 Loss of Function

As of the cutoff date of 15-Jan. 2016, subjects with advanced solid tumors or B-cell lymphoma (N=88), or with INI-negative tumors (N=1) have been enrolled and exposed to tazemetostat in these 3 studies.

As of the 15-Jan. 2016 cutoff date, 78 of 89 (87.6%) subjects experienced one or more treatment-emergent adverse events (TEAEs) and 51 of 89 (57.3%) subjects experienced TEAEs that were considered by the investigator to be related to tazemetostat. The most common TEAEs, any grade, in descending order of frequency were asthenia, nausea, thrombocytopenia, decreased appetite, anemia, constipation, dysgeusia, vomiting, diarrhea, dry skin, dyspnea, muscle spasms, and abdominal pain. Twenty-two (22) of 89 (24.7%) subjects experienced Grade 3 or 4 AEs, 7 (7.9%) of which were considered related to study drug. Five (5.6%) subjects in the study discontinued tazemetostat treatment due to AEs.

In addition, 22 subjects experienced a total of 31 serious adverse events (SAE). Of these, 4 (12.9%) were considered possibly related to study drug (neutropenia [2], anemia [1], and thrombocytopenia [1]). Eleven subjects died in Study E7438-G000-101. Nine of the deaths were attributed to progressive disease, one event was attributed to an AE, and one death was reported as "not due to progressive disease" (no further information available at time of data cutoff date of 15-Jan. 2016).

As of 07-Nov. 2015, antitumor activity has been noted (phase 1 part only) in subjects with B-cell lymphoma and with INI1-deficient tumors. Objective responses were demonstrated in 9 of 16 subjects (5/10 with DLBCL, 3/5 with FL, and 1/1 with MZL) with B-cell lymphoma (2 complete responses [CR] and 7 partial responses [PR]) and in 4 of 11 subjects with INI1-deficiency (one CR and 3 PRs) who were evaluable for response per protocol (defined as having measurable disease, and least one post-baseline scan, and received at least one dose of study drug). Of the 9 subjects with objective responses, 4 remained on study treatment for 41 to 68 weeks. Tazemetostat has shown clear evidence of robust clinical activity in subjects with genetically defined INI1 negative tumors consisting of 3 of 6 subjects showing objective response (1 CR + 2 PRs) within 8 weeks of receiving the first dose of study treatment. A fourth INI1-negative subject has experienced tumor reduction, but did not meet RECIST 1.1 criteria for PR at the first re-staging at 8 weeks. Further information on clinical efficacy and safety can be found in the tazemetostat Investigator's Brochure (IB), Version 8.0.

2.5. Study and Dose Rationale

2.5.1 Study Rationale

Tazemetostat is metabolized primarily by CYP3A4 in vitro. Inhibition of CYP3A4/5 in vivo is expected to result in increased systemic exposure to tazemetostat. Therefore, Part A of this study will determine the effect of a moderate CYP3A inhibitor, fluconazole, on tazemetostat PK.

Tazemetostat inhibited multiple CYP isoforms in vitro. The most potent inhibition (lowest Ki values) was for the CYP2C8 and CYP3A isoforms followed by CYP2C19. The effect of tazemetostat on the PK of the sensitive CYP3A probe midazolam was determined in Study E7438-G000-101. Therefore, Part B of this study will determine the effect of tazemetostat on the PK of the CYP2C8 probe medication repaglinide and the CYP2C19 probe medication omeprazole.

The solubility of tazemetostat is pH dependent and an increase in gastric pH may alter the oral absorption of tazemetostat. In addition to a CYP2C19 probe medication, omeprazole is a

medication that increases gastric pH. The effect of increased gastric pH on the PK of tazemetostat will be determined in Part B by the concomitant administration of omeprazole for 4 days.

2.5.2 Dose Rationale

2.5.2.1. Tazemetostat

The safety, tolerability, clinical activity, PK, and pharmacodynamic (PD) assessments from the subjects treated in the Dose Escalation part of Study E7438-G000-101 were used to select the recommended Phase 2 dose (RP2D). As of 07-Nov. 2015, 58 subjects with advanced or metastatic solid tumors or B-cell lymphomas had been included in the Phase 1 Dose Escalation part of the study. Clinical activity of tazemetostat was observed at dose levels of 100, 200, 800, and 1600 mg BID, including objective responses observed in 9 of 16 response-evaluable subjects with B-cell lymphoma who have had tumor assessments while on study drug. Objective responses were observed in 5/10 DLBCL, 3/5 FL, and 1/1 MZL subjects. An MTD was not established with tazemetostat doses of up to 1600 mg BID.

A relationship between tazemetostat AUC on Day 15 and inhibition of H3K27Me3 in the stratum spinosum was observed and described by an inhibitory E_{max} model. The tazemetostat AUC_{0-12} at which the H3K27Me3 inhibition was 50% of maximal (EC_{50}) was 848 ng*h/mL and the maximum effect (E_{max}) was 51% inhibition. The predicted inhibition of H3K27Me3 in the stratum spinosum skin layer at the observed median Day 15 AUC_{0-12} in the 800 mg BID dose cohort (3670 ng*h/mL) was over 80% of E_{max}. These results suggest that target inhibition in the skin was near maximal at 800 mg tazemetostat BID and doubling the dose to 1600 mg BID results in only an incremental increase in the inhibition of the H3K27 methylation. Furthermore, the greatest number of objective responses was observed in the 800 mg BID cohort during the Dose Escalation part of the study. Therefore, 800 mg tazemetostat BID was selected as the RP2D. The RP2D was selected to investigate the effect of tazemetostat on CYP2C8- and CYP2C19-mediated metabolism and the effect of increased gastric pH on the PK of tazemetostat in the current study.

2.5.2.2. Fluconazole plus Tazemetostat

Fluconazole doses up to 400 mg daily may be used to treat candida infections and for prophylaxis in patients undergoing bone marrow transplantation. Administration of a single dose of 400 mg fluconazole followed by 200 mg fluconazole daily for 5 days increased midazolam (a sensitive CYP3A probe substrate) AUC and C_{max} 259% and 150%, respectively, after oral

administration of 7.5 mg relative to administration of midazolam alone. The highest dose of tazemetostat investigated in the Dose Escalation and Dose Expansion phases of Study E7438-G000-101 was 1600 mg BID. The results of the effect of fluconazole on systemic exposure to midazolam suggest that administration of tazemetostat 800 mg BID in the presence of CYP3A inhibition by 400 mg fluconazole once daily may result in systemic exposure to tazemetostat greater than that observed in the 1600 mg BID cohort in Study E7435-G000-101. Therefore, tazemetostat 400 mg BID will be administered in Part A of the current study and continue through Day 24 to allow for sufficient wash-out of fluconazole. The tazemetostat RP2D of 800 mg BID will then be administered starting on Day 25, 6 days following the last dose of fluconazole.

2.5.2.3. Repaglinide

The starting dose for repaglinide in patients not previously treated or whose hemoglobin A1c (HbA_{1c}) is < 8% is 0.5 mg administered with each meal. A dose of 0.25 mg repaglinide was selected to minimize the effect on blood glucose in subjects in this study.

2.5.2.4. Omeprazole

The recommended dose of omeprazole to treat duodenal ulcers and gastro-esophageal reflux is 20 mg once daily for 4 to 8 weeks. A daily dose of 20 mg omeprazole was reported to maintain a median gastric pH of 4.5 over 24 hours [Houben, 1995]. Therefore, omeprazole 20 mg once daily was selected to determine the effect of tazemetostat on CYP2C19-mediated metabolism and to investigate the effect of increased gastric pH on the PK of tazemetostat.

2.6. Benefit: Risk Assessments

2.6.1 Animal Toxicology

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

bone marrow effects (hypocellularity, rat), and gastrointestinal toxicity (distention, ulceration, and degeneration, rat).

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

2.6.2 Photo-Reactive Potential

There are nonclinical data supporting a potential for phototoxicity, which has not been evaluated in humans. Hence, prolonged exposure to sunlight should be avoided during treatment. In addition, subjects should take other measures to avoid ultraviolet (UV) exposure such as wearing sun screen and sun glasses, wearing protective clothing, and avoiding tanning beds. Refer to the tazemetostat Investigator's Brochure 8.0 for details.

2.6.3 Metabolism and Transporters

Tazemetostat is metabolized primarily by CYP3A and is a substrate for P-glycoprotein (Pgp). Therefore, treatment with strong inhibitors or strong inducers of CYP3A within 7 days prior to the first dose of tazemetostat and for the duration of study treatment is prohibited. Treatment with moderate inhibitors, other than fluconazole administered in Part A of the current study, is prohibited within 7 days prior to the first dose of tazemetostat until after the final PK sample is drawn on Day 19. Tazemetostat also was shown to be a time-dependent CYP3A inhibitor and a CYP3A4 inducer as well as an inhibitor of Pgp, CYP2D6, and the CYP2C family in vitro. Pgp, CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 substrates should be used with caution. Medications that are substrates for CYP3A, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, and that have a narrow therapeutic range should be avoided if possible.

2.6.4 Anticipated Safety Profile

In addition to the overall incidence of TEAEs as described in Section 2.2.5, the most frequently reported TEAEs (all grades and in descending order) that occurred in ≥ 5% of subjects enrolled in the Phase 1 part of study E7438-G000-101 included the following (as of the 15-Jan.2016 cutoff date, n = 62): Asthenia (34.8%), nausea (15.7%), thrombocytopenia (14.6%), decreased

appetite (13.5%), anemia (12.4%), constipation (12.4%), dysgeusia (7.9%), vomiting (7.9%), diarrhea (6.7%), dry skin (6.7%), dyspnea (6.7%) muscle spasms (6.7%), abdominal pain (5.6%) and neutropenia (5.6%). TEAEs did not appear to be dose dependent. There have been 3 Grade 4 TEAEs, which occurred in one subject each: thrombocytopenia (1 subject) and neutropenia (2 subjects). All 3 events were considered related to study drug and required withdrawal of study drug. For up-to date information on AESIs, see Section 11.5. Additionally, there is the unknown risk of abnormal pregnancy outcomes and drug-drug interactions (DDI). Based on the preclinical toxicology of tazemetostat, the potential risks associated with treatment include bone AEs and photosensitivity.

2.7. Good Clinical Practice (GCP)

The principal investigator will ensure that the basic principles of GCP, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50 (1998) and 21 CFR, Part 56, (1998) are followed.

Since this is a covered clinical trial, the principal investigator is adhered to 21 CFR, Part 54, (1998). A covered clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Epizyme, Inc. or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the principal investigator and any sub-investigator. The principal investigator and sub-investigator agree to notify Epizyme, Inc. of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
Part A • To determine the effect of CYP3A inhibition by fluconazole on the PK of tazemetostat	Part A • AUC_{0-t}, AUC_{0-8}, AUC_{0-12}, and C_{max} of tazemetostat on Days 15 and 19
Part B: • To investigate the potential of tazemetostat to inhibit or induce CYP2C8 using repaglinide as a probe substrate.	Part B: • AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of repaglinide on Days 1 and 16
• To investigate the potential of tazemetostat to inhibit or induce CYP2C19 using omeprazole as probe a substrate.	• AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of omeprazole on Days 1 and 16
• To investigate the effect of increased gastric pH by omeprazole on the PK of tazemetostat.	• AUC_{0-t}, AUC_{0-8}, AUC_{0-12}, and C_{max} of tazemetostat on Days 16 and 19
Secondary:	
Part A • To investigate the safety profile of tazemetostat 400 mg BID after co-administration with fluconazole.	Part A • Safety and tolerability parameters including AEs, clinical laboratory assessments, and vital signs
• To determine the PK of tazemetostat and its metabolites after administration alone and with fluconazole.	• T_{max}, and $t_{1/2}$ of tazemetostat and AUC_{0-t}, AUC_{0-8}, C_{max}, $T_{max,}$ and $t_{1/2}$ of tazemetostat metabolites on Days 15 and 19.
• To determine the systemic exposure of fluconazole after administration of 400 mg once daily for 4 days.	• Plasma fluconazole AUC_{0-8}, C_{max}, and T_{max} on Day 19
Part B • To investigate the safety profile of tazemetostat, repaglinide, and omeprazole after co-administration.	Part B • Safety and tolerability parameters including AEs, clinical laboratory assessments, and vital signs

Objectives	Endpoints
• To determine the PK of repaglinide and its metabolites after administration with omeprazole and administration with omeprazole and tazemetostat	• T_{max} and $t_{1/2}$ of repaglinide; AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$ of repaglinide metabolites on Days 1 and 16. The metabolite to repaglinide ratio for $AUC_{0-\infty}$ and AUC_{0-t} on Days 1 and 16. The plasma metabolite to repaglinide concentration ratios at 1, 2, 3, 5, and 7 hours after administration of repaglinide on Days 1 and 16
• To determine the PK of omeprazole and its metabolites after administration with repaglinide and administration with repaglinide and tazemetostat	• T_{max} and $t_{1/2}$ of omeprazole on Days 1 and 16. AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$ of 5-hydroxyomeprazole (5-OH-omeprazole) and omeprazole sulfone. The 5-OH-omeprazole to omeprazole and the omeprazole sulfone to omeprazole ratios for $AUC_{0-\infty}$ and AUC_{0-t} on Day 1 and Day 16. The plasma 5-OH-omeprazole to omeprazole and omeprazole sulfone to omeprazole concentration ratios at 1, 2, 3, 5, and 7 hours after administration of omeprazole on Days 1 and 16
•	•
Parts A and B: • To assess antitumor activity of tazemetostat in subjects with DLBCL, PMBCL, MCL, MZL, FL, or advanced solid tumors	Parts A and B: • Overall response rate (ORR: CR or PR) and disease control rate (DCR: CR or PR, or SD lasting 24 weeks or longer from start of treatment with tazemetostat) using Lugano Classification [Cheson 2014] for subjects with lymphoma and RECIST 1.1 for subjects with solid tumors
Exploratory:	
• To investigate the effects of variations in genes encoding for CYP enzymes and transporters on the potential DDI profile of tazemetostat	• Genotype for genes encoding for CYP enzymes and transporters
• To explore the effect of tazemetostat on OS	• OS

4. STUDY DESIGN

4.1. Study Sites

This study will be conducted at 3 sites in the US.

4.2. Overview of Study Design

This is a Phase 1, open-label, 2-part, safety, PK, and activity study designed to characterize the DDI potential of tazemetostat. Tazemetostat will be taken orally BID continuously in 28-day cycles in both study parts. Subjects in Part A will receive tazemetostat 400 mg BID continuously for 24 days starting on Day 1. Tazemetostat 800 mg BID then will be administered continuously starting the morning of Day 25. Subjects in Part B will receive tazemetostat 800 mg BID continuously starting on Day 2. Adequate supplies of tazemetostat to be taken at home will be dispensed to subjects on scheduled clinic days. On clinic days when blood samples are taken, subjects will be given morning tazemetostat doses at the clinic.

Part A. On the morning of Day 1, subjects will begin treatment with oral tazemetostat tablets 400 mg BID. Subjects will be given sufficient supply of tazemetostat to continue treatment through Day 14. Subjects will check in to the clinic on the morning of Day 15 prior to the morning dose of 400 mg tazemetostat. Blood samples for the analysis of tazemetostat and metabolites will be collected predose and over 8 hours after the morning dose of tazemetostat on Day 15. Subjects will receive fluconazole 400 mg tablets, which will be taken once daily for 4 days starting on Day 16. On the morning of Day 19, subjects will check in to the clinic and serial blood samples for the analysis of tazemetostat and its metabolites, and fluconazole will be collected predose and over 8 hours after the morning tazemetostat dose. Subjects will receive tazemetostat 400 mg BID until the evening dose on Day 24. Tazemetostat 800 mg BID will be administered starting on Day 25 and continue until the subject withdraws from the study.

Part B. Subjects enrolled in Part B will check in to the clinic on the morning of Day 1 and will receive oral doses of repaglinide 0.25 mg and omeprazole 20 mg. Blood samples for analysis of plasma repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone will be collected over 7 hours after administration on Day 1. Subjects will be able to leave the clinic after the last PK blood sample is collected and also will be given a sufficient supply of tazemetostat for home administration of tazemetostat 800 mg BID for 14 days starting on Day 2. Subjects will return to the clinic on Day 16, prior to the scheduled morning dose of tazemetostat. Subjects will receive the morning dose of tazemetostat, followed 1 hour (± 5 minutes) later by oral doses of repaglinide 0.25 mg and omeprazole 20 mg. Blood samples for analysis of plasma tazemetostat and its metabolites, repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone will be collected predose and over 8 hours after administration of

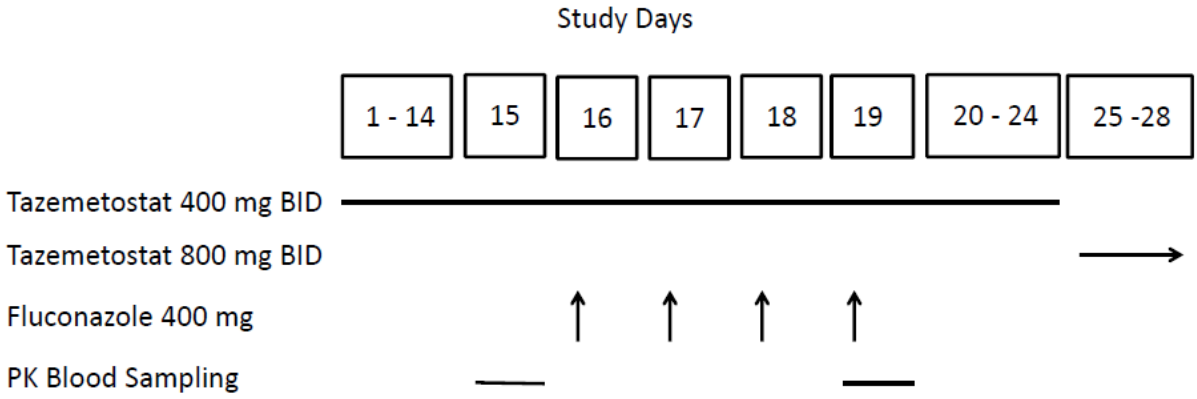
tazemetostat on Day 16. Subjects will continue to receive omeprazole 20 mg once daily in the morning on Days 17 through 19, inclusive. On Day 19, blood samples for analysis of plasma tazemetostat and its metabolites will be collected over 8 hours after the morning dose. Subjects will again be given an adequate supply of tazemetostat to last until the next scheduled clinic day.

Upon initiation of tazemetostat treatment, all subjects enrolled in this study will receive oral tazemetostat for up to 6 months (24 weeks) or until they have an unacceptable toxicity, disease progression, or withdraw consent. Subjects may be transitioned to Study EZH-501, at the investigator's discretion, after completing all study assessments in EZH-105 and at least 6 months of treatment with tazemetostat. Subjects enrolling in the EZH-501 study will transition to 200 mg tazemetostat tablets from 400 mg tablets (as administered in EZH-105). Subjects who are enrolled in the study and do not complete all study assessments, or who do not transition to Study EZH-501 must have a post-treatment follow-up visit within 30 days of the last dose of tazemetostat. In addition, subjects who discontinue treatment with tazemetostat and do not transition to the EZH-501 study, will be followed for OS.

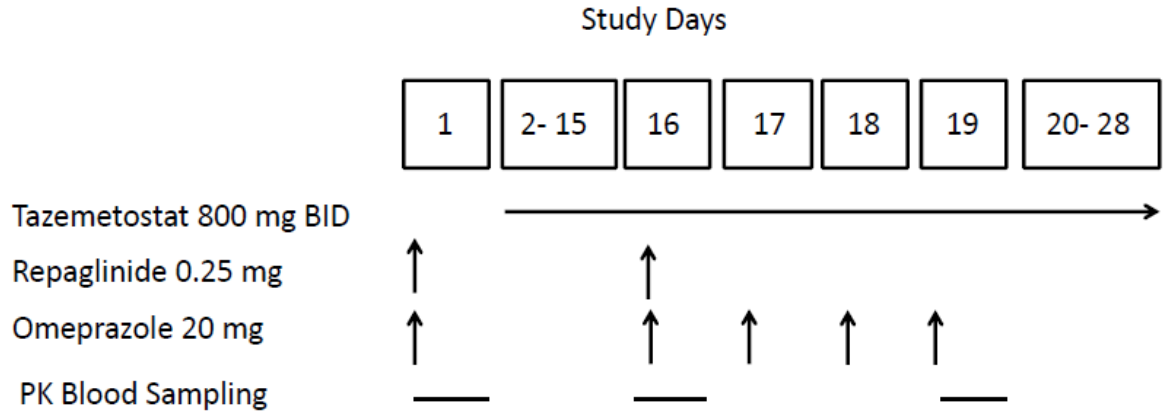
Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying procedure manuals (i.e., laboratory, pharmacy, ECG, and imaging manuals). Such manuals will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

4.3. Study Schema for the First 28 Days of Treatment

Part A:



Part B:



BID = twice daily.

4.4. Rules for Suspension of Enrollment

The investigators, IRBs/ECs, and regulatory agencies will be urgently informed and a Safety Review committee comprised of the investigators and Epizyme medical monitor convened to review the data and to make recommendations for potential changes in study conduct if one or more subjects develop any of the following AEs deemed to be definitely related to study treatment by the investigator and/or Medical Monitor, based upon close temporal relationship or other factors:

- Death
- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress)
- Secondary lymphoma

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

5. STUDY POPULATION

5.1. Target Population

Approximately 32 subjects will be enrolled to achieve 12 subjects who complete each part of the study. Subjects will complete either Part A or Part B.

See Section 13.2.1 for sample size assumptions.

5.2. Inclusion Criteria

A subject must meet the following criteria to be eligible for entry into the study:

1. Male or female ≥ 18 years of age at time of consent
2. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix 3)
3. Has the ability to understand informed consent and provided signed written informed consent

Must meet one of the following criteria:

4. Has histologically confirmed diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), marginal zone lymphoma (MZL), or mantle cell lymphoma (MCL), and have relapsed or refractory disease following at least 2 standard lines of systemic therapy, including alkylator/anthracycline (unless anthracycline–based chemotherapy is contraindicated)/anti-CD20-based therapy (R-CHOP or equivalent) AND must be considered unable to benefit from intensification treatment with autologous hematopoietic stem cell transplantation (ASCT), as defined by meeting at least 1 of the following criteria:
    a. Relapsed following, or refractory to, previous ASCT
    b. Did not achieve at least a PR to a standard salvage regimen (e.g., R-ICE or R-DHAP)
    c. Ineligible for intensification treatment due to age or significant comorbidity
    d. Ineligible for intensification treatment due to failure to mobilize an acceptable number of hematopoietic stem cells
    e. Refused intensification treatment and/or ASCT.

Note: Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen.

OR

5. Has histologically confirmed FL, all grades. Subjects must have relapsed/refractory disease following at least 2 standard lines of systemic therapy, including at least 1 anti-CD20-based regimen (eg, rituximab), as well as alkalating agents (eg, cyclophosphamide or bendamustine), and have no curative option with other available therapies OR have a contra-indication to their use. Subjects with prior ASCT may be included. Transformed disease is permitted.

   Note: Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen.

OR

6. Histologically and/or cytologically confirmed advanced or metastatic solid tumor that has progressed after treatment with approved therapies or for which there are no standard therapies available
7. Must have evaluable or measurable disease
8. Has all prior treatment (i.e., chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per NCI CTCAE, Version 4.03 or are clinically stable and not clinically significant, at time of consent
9. Time required between the last dose of the latest therapy and the first dose of study drug:

Prior Therapy	**Time from Last Prior Therapy**
Chemotherapy: cytotoxic	At least 21 days
Chemotherapy: nitrosoureas	At least 6 weeks
Chemotherapy: non-cytotoxic (e.g., small molecule inhibitor)	At least 14 days
Monoclonal antibody (ies)	At least 28 days
Non-antibody immunotherapy (e.g., tumor vaccine)	At least 42 days
Radiotherapy (RT)	At least 14 days for stereotactic radiosurgery At least 12 weeks for craniospinal, ≥50% radiation of pelvis, or total body irradiation
Autologous hematopoietic cell infusion after high dose therapy	At least 60 days
Hematopoietic growth factor	At least 14 days

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

System	Laboratory Value
Hematologic (BM Function)	
Hemoglobin[a]	≥9 g/dL
Platelets[b]	≥75,000/mm^3 (≥75 × 10^9/L)
ANC[c]	Lymphoma subjects: ≥750/mm^3 (≥0.75 × 10^9/L) Solid tumor subjects: ≥1,000/mm^3 (≥1.0 x 10^9/L
Hematologic (Coagulation Factors)	
PT	<1.5 ULN
PTT	<1.5 ULN
Renal Function	
eGFR[d]	≥ 50 mL/min/1.73 m^2
Hepatic Function	
Conjugated bilirubin	<1.5 × ULN
AST[e]	<3 × ULN
ALT[e]	<3 × ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BM = bone marrow; eCGR = estimated glomerular filtration rate; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

a. May receive transfusion
b. Should be evaluated after at least 7 days since last platelet transfusion
c. Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
d. Calculate eGFR per institutional standard formula
e. If attributed to tumor involvement, AST and ALT <5×ULN

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

11. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec
12. Subjects with a history of Hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion No. 10 and are hepatitis B surface antigen negative and/or have undetectable HCV RNA.
13. Male subjects must refrain from donating sperm starting at the planned first dose of investigational product (IP) until 30 days following the last dose of IP.
14. **Male subjects with a female partner of childbearing potential must:**
    a. Be vasectomized, or

b. Remain abstinent or use a condom as defined in Section 8.3.10.4.2 starting at the planned first dose of IP until 30 days following the last dose of IP. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

15. **Female partners of male subjects who are of childbearing potential must also adhere to one of the following:**

    a. Placement of an intrauterine device or intrauterine system.
    b. Established use of oral, injected, or implanted hormonal methods of contraception plus an additional barrier method.
    c. Progesterone-only oral contraception, where inhibition of ovulation is not the primary mode of action.

16. **Women of childbearing potential:**

    a. A woman is considered to be of childbearing potential if she is post menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    b. Must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year starting at the planned first dose of IP until 30 days following the last dose of IP.
    c. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    d. Due to the potential of enzyme induction with tazemetostat, female subjects who use hormonal contraceptives should use an additional barrier method of birth control while on study treatment and for 30 days after discontinuation of study treatment.
    e. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    f. Barrier methods must always be supplemented with the use of a spermicide.

5.3. Exclusion Criteria

A subject who meets any of the following criteria is ineligible for entry into the study:

1. Is pregnant or nursing
2. Has active central nervous system (CNS) or leptomeningeal metastasis
3. Has had a prior malignancy other than the malignancies under study

   Exception: Subject who has been disease-free for 3 years, or a subject with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.
4. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) and any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).

   NOTE: Bone marrow aspirate/biopsy will be conducted following abnormal peripheral blood smear morphology assessment conducted by the local laboratory. Cytogenetic testing and DNA sequencing will be conducted following an abnormal result of bone marrow aspirate/biopsy.
5. Has a prior history of T-LBL/T-ALL.
6. Has had major surgery within 3 weeks prior to enrollment

   NOTE: Minor surgery (e.g., minor biopsy, central venous catheter placement) is permitted within 3 weeks prior to enrollment.
7. Is unwilling to exclude grapefruit juice, Seville oranges, and grapefruit from the diet and all foods that contain those fruits from time of enrollment to the last dose of tazemetostat
8. Has cardiovascular impairment, history of congestive heart failure greater than NYHA Class II (see Appendix 4), uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of tazemetostat; or ventricular cardiac arrhythmia requiring medical treatment
9. Subjects taking medications that are known potent or moderate inducers/inhibitors of CYP3A4 (including St. John's Wort)
10. Has an active infection or recent history (<30 days before study drug administration) requiring systemic treatment
11. Is immunocompromised, including subjects with known human immunodeficiency virus (HIV) infection
12. Has known hypersensitivity to any of the components of IP
13. Is unable to take oral medications, has a history of surgery that would interfere with the administration or absorption of oral medication, has malabsorption syndrome or any other

uncontrolled gastrointestinal condition (e.g., nausea, diarrhea or vomiting) that might impair the bioavailability of IP

14. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements
15. Is unwilling to adhere to contraception criteria from time of enrollment in study to at least 30 days after last dose of IP
16. A history of bleeding (i.e., hemoptysis, hematuria, GI blood loss, epistaxis, or others with greater than Grade 1 according to NCI CTCAE Version 4.03) within 1 month prior to beginning therapy or any clinical indications of current active bleeding
17. Clinical history, current alcohol (ethanol), or illicit drug use which, in the judgment of the investigator, will interfere with the subject's ability to comply with the dosing schedule and protocol-specified evaluations
18. Regular alcohol consumption averaging more than 7 drinks/week for women and 14 drinks/week for men within 6 months of screening. A drink is defined as follows:

Alcohol	**1 Drink (12 g alcohol)**	**7 Drinks/week (84 g alcohol)**	**14 Drinks/week (168 g alcohol)**
Wine	150 mL (5 ounces)	1050 mL (35 ounces)	2100 mL (70 ounces)
Beer	360 mL (12 ounces)	2520 mL (84 ounces)	5040 mL (168 ounces)
Distilled spirits 80 proof	45 mL (1.5 ounces)	315 mL (10.5 ounces)	630 mL (21 ounces)

6. STUDY MEDICATIONS

6.1. Investigational Product - Tazemetostat

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

	Investigational Product
Product Name:	Tazemetostat
Formulation Description:	200 and 400 mg tablets
Dosage Form:	Tablet
Physical Description:	The 400-mg tablets are red, modified oval, biconvex, film-coated tablets with a length of approximately 18 mm. The 200-mg tablets are red, round, biconvex, film-coated tablets with a diameter of approximately 10 mm. Each strength is packaged in white high-density polyethylene bottle with a child resistant, tamper-evident polypropylene screw cap.
Dose/Route/Schedule/Duration:	400 mg or 800 mg / oral / BID / For up to 6 months

Abbreviations: BID = twice daily.

6.1.1 Preparation, Handling and Storage of Investigational Product

Preparation: No preparation is needed.

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

Storage: IP must be stored at less than 25°C in a secure area with access limited to the investigator and authorized site staff. Refer to study procedures manual for additional information on storage requirements. Refer to Pharmacy Manual for additional details.

6.1.2 Procurement of Investigational Product

The initial shipment of IP, tazemetostat, to a clinical site will occur after all essential regulatory documents (including, but not limited to the receipt of the signed protocol signature page, signed Form FDA 1572, curriculum vitae of principal investigator and designees, Institutional Review Board (IRB)/Ethics Committee (EC) approval letter, and approved informed consent form [ICF]) are collected. Refer to the Pharmacy Manual for directions on re-supply shipments.

6.1.3 Accountability

The investigator/designee will be responsible for taking an inventory of each shipment of IP received and comparing it with the accompanying accountability form. The investigator/designee will verify the accuracy of the information on the form, sign and date it, and return it to the sponsor or its designee.

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

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

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

6.2. Other Medications

6.2.1 Fluconazole

Product Name:	Fluconazole
Formulation Description:	200 mg tablet
Dosage Form:	Immediate release tablet
Dose/Route/Schedule/Duration:	400 mg/oral /once daily/ Days 16 – 19

6.2.2 Repaglinide

Product Name:	Repaglinide
Formulation Description:	0.5 mg tablet
Dosage Form:	Immediate release tablet
Dose/Route/Schedule/Duration:	0.25 mg/oral/single dose/Day 1 and Day 16

6.2.3 Omeprazole

Product Name:	Omeprazole
Formulation Description:	20 mg capsule
Dosage Form:	Delayed release capsule
Dose/Route/Schedule/Duration:	20 mg/oral/once daily/Day 1 and Days 16 −19

6.2.4 Procurement of Other Medications

Fluconazole, repaglinide, and omeprazole will be locally supplied by each site.

6.3. Dosage and Administration

Tazemetostat must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

6.3.1 Tazemetostat

Upon initiation of tazemetostat administration, tazemetostat will be administered BID (no less than 8 hours between doses) as 400 mg tablets for the duration of the study. Tazemetostat 400 mg BID administration will start on Day 1 and continue through Day 24 in Part A, and will increase to 800 mg BID, continuously, starting on Day 25. Tazemetostat 800 mg BID administration will start on Day 2 in Part B. Tazemetostat will be administered without regards to meals, with the exception of the morning doses on Day 15 and Day 19 in Part A and the morning doses on Day 16 and Day 19 of Part B when tazemetostat should be administered at least 1 hour before and 2 hours after a meal. An adequate supply will be provided with instructions on home administration.

Subjects who complete 6 cycles of treatment in the EZH-105 study and transition to the EZH-501 study will be provided 200 mg tazemetostat tablets as part of the EZH-501 study.

6.3.2 Fluconazole

Subjects enrolled Part A of the study will receive fluconazole 400 mg orally once daily with tazemetostat on Days 16 through 19, inclusive. Fluconazole can be administered without regards to meals.

6.3.3 Repaglinide

Subjects enrolled in Part B of the study will receive a single oral dose of repaglinide 0.25 mg in the morning on Days 1 and 16. Repaglinide administered on Day 16 should be administered 1 hour (± 5 minutes) after the tazemetostat dose. Repaglinide should be administered at least 1 hour before and 2 hours after a meal.

6.3.4 Omeprazole

Subjects enrolled in Part B of the study will receive a single oral dose of omeprazole 20 mg in the morning on Day 1. Omeprazole 20 mg also will be administered once daily, in the morning, on Days 16 through 19, inclusive. Omeprazole administered on Day 16 should be administered 1 hour (± 5 minutes) after the tazemetostat dose. Omeprazole should be administered at least 1 hour before and 2 hours after a meal.

7. STUDY TREATMENT

7.1. Treatment Assignment

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

7.2. Restrictions During Study Treatment

Subjects will abstain from ingesting Seville oranges and grapefruit or grapefruit juice and foods/beverages that contain those, for 24 hours prior to the first dose of study treatment until the last dose of study treatment. Subjects should maintain their usual diet from 7 days prior to the first dose of study treatment until the last PK blood sample is collected. Subjects should avoid prolonged exposure to sunlight while receiving study drug. In addition, subjects should take other measures to avoid UV exposure such as wearing sun screen and sun glasses, wearing protective clothing, and avoiding tanning beds.

7.3. Dose Modifications: Criteria for Retreatment, Temporary Discontinuation of Treatment, Dose Reduction, and Resumption of Treatment

Tazemetostat dose reductions and interruptions are not permitted during the first 19 days of treatment (both parts of the study). However, subjects will be replaced if a dose reduction is necessary in order to manage toxicity within the first 19 days. Subjects who miss 2 or more consecutive tazemetostat doses during the first 19 days of treatment or miss more than 3 tazemetostat doses total during the first 19 days of treatment may be replaced. Tazemetostat dose reductions and interruptions will be allowed following the first 19 days. 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 Reduction and Interruption Instructions in Table 7, which follows. For any case of T-LBL/T-ALL tazemetostat will be discontinued and patient will be followed until resolution of the event. For any case of MDS/MPN/AML or other myeloid malignancy, tazemetostat will be held and after discussion with the Investigator, dose modify or discontinue the drug.

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 according to the Dose Reduction and Interruption Instructions in Table 7.

Table 7: Tazemetostat Dose Reduction and Interruption Instructions

	During Therapy	Approximate Dose Adjustment[b]
Grade 1		
All occurrences	Continue tazemetostat	Maintain dose level
Grade 2[e]		
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	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID
2nd occurrence (same or new toxicity)		Restart at 400 mg BID
3rd occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 Neutropenia (ANC: < 1 – 0.5 × 10^9/L)		
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		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID
2nd occurrence		Restart at 400mg BID
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 4		
Any occurrence	Interrupt tazmetostat until resolved to Grade 2 or less	Discuss with medical monitor

Abbreviations: ANC = absolute neutrophil count, 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 Sponsor 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.

7.4. Continuation of Treatment

Subjects who are potentially benefitting (no signs or symptoms of progressive disease) from study treatment and have not incurred unacceptable toxicity, may continue treatment with tazemetostat by enrolling in Study EZH-501 at the investigator's discretion with the subject's or his/her legal representative consent after completion of all study procedures and at least 6 months of treatment with tazemetostat.

7.5. Treatment Compliance

The subject will be requested to maintain a medication diary of each dose of study treatment. The dosing diary will be returned to the site staff at each visit. Tazemetostat will be self-administered at home on non-clinic days.

7.6. Treatment of Overdose

In the event of an overdose of tazemetostat (defined as administration of more than the protocol-specified dose), the investigator should contact the medical monitor or their designee immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor or their designee based on the subject's clinical evaluation. If tazemetostat treatment is interrupted or discontinued due to an overdose, the subject should be monitored closely until tazemetostat can no longer be detected systemically. For reference, 5 half-lives of tazemetostat would be at minimum 25 hours, longer in subject with delayed clearance.

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

The quantity of the excess dose as well as the duration of the overdosing should be documented in the electronic case report form (eCRF).

7.7. Tazemetostat Duration of Treatment

Treatment with tazemetostat for both parts in this study may continue for up to 6 months (24 weeks) or until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study by the sponsor.

8. STUDY ASSESSMENTS AND PROCEDURES

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

8.1. Consent

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

8.2. Screening Assessments

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

All screening assessments, including tumor assessment, must be performed within 28 days of enrollment.

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

8.2.1 Demographics and Medical History

A complete medical history will be taken and is to include medical conditions at screening. Information to be documented includes demographic information, prior medical illnesses and conditions, and surgical procedures.

8.3. Study Assessments

For study assessments not included in sections below (e.g., vital signs, ECOG performance status), refer to the Schedule of Assessments and Procedures (Table 1 and Table 2) for details. A cycle is defined as 28 days.

8.3.1 Physical Examinations

8.3.1.1. Comprehensive Physical Examination

A comprehensive physical examination of all body systems must be performed at screening and on Day 1 of each treatment cycle starting with Cycle 2 by a qualified licensed individual. A review of body systems will include the following:

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

Weight is required to be measured at screening, on the first day of each cycle starting with Cycle 2 and at the post-treatment visit.

Height measurement is required at screening only.

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

These assessments will be completed as indicated in the Schedule of Assessments and Procedures (Table 1 and Table 2).

8.3.1.2. Symptom-Directed Physical Examination

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

These assessments will be completed as indicated in the Schedule of Assessments and Procedures (Table 1 and Table 2).

8.3.2 Electrocardiograms (ECGs)

The ECGs will be performed as indicated in the Schedule of Assessments and Procedures (Table 1 and Table 2). Machine-read ECGs should be reviewed by the investigator at the time of the assessment. A single ECG will be recorded unless there is an abnormality, such as prolonged QTc F > 480 msec, new arrhythmia, or other clinically significant finding. If such an abnormality is detected, the ECG should be performed in triplicate at least 2 minutes apart.

Data from ECGs will be entered in the appropriate eCRFs.

8.3.3 Optional Chest Ultrasound

An optional chest ultrasound may be conducted every 8 weeks at the Investigator's discretion while on study to identify early signs of T-LBL/T-ALL.

8.3.4 End of Study Assessments

End of study assessments will be conducted to review AESIs, PK and tumor response. A 3 mL blood sample will be required for end of study PK assessments.

8.3.5 Disease Assessment

Disease assessment will be performed as indicated in the Schedule of Assessments and Procedures (See Schedule of Events Table 1 and Table 2). Investigator tumor assessments will be performed based on Lugano Classification (Cheson 2014, Appendix 1) for lymphoma and RECIST v1.1 (Appendix 2) for solid tumors at each assessment timepoint and entered into the appropriate eCRFs.

8.3.6 Pharmacokinetics

All PK blood samples may be drawn from either a central venous catheter or a peripherally placed intravenous catheter.

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

8.3.6.1. Part A

In Part A of the study, blood samples for analysis of plasma tazemetostat and metabolite concentrations will be collected on Study Days 15 and 19 and EOS:

Study Day	Sample Size	Collection Timepoints[a]
15	1 mL	Predose (within 30 minutes prior to dose), 0.5, 1, 2, 3, 4, 6, and 8 hours postdose
19	2 mL	Predose (within 30 minutes prior to dose), 0.5, 1, 2, 3, 4, 6, and 8 hours postdose
EOS	3 mL	No specified timepoint

a: Allowable windows for collection of PK blood samples are ± 5 minutes for sample timepoints ≥ 0.5 and ≤ 4 hours and ± 30 minutes sample timepoints > 5 hours.

Approximately 24 mL of blood will be obtained for PK analysis in Part A. Subjects who miss 2 or more PK blood sample collections may be replaced.

8.3.6.2. Part B

In Part B of the study, blood samples for analysis of plasma tazemetostat and metabolite concentrations will be collected on Study Days 1, 16, and 19 and EOS:

Study Day	Sample Size	Collection Timepoints[a]
1	2 mL	Predose (within 90 minutes prior to dose) and 0.25, 0.5, 1, 2, 3, 5, and 7 hours postdose
16	1 mL	***For analysis of plasma tazemetostat and metabolites***: Predose (within 30 minutes prior to dose) and 0.5, and 1 hours after administration of tazemetostat.
	2 mL	***For analysis of repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone:*** Predose (within 30 minutes prior to tazemetostat administration) and 1.25 and 1.5 h after tazemetostat administration (0.25 and 0.5 h after repaglinide and omeprazole administration).
	3 mL	***For analysis of tazemetostat and its metabolites, repaglinide and its metabolite, omeprazole, 5-OH-omeprazole, and omeprazole sulfone:*** 2, 3, 4, 6, and 8 hours after tazemetostat administration.
19	2 mL	Predose (within 30 minutes prior to dose) and 0.5, 1, 2, 3, 4, 6, and 8 hour postdose
EOS	3 mL	No specified timepoint

a: Allowable windows for collection of PK blood samples are ± 5 minutes for sample timepoints ≥ 0.25 and ≤ 4 hour and ± 30 minutes sample timepoints > 5 hours.

Approximately 56 mL of blood will be obtained for PK analysis in Part B. Subjects who miss 2 or more PK blood sample collections may be replaced.

8.3.7 Pharmacogenomics (PGx)

A single whole blood sample (10 mL) is to be collected during the screening phase to provide DNA for analysis of genes involved in drug disposition (i.e., absorption, distribution, metabolism, and excretion [ADME]). This will support investigation of whether subject genotype, specifically of ADME genes, is related to the DDI potential of tazemetostat.

8.3.8 Tumor Tissue Collection

Archive formalin-fixed tumor tissue block or 10-15 unstained slides are requested at screening from all subjects for molecular characterization, e.g., somatic mutation detection, gene expression profiling, and/or proteomic analysis. As available the diagnostic pathology block or slides obtained at the time of the subject's diagnosis and/or time of subsequent procedures is acceptable. The sponsor or designee will return all blocks to the original site on completion of the planned analyses.

An effort will be made to obtain paired tumor tissue biopsies before and after initiation of treatment with tazemetostat. An optional lymph node, core-needle biopsy, or bone marrow biopsy will be performed during the screening period and on Day 1 of Cycle 2. A window of 14 days before and after Day 1 of Cycle 2 will be allowed (i.e., biopsy must be done between Day 14 of Cycle 1 and Day 14 of Cycle 2). Biopsies will be performed by a surgeon, if necessary, or by interventional radiology. A cytopathologist will evaluate the biopsy microscopically for tumor cells at the time of the biopsy. If multiple lymph nodes are available, the safest lymph node will be selected. The choice of core biopsy versus incisional or excisional biopsy will be made based on safety, accessibility, and the likelihood of being pathologic. If the subject has a single target lesion, this lesion will not be eligible for correlative biopsy.

All subjects will indicate consent or denial for the optional studies within the main consent form for this study.

Tumor tissue may be analyzed for DNA, mRNA and/or protein endpoints up to and including whole genome analysis. The data generated (from subjects who enroll in EZH-501) will be combined with equivalent data from additional tazemetostat single-agent studies of NHL subjects to determine candidate biomarkers of response to tazemetostat. The results of these analyses will be reported outside of this protocol.

8.3.9 Clinical Laboratory Assessments

All clinical laboratory assays will be performed at local laboratories according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated until confirmed, explained, or resolved. Laboratory value changes starting from the initial tazemetostat exposure will be recorded in the eCRF as an AE if clinically significant.

Hematology: Hemoglobin, hematocrit, WBC, differential blood count with ANC, platelet count and peripheral blood smear morphology are performed at screening and at regular intervals.

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

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

Coagulation Profile: This will include: partial thromboplastin (PT), partial thromboplastin time (PTT).

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

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

Refer to the Schedule of Assessment and Procedures (Tables 1 and 2) for additional details.

8.3.9.1. Vital Sign Measurements

Blood pressure (BP), heart rate (HR), and temperature must be measured after the subject has been sitting for 5 minutes.

8.3.9.2. ECOG Performance Status

Subject's performance status will be assessed using the ECOG performance status tool (see Appendix 3).

8.3.10 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.

8.3.10.1. Definition of Childbearing Potential: Female Subjects

A female subject is considered of childbearing potential if she:

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

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

- Is postmenopausal (at least 12 months consecutive amenorrheic, at least 45 years of age, and has a follicle stimulating hormone level of >40 mIU/mL), or
- Is surgically sterilized (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) with surgery at least 1 month before the first dose of study treatment
- Has a documented congenital or acquired disorder that is incompatible with pregnancy

8.3.10.2. Definition of Childbearing Potential: Male Subjects

A male subject is considered of childbearing potential if he:

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

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

- Has a documented successful vasectomy (with confirmed azoospermia)

8.3.10.3. Pregnancy Testing

All female subjects must have a negative pregnancy test (urine or serum) at screening within 28 days of the first dose of study treatment.

Subsequent pregnancy tests should be performed predose on the first day of each treatment cycle, beginning with Cycle 2, and can be either serum or urine. Any positive urine pregnancy test must be confirmed with a serum test.

8.3.10.4. Prevention

8.3.10.4.1. Female Subjects

Females of childbearing potential must agree to use a highly effective method of contraception, that results in a failure rate of < 1% per year when used consistently and correctly, starting at screening, during study treatment, and for 30 days after the final dose of study treatment, and have a male partner who uses a condom when using hormonal contraceptives.

Acceptable highly effective contraception includes:

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

  NOTE: Female subjects who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to the first dose of study treatment and must continue to use the same contraceptive during study treatment and for 30 days after discontinuation of study treatment.

  Due to the potential of enzyme induction with tazemetostat, female subjects who use hormonal contraceptives should use an additional barrier method of birth control while on study treatment and for 30 days after discontinuation of study treatment.

Female subjects exempt from this requirement are subjects who practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, sympto-thermal, post-ovulation methods], declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception), or have a

male partner who is vasectomized. If currently abstinent, the subject must agree to use a highly effective method of contraception as described above if they become sexually active during study treatment, and for 30 days after discontinuation of study treatment.

8.3.10.4.2. Male Subjects

Male subjects of childbearing potential must agree to use of condoms with their female partner prior to enrollment, during study treatment, and for 30 days after the final dose of study treatment.

8.3.10.5. Reporting of Pregnancy

The investigator must attempt to collect and report to the sponsor or its designee pregnancy information on any female subjects or female partner of male study subjects who became pregnant while the subject is enrolled in the study. Pregnancy will not be considered an SAE. Any incidence of pregnancy recorded for a female subject or female partner of a male subject should be reported. To ensure subject safety, each pregnancy must be reported to the sponsor or its designee within 2 weeks of learning of its occurrence using a clinical trial pregnancy report form. A Pregnancy Report Form should be completed and submitted by email and/or fax to the sponsor or its designee.

Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the investigator to obtain all pregnancy related information.

Pregnancy complications must be reported as an AE or SAE in addition to spontaneous abortions must be reported as an SAE.

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

9. CONCOMITANT MEDICATIONS

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

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

9.1. Permitted Medication(s)

- Supportive care measures and symptomatic treatment for any treatment-related toxicity, including short courses (≤ 5 days) of corticosteroids, if clinically indicated
- Non-enzyme inducing anti-epileptic drugs
- Prophylactic use of standard anti-emetics
- Intermittent use of dexamethasone is permitted as an antiemetic (not to exceed 0.3 mg/kg/dose dexamethasone or maximum dose of 10 mg/dose) every 12 hours as needed
- Blood and platelet transfusions, as needed per the judgment of the investigator

9.2. Medications to be used with Caution

Substrates of Pgp, CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 should be used with caution. Medications that are substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, and have a narrow therapeutic range should be avoided if possible. Medications that are CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 substrates that have a narrow therapeutic range include, but are not limited to, medications listed in Table 8.

Table 8: Medications That Are Substrates for CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 That Have a Narrow Therapeutic Range

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

Abbreviations: CYP= cytochrome

This list is not exhaustive. Please contact the medical monitor for additional questions.

NOTE: A listing of CYP substrates can be found using the following link:

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

9.3. Prohibited Medication(s)

9.3.1 All Subjects

- Antineoplastic therapy or other investigational therapy for the treatment of cancer
- Prophylactic use of hematopoietic colony-stimulating factors
- **NOTE:** Therapeutic use of hematopoietic colony-stimulating factors is discouraged and should be discussed with the medical monitor and should be conducted according to the 2006 American Society for Clinical Oncology (ASCO) Guideline for use of white blood cell (WBC) growth factors [Smith, 2006].
- Treatment with strong inhibitors or inducers of CYP3A4 is prohibited within 7 days prior to first dose of study treatment and for the duration of study. Medications that are strong inhibitors or strong inducers of CYP3A4 include, but are not limited to those listed in Table 9, which follows.
- Treatment with moderate inhibitors or inducers of CYP3A4 are prohibited within 7 days of the first dose of study treatment until after the final PK blood sample is collected on

Day 19 with the exception of fluconazole administered as described in Part A. Medications that are moderate inhibitors or moderate inducers of CYP3A4 include, but are not limited to those listed in Table 9.

- Non-approved herbal medications or supplements.

9.3.2 Part A

- Medications that are substrates for CYP3A4 and have a narrow therapeutic range (see Table 8) are prohibited from 24 hours prior to the first dose of tazemetostat on Day 1 until 5 days after the last dose of fluconazole.

9.3.3 Part B

- Administration of repaglinide or omeprazole other than as part of this study is prohibited for 7 days prior to administration of the first study dose until the last PK blood sample is collected on Day 19.
- Treatment with strong or moderate inhibitors or inducers of CYP2C8 or CYP2C19 (including Ginkgo biloba and common sage) is prohibited within 7 days prior to first dose of study treatment until after the final PK blood sample is collected on Day 19. Medications that are strong or moderate inhibitors or inducers of CYP2C8 or CYP2C19 include, but are not limited to, those listed in Table 9.
- Treatment with other oral hypoglycemic medications is prohibited from 7 days prior to the first dose of study medication until after the final PK blood sample is collected on Day 19.
- Treatment with medications that increase gastric pH, other than omeprazole as part of this study, is prohibited from 7 days prior to the first dose of study medication until after the final PK blood sample is collected on Day 19.
- Concomitant administration of clopidogrel and omeprazole should be avoided.

Table 9: Classification of Medications That Are Inhibitors or Inducers of CYP Enzymes

CYP Enzyme	Strong Inhibitors	Moderate Inhibitors	Strong Inducers	Moderate Inducers
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil	Avasimibe, barbiturates, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin
CYP2C8	Gemfibrozil			Rifampin
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone		Carbamazepine, rifampin
CYP2C19	Fluconazole, fluvoxamine, ticlopidine	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole		Rifampin
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine		
Transporter	**Inhibitors**		**Inducers**	
Pgp	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, verapamil		Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir	

NOTE: The list of medications in Table 9 is not exhaustive. A listing of CYP inhibitors, inducers, and substrates can be found using the following links:

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

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

9.4. Non-Drug Therapies

Radiation Therapy: Palliative radiation therapy will be permitted for pain or severe symptom control after discussion with the medical monitor.

10. WITHDRAWAL AND REPLACEMENT OF SUBJECTS

10.1. Withdrawal from Treatment

The investigator or sponsor may withdraw the subject at any time in the interest of subject safety. Additionally, a subject is free to withdraw from treatment at any time for any reason without prejudice to future medical care by the physician or at the institution. When the subject withdraws from treatment, the reason for the withdrawal and date of last dose of tazemetostat (as well as the total treatment period) must be recorded in the eCRF and source documents. Similarly, if a subject has died on study, the cause and date of death must be reported as well.

10.1.1 Withdrawal of Subjects from Study

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

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

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

10.2. Survival Follow-Up

Subjects who permanently discontinue study treatment will be followed (by phone, email, or clinic visit) for survival every 12 weeks until death, withdrawal of consent, or lost to follow-up. Subjects will be followed for up to 2 years.

Subjects who are continuing on study treatment and have received 6 months of treatment on the current study will be followed and treated on Study EZH-501.

10.3. Subsequent Therapy After Discontinuation of Study Treatment

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

10.4. Evaluation of Response to Subsequent Anti-Cancer Therapy

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

10.5. Replacement of Subjects

For both parts of the study, subjects who require a dose reduction of tazemetostat during the first 19 days of treatment will be replaced. Subjects who miss 2 or more consecutive tazemetostat doses during the first 19 days of treatment or miss more than 3 tazemetostat doses during the first 19 days of treatment may be replaced. Subjects who miss 2 or more PK blood sample collections may be replaced.

11. SAFETY

11.1. Safety Monitoring

11.2. Adverse Event Definition

11.2.1 Adverse Events

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

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

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

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or signs or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

11.2.2 Serious Adverse Events

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

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

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions (in subjects without pre-existing seizure disorder) that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3. Laboratory Abnormalities

A clinical laboratory AE is any laboratory value that is considered clinically significant by the investigator and has caused a medical intervention or is accompanied by clinical symptoms. Laboratory abnormalities that have not required medical intervention should not be recorded as

AEs and will be captured and reported in the laboratory section of the clinical study report (CSR). If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (e.g., anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded on concomitant medications).

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

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

11.4. Other Safety Assessment Abnormalities

Other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline and events in the medical and scientific judgment of the investigator are considered to be clinically significant, are to be recorded as an AE or SAE, in accordance with the definitions provided in Sections 11.2.1 and 11.2.2, respectively.

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

Events that meet the criteria for serious but are thought to be associated with progression of disease under study should be reported as SAEs but will not typically processed as an expedited report to regulatory authorities.

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

11.5. Adverse Events of Special Interest (AESIs)

11.5.1 T-LBL/T-ALL

Lymphoblastic lymphomas are considered thymus derived malignancies that have not yet completed T-cell maturations. Approximately 90% of lymphoblastic lymphomas are the T-cell phenotype and typically occur in young adults and adolescents, accounting for 29% of pediatric and 2% of adult NHL with a median age at diagnosis of 25 years (Lai, 2013; Cortelazzo, 2017;

Lones, 2007). T-LBL is morphologically and immunophenotypically indistinct from T-ALL, with both diseases arising from precursor lymphoid cells of the T-cell lineage (Portell, 2012; Patel, 2014). Despite the similarities of the two diseases, significant yet unknown characteristics lead to differences in clinical presentations (Burkhardt, 2009). Initial clinical manifestation of both adult and pediatric T-LBL includes a mediastinal mass or lymphadenopathy with <25% bone marrow blasts. Adult T-LBL patients tend to have less thymic disease and greater lymph node disease and bone marrow involvement (Baleydier, 2008; Swerdlow, 2008; Campo, 2011). In contrast, T-ALL cases predominantly present with bone marrow and peripheral blood disease, and >25% bone marrow blasts (Swerdlow, 2008; Campo, 2011).

On 06 April 2018 an event of T-LBL was observed in a subject on study EZH-102. This event was reported to regulatory authorities as a 7-day SUSAR on 13 April 2018 (Case number 2018USEPZ64380299).

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

- Review of literature and available preclinical/clinical data to better understand event of 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 (PK) at various doses tested, benefit-risk across tumor types in adults and children.
- Consultation with well recognized external experts in T-cell lymphoma 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 patients 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 patients based on 1) higher $AUC_{0\text{-}24h}$ exposures in pediatric patients and 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, over 702 adults have been treated with tazemetostat with no observed cased of T-LBL/ALL.

T-LBL Case

The event of T-LBL in a 9-year-old (at the time of enrollment) female subject diagnosed with poorly differentiated chordoma occurred on Study Day 432 of treatment with tazemetostat 900 mg/m^2 BID. At the time of the event of T-LBL, the subject was in complete response of her target lesions of the disease under study, yet due to presence of 1 of 2 non-target lesion in her lung (1 lesion disappeared), was considered overall as a partial responder. The first response was observed and measured at Day 54 on treatment. The steady-state $AUC_{0\text{-}24h}$ at Cycle 1 Day 15 in this subject was 18,784 ng•h/mL and is similar to the mean $AUC_{0\text{-}24h}$ at Cycle 1 Day 15 for the 900 mg/m^2 dose group overall (21,000 ng•h/mL, n=5). The study medication was discontinued and the subject withdrawn from the study due to the event.

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

The SUSAR of T-LBL resulted in the Sponsor initiating a temporary global halt in enrollment for the pediatric study EZH-102. In addition, this event led to a partial clinical hold (PCH) on new subject enrollment for tazemetostat by the U.S. (FDA), France (ANSM), and Germany (BfArM) across all studies of the Tazemetostat Development Program. For further details, see the Investigator's Brochure, version 8.0. In the event of suspicion of T-LBL/T-ALL or related concerns, please refer to Section 7.3 for evaluation and dose adjustments.

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

11.5.2 MDS/AML/MPN

As of the May 01 2018 data cut, 3 cases of MDS/AML/MPN have been reported. One case of MDS/MPN was in a subject with follicular lymphoma receiving 800 mg BID in the E7438-G000-101 study. The second case of MDS was reported in the EZH-501 rollover study in a subject with DLBCL treated with 800 mg BID tazemetostat. A third case, a non-serious AE of myelofibrosis was reported in a subject with follicular lymphoma receiving 800 mg BID Tazemetostat in E7438-G000-101. For all three cases, the causality assessment was confounded by the subject's prior treatment history or the presence of the disease before starting

tazemetostat. A summary of these 3 cases please refer to the Investigator's Brochure, Version 8.0. In the event of suspicion of these malignancies or related concerns, please refer to Section 6.5 for evaluation and dose adjustments. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any MDS/AML and other myeloid malignancies like MPN. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be held, and after discussion with the Investigator, tazemetostat will be modified or discontinued. All AESIs are to be reported on the eCRF whether or not they meet the criteria for an SAE.

11.5.3 Other Identified Risks

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

11.5.4 Tazemetostat Safety Committee

A safety monitoring committee composed of internal and external medical experts will review all AESI cases, including T-LBL/ALL, MDS/AML and other myeloid malignancies like MPN (both related and unrelated), and other solid tumor malignancies. Cases will be evaluated for suspected relationship to tazemetostat and adjudicated by the experts. Recommendations for next steps per the risk management plan will be communicated to the CMO.

11.6. Grading and Severity

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

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

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

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

ADL = Activities of Daily Living; AE = adverse event

a. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event (as in 'mild', 'moderate', or 'severe'); both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in Section 11.2.2 which are based on patient/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning

11.7. Relationship Categorization

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

11.7.1 Assessing Relationship to Study Treatment

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

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

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

- **Not Related:** A causal relationship between tazemetostat and the AE is not a reasonable possibility.
- **Related:** A causal relationship between tazemetostat and the AE is a reasonable possibility (includes probably, possibly, and definitely related).

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

11.8. Outcome Categorization

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

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

11.9. Timeframe for Reporting AEs and SAEs

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

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

After discontinuation of study treatment: The investigator will monitor all ongoing AEs/SAEs until resolution or stabilization of the event or until the subject is lost to follow-up. Up until 30 days after the last dose of study treatment or until the initiation of subsequent anti-cancer therapy, whichever is earlier, the investigator may report any AE that they consider to be possibly related to study treatment.

11.10. Reporting of SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IP under clinical investigation. The sponsor and its designee will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC/CEC and investigators.

Any AE that is both unexpected (not consistent with the applicable product information) and also meets the definition of a suspected unexpected serious adverse reaction (SUSAR). All SUSARs will be reported within 24 hours of the investigator becoming aware of the event. Investigator safety reports are prepared for SUSARs according to local regulatory requirements and the sponsor policy and are forwarded to investigators as necessary. The sponsor is legally obligated to report the event to the regulatory authorities within 7 days for fatal or life-threatening SUSARs or 15 days for all other SUSARs.

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

11.10.1 Regulatory Authorities, IRB/EC, and Central Ethics Committees (CEC)

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

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

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

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

12. DATA MANAGEMENT

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

12.1. Coding

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

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

13. STATISTICAL METHODS

13.1. Hypotheses

Results of this study will be descriptive and no hypothesis will be tested.

13.2. Study Design Considerations

13.2.1 Determination of Sample Size

The sample size was determined based on feasibility considerations. A total of 12 subjects per part is adequate to describe the effect of CYP3A inhibition on the PK of tazemetostat, the effect of tazemetostat on the PK of repaglinide and omeprazole, and the effect of medications that increase gastric pH on tazemetostat PK.

This study will provide a point estimate and associated 90% confidence intervals on the magnitude of the effect of the perpetrator drugs on the PK of the victim drugs. The default no effect boundary of 80 – 125% for the 90% confidence interval for an effect size will be used as a reference. This is equivalent to a hypothesis test with a null hypothesis that there is a nonzero effect and alternative of no effect. If the 90% confidence interval for any effect tested in this study falls completely within 80 – 125%, it will be concluded that no clinically significant differences are present. The operating characteristics of this hypothesis test depend on the underlying within-subject correlation of subsequent measurements of the same PK parameter. If subsequent measurements of tazemetostat AUC have a correlation of at least 0.885, this test is powered at 80% or higher (results from simulation assuming standard deviation of log AUC = 0.5149 from the pilot study). Assuming the null hypothesis of this test is assumed to be >±5% effect, the simulated alpha level is 0.006.

The precision in the confidence limits is difficult to succinctly characterize given the unknown intra-subject variability and the exponential transformation. The corresponding hypothesis test to the 90% CI has at least 93% power for the alternative of doubling (or halving) of the tazemetostat AUC, assuming within-subject correlation of at least 0.8.

13.2.2 Sample Size Re-Estimation

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

13.3. Data Analysis Considerations

13.3.1 Analysis Populations

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

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

The **Pharmacokinetic (PK) population** will include all subjects in the ITT population who have sufficient postdose samples collected to allow estimation of the PK parameters. The PK population will be used for PK summaries and analyses.

The Pharmacogenomic (PGx) population will include all subjects in the PK population from whom PGx results are available. The PGx population will be used for summary of PK parameters by presence or absence of polymorphic genetic markers.

13.3.2 Interim Analyses

Interim analyses will not be performed.

13.3.3 Key Elements of the Analysis Plan

The statistical analyses will be performed on log-transformed PK parameters. The log-transformed PK parameters will be analyzed by an analysis of variance (ANOVA). The ANOVA will use a mixed-effects model with treatment as a fixed effect and subject as a random effect. The anti-logs of the confidence limits of the 90% CI for the difference in the treatment means of the log-transformed data are a 90% CI for the ratio of geometric means between the test and reference treatment. The geometric least squares (adjusted) mean and associated 90% CI for the test treatment to reference treatment ratio of adjusted geometric means will be provided after transformation of the results from the log-transformed analysis back to the original scale.

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

13.3.3.1. Part A

Descriptive statistics will be calculated. Plasma concentrations of tazemetostat and its metabolites will be listed for each subject and summarized by treatment (tazemetostat alone and tazemetostat plus fluconazole) and time point. PK parameters will be listed for each subject and summarized by treatment (tazemetostat alone and tazemetostat plus fluconazole). Plasma concentrations of fluconazole will be listed for each subject and summarized by time point. PK parameters for fluconazole will be listed for each subject and summarized.

To evaluate the effect of fluconazole on the PK of tazemetostat, a 90% CI for the ratio of adjusted geometric means for the test treatment to the reference treatment for tazemetostat C_{max} and AUC will be calculated. Tazemetostat administered without fluconazole will be considered the reference treatment and tazemetostat administered in combination with fluconazole will be considered the test treatment.

13.3.3.2. Part B

Descriptive statistics will be calculated. Plasma concentrations of repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone will be listed for each subject and summarized by treatment (repaglinide and omeprazole; repaglinide and omeprazole plus steady-state tazemetostat) and time point. PK parameters will be listed for each subject and summarized by treatment (repaglinide and omeprazole; repaglinide and omeprazole plus steady-state tazemetostat). Plasma concentrations of tazemetostat will be listed for each subject and summarized by day (Day 16 and Day 19) and time point. PK parameters for tazemetostat will be listed for each subject and summarized by treatment (tazemetostat administered 1 h before repaglinide and omeprazole and tazemetostat administered after 4 days of omeprazole administration).

To evaluate the effect of tazemetostat on the PK of repaglinide and omeprazole, a 90% CI for the ratio of adjusted geometric means for the test treatment to the reference treatment for repaglinide and omeprazole C_{max} and AUC will be calculated. Repaglinide and omeprazole administered without tazemetostat will be considered the reference treatment. Repaglinide and omeprazole administered in combination with steady-state tazemetostat will be considered the test treatment.

To evaluate the effect of omeprazole on the PK of tazemetostat, a 90% CI for the ratio of adjusted geometric means for the test treatment to the reference treatment for tazemetostat C_{max} and AUC will be calculated. Tazemetostat administered 1 hour before repaglinide and

omeprazole on Day 16 will be considered the reference treatment. Tazemetostat administered after 4 days of omeprazole administration (Day 19) will be considered the test treatment

13.4. Pharmacogenomic Analyses (PGx)

Subjects who consent to PGx research will be genotyped for polymorphisms on genes for CYP enzymes. PGx parameters will be summarized by treatment and the presence or absence of polymorphic genetic markers.

13.5. Efficacy Analyses

Overall response rate is defined as the percentage of subjects achieving a CR or PR from the start of treatment until disease progression or the start of subsequent anti-cancer therapy, as per Lugano Classification [Cheson 2014] for subjects with lymphoma or RECIST v1.1 [Eisenhauer] for subjects with solid tumors. Subjects evaluated with RECIST require confirmation of CR or PR at least 28 days from the initial response assessment. Subjects with an unknown or missing response will be treated as non-responders, i.e., they will be included in the denominator when calculating the percentage. An exact 90% CI for the overall response rate will be provided.

Response duration, for the subset of subjects with CR or PR response, is defined as the interval of time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, using disease-appropriate standardized response criteria.

The duration of response (DOR) will be calculated for each subject with a CR or PR (lymphoma) or confirmed CR or PR (solid tumors). A listing of DOR will be provided.

Disease control rate (DCR) is defined as the percentage of subjects achieving CR or PR, or SD lasting 24 weeks since start of treatment until disease progression or the start of subsequent anti-cancer therapy. The DCR will be summarized in a similar manner as overall response rate and duration.

Overall survival (OS) is defined as the interval of time between the date of the first dose of tazemetostat and the date of death due to any cause. For subjects surviving at the time of the OS analysis, the time of death will be censored at the date of last contact. OS will be calculated using the Kaplan-Meier method. If there are a sufficient number of deaths at the time of the analysis, median OS, first and third quartiles, and 90% CI (Brookmeyer-Crowley method) will be summarized. A figure and listing of OS will also be provided.

Summaries will be presented by study part and overall. Data on disease status in subjects enrolled in this study will be listed.

13.6. Safety Analyses

13.6.1 Extent of Exposure

The data on exposure to tazemetostat will be listed. Details pertaining to dose interruption or dose modification will also be listed.

13.6.2 Adverse Events

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

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

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

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

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

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

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

Listings will be provided for the following:

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

13.6.3 Clinical Laboratory Evaluation

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

Complete blood counts, serum chemistries and coagulation will be summarized at each planned visit assessment, and for change from baseline using descriptive statistics (mean, STD, median, minimum, and maximum). Categorical values will be summarized using number of observations and percentages (urinalysis assessment).

Low, normal, and high (LNH) classifications will be applied to determine whether the laboratory test value was below (L), within (N), or above (H) its reference range. Shifts from baseline in LNH classification and clinically significant findings for each parameter will be summarized by study part and overall at each planned post-baseline visit. The summary will include the worst-case shift from baseline during the post-baseline period, which will include both planned (scheduled) and unscheduled visits after the first dose of study drug. Subjects with laboratory data outside the normal range will be flagged as “L” (Low) or “H” (High) in the data listing.

The worst-case shift from baseline in terms of the clinically significant findings in each laboratory test group will be summarized separately.

Unless otherwise specified, the denominator in percentage calculation at each visit will be based on the number of subjects with non-missing value at the specified visit.

13.6.4 Other Safety Measures

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

13.7. Pharmacokinetic Analyses

Plasma concentrations of all analytes will be determined by validated bioanalytical methods. Plasma concentrations of all analytes will be listed for each subject and summarized by study part, treatment, day, and nominal time. Standard summary statistics will be calculated (i.e., arithmetic mean, STD, median, minimum, and maximum) for each endpoint.

13.7.1 Plasma Pharmacokinetics

All PK parameters will be calculated with noncompartmental methods using actual times. The following PK parameters will be determined as data permit:

Part A: Plasma AUC_{0-8}, C_{max}, T_{max}, and $t_{1/2}$ for tazemetostat and tazemetostat metabolites on Day 15 and Day 19. Plasma AUC_{0-12} will be calculated for tazemetostat only on Day 15 and Day 19. Plasma AUC_{0-8}, C_{max}, and T_{max} for fluconazole on Day 19.

Part B: Plasma AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$ of repaglinide and its metabolites, omeprazole, 5-OH-omeprazole, and omeprazole sulfone on Days 1 and 16. The metabolite to repaglinide ratio for $AUC_{0-\infty}$ and AUC_{0-t} after administration with omeprazole on Day 1 and after administration with omeprazole and tazemetostat on Day 16. The metabolite to repaglinide concentration ratio at 1, 2, 3, 5, and 7 hours after administration on Days 1 and 16. The 5-OH-omeprazole to omeprazole ratio for $AUC_{0-\infty}$ and AUC_{0-t} and the omeprazole sulfone to omeprazole ratio for $AUC_{0-\infty}$ and AUC_{0-t} after administration with repaglinide on Day 1 and after administration with repaglinide and tazemetostat on Day 16. The 5-OH-omeprazole to omeprazole concentration ratio at 1, 2, 3, 5, and 7 hours after administration on Days 1 and 16. The omeprazole sulfone to omeprazole concentration ratio at 1, 2, 3, 5, and 7 hours after administration on Days 1 and 16. Plasma AUC_{0-8}, AUC_{0-t}, C_{max}, T_{max}, and $t_{1/2}$ of tazemetostat on Days 16 and 19.

Plasma AUC_{0-8}, C_{max}, T_{max}, and $t_{1/2}$ for tazemetostat and tazemetostat metabolites on Day 16 and Day 19. Plasma AUC_{0-12} will be calculated for tazemetostat only on Day 16 and Day 19.

14. STUDY CONDUCT CONSIDERATIONS

14.1. Posting of Information on Publicly Available Clinical Trial Registers

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

14.2. Regulatory and Ethical Considerations

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

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

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

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

14.2.1 Institutional Review Board (IRB)/ Ethics Committee (EC)/Central Ethics Committee (CEC)

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

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

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

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

14.2.2 Informed Consent Process

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

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

14.3. Subject Confidentiality and Access to Source Documents/Data

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

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

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

14.4. Study Monitoring

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

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

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

14.5. Protocol Deviations

The clinical sites will adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the clinic. All such deviations will be documented in the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the CSR. Investigative sites will contact the medical monitor to request clarifications regarding any aspect of the clinical study or eligibility of subjects.

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

14.6. Protocol Amendment

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

14.7. Suspension or Termination of Study

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

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

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

15. ADMINISTRATIVE PROCEDURES

15.1. Recording and Access and to Study Records

As described in the ICH GCP Guidelines, 'essential documents', including eCRFs, source documents, consent forms, laboratory test results, and the IP inventory records, should be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor or its designee. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator must obtain written permission from the sponsor or its designee prior to the destruction of any study document.

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

15.2. Case Report Forms

eCRFs will be used for data collection for this study.

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

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

The eCRFs must be reviewed and electronically signed and dated by the investigator once all data has been entered and all queries resolved. Once the study monitor has verified the contents of the completed eCRFs against the source data, queries may be raised if the data are unclear or contradictory. The investigator must address all queries.

15.3. Quality Assurance and Quality Control

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

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

Initial site training will be provided by the sponsor or its designee. Training for new site staff will be provided by current study nurses and study coordinators under the supervision of the primary investigator. Additional training will be provided by the sponsor or its designee as needed.

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

15.4. Data Quality Assurance

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

15.5. Confidentiality

Data collected during this study may be used to support the development, registration, or marketing of tazemetostat. After a subject or his/her legal representative have consented to take part in the study their medical records and the data collected during the study will be reviewed by the sponsor and/or its designee. These records and data may be reviewed by the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the

sponsor may develop, register, or market tazemetostat; national or local regulatory authorities, and the IRB/EC/CEC(s) which gave its/their approval for this study to proceed.

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

15.6. Audit/Inspection

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

15.7. Record Retention

As applicable, study records will be maintained a minimum of 5 years beyond (1) the publication of any abstract or manuscript reporting the results of the protocol; (2) the submission of any sponsored research final report; or (3) submission of a final report to clinicaltrials.gov.

15.8. Provision of Study Results and Publication

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

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

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

16. REFERENCES

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

Arvey A, van der Veeken J, Samstein RM, Feng Y, Stamatoyannopoulos JA, Rudensky AY. Inflammation-induced repression of chromatin bound by the transcription factor Foxp3 in regulatory T cells. *Nat Immunol*. 2014;15(6):580-587.

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

Béguelin W, Popovic R, Teater M, Jiang Y, Bunting KL, Rosen M, et al., EZH2 is required for germinal center formation and somatic EZH2 mutations promote lymphoid transformation. Cancer Cell. 2013;23(5):677-692.

Bracken AP, Pasini D, Capra M, Prosperini E, Colli E, Helin K. EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *EMBO J.* 2003;22:5323-35.

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

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

Chan-Penebre E, Armstrong K, Drew A, Grassian AR, et al. Selective killing of SMARCA2- and SMARCA4-deficient small cell carcinoma of the ovary hypercalcemic type cells by inhibition of EZH2: *In vitro* and *in vivo* preclinical models. *Mol Cancer Ther, 2017; 16 (5);* 850-60.

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

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol. 2014;32:3059-3068

Comet I, Riising EM, Leblanc B, Helin K. Maintaining cell identity: PRC2-mediated regulation of transcription and cancer. *Nat Rev Cancer*, 2016 Sep 23. doi: 10.1038/nrc.216.83

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

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

DuPage M, Chopra G, Quiros J, Rosenthal WL, Morar MM, Holohan D, et al. The chromatin-modifying enzyme EZH2 is critical for the maintenance of regulatory T-cell identity after activation. *Immunity*. 2015;42(2):227-238.

Harbour JW, Onken MD, Roberson EDO, Duan S, et al. Frequent Mutation of BAP1 in Metastasizing Uveal Melanomas. *Science* 2010; 330 1410-3.

Houben GMP, Hooi J, Hameeteman W, Stockbrüggen. Twenty-four-hour intragastric acidity: 300 mg ranitidine b.d., 20 mg omeprazole o.m., 40 mg omeprazole o.m. vs. placebo. *Aliment Pharmacol Ther*. 1995;9:649-654

Jellinic P, Mueller JJ, Olvera N, Dao F, Scott SN, Shah R, et al., Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. *Nature Genetics* 2014;46:424-426.

Jiao Y, Pawlik TM, Anders RA, Selaru FM, et al. Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. *Nat Gen.* 2013; (45): 1470-3.

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

Kleer CG, Cao Q, Varambally S. et al. EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. *Proc Natl Acad Sci U.S.A*. 2003;100:11606-11.

Knutson SK, Wigle TJ, Warholic NM, Sneeringer CJ, Allain CJ, Klaus CR, et al. A selective inhibitor of EZH2 by EPZ-6438 leads to potent antitumor activity in EZH2-mutant non-Hodgkin lymphoma. *Mol Cancer Ther.* 2014;13(4):842-854.

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

Kuroki H, Hayashi H, Okabe H, Hashimoto D, Takamori H, Nakahara O, et al. (2014) EZH2 Is Associated with Malignant Behavior in Pancreatic IPMN via $p27^{Kip1}$Downregulation. PLoS ONE 9(8): e100904. https://doi.org/10.1371/journal.pone.0100904

LaFave LM, Beguelin W, Koche R, Teater M, Spitzer B, Chramiec A, et al. Loss of BAP1 function leads to EZH2-dependent transformation. *Nature Med*. 2015; 21: 1344-9.

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

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

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

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

Min J, Zaslavsky A, Fedele G, et al. An oncogene-tumor suppressor cascade drives metastatic prostate cancer by coordinately activating Ras and nuclear factor-kappaB. *Nat Med.* 2010;16:286-94.

Morin RD, Johnson NA, Severson TM, Mungall AJ, An J, Goya R, et al. Somatic mutations altering EZH2 (Try641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet*. 2010;42(2):181-185.

Oken MM, Creech RH, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American J of Clinical Oncology.* 1982;5:649-655.

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

Peña-Llopis S, Vega-Rubín-de-Celis S, Liao A, Leng N et al. BAP1 loss defines a new class of renal cell carcinoma. *Nat Gen.* 2012; 10;44(7):751-9.

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

Ramos P, Karnezis AN, Craig DW, Sekulic A, Russell ML, Hendricks WP, et al. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. *Nature Genetics* 2014;46:427--429.

Scott DW, Gascoyne RD. The tumour microenvironment in B-cell lymphomas. *Nat Rev Cancer*. 2014;14(8):517-534.

Smith TJ, Khatcheressian J, et al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. *Journal of Clinical Oncology*. 2006; 24 (19): 3187 – 3205.

Study E7438-G000-101: An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B cell Lymphomas.

Study E7438-PD001: Antitumor Activity of Tazemetostat in Xenograft Models of INI-1 Deficient Tumors.

Study EZH-501, Tazemetostat Rollover Study (TRuST): An Open-Label, Rollover Study.

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.

Takawa M, Masuda K, Kunizaki M, et al. Validation of the histone methyltransferase EZH2 as a therapeutic target for various types of human cancer and as a prognostic marker. *Cancer Sci* 2011;102:1298-305.

Testa JR, Cheung M, Pei K, Below JE, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet*. 2011;43:1022-5.

Tumes DJ, Onodera A, Suzuki A, Shinoda K, Endo Y, Iwamura C, et al. The polycomb protein EZH2 regulates differentiation and plasticity of CD4(+) T helper type 1 and type 2 cells. *Immunity*. 2013;39(5):819-832.

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

Witkowski L, Carrot-Zhang J, Albrecht S, Fahiminiya S, Hamel N, Tomiak E, et al. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. *Nature Genetics* 2014;46:438-443.

Wrangle J, Wang W, Koch A, Easwaran H, Mohammad HP, Vendetti F, et al. Alterations of immune response of non-small cell lung cancer with azacytidine. *Oncotarget*. 2013;4(11):2067-2069.

Yang XP, Jiang K, Hirahara K, Vahedi G, Afzali B, Sciume G, et al. EZH2 is crucial for both differentiation of regulatory T cells and T effector cell expansion. Sci Rep. 2015;5:10643.

APPENDIX 1: LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT

Revised Criteria for Response Assessment		
Response and Site	**PET-CT-Based Response**	**CT-Based Response**
Complete	**Complete metabolic response**	**Complete radiologic response (all**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	> 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

Revised Criteria for Response Assessment		
Response and Site	**PET-CT-Based Response**	**CT-Based Response**
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following:**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/o	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by > 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of pre-existing nonmeasured lesions

Revised Criteria for Response Assessment		
Response and Site	**PET-CT-Based Response**	**CT-Based Response**
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1 = no uptake above background; 2 = uptake < mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

Abstracted from: Cheson BC, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol.* 2014; 3(32)27:3059-3067.

APPENDIX 2: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Tumor response assessments in this clinical trial will utilize Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the following 2009 article:

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

The modifications to RECIST 1.1 to be implemented in this trial are: 1) chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease, and 2) the minimum duration of stable disease (or non-CR/non-PD for subjects with nontarget lesions only) is 7 weeks following the date of first dose of study drug.

The Eisenhauer article, published in the European Journal of Cancer, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

APPENDIX 3: ECOG PERFORMANCE STATUS

Assessment of Eastern Cooperative Oncology Group (ECOG) performance status to evaluate daily living abilities is required at screening as well as routinely throughout the treatment and at treatment discontinuation.

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

Reference: Oken MM, Creech RH, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American J of Clinical Oncology.* 1982;5:649-655.

APPENDIX 4: NYHA FUNCTIONAL CLASSIFICATION SYSTEM

The New York Heart Association (NYHA) Functional Classification: Class I, II, III, or IV Heart Failure provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity.

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reference: The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.