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Epizyme, Inc

STATISTICAL ANALYSIS PLAN

An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphomas and Tazemetostat in Combination With Prednisolone in Subjects With Diffuse Large B Cell Lymphoma

Protocol E7438-G000-101

SAP Version:	Date of Statistical Analysis Plan:
Version 3.0	20 April 2022

SIGNATURE PAGE

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
^{18}FDG-PET	^{18}fluorodeoxyglucose-positron emission tomography
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
COO	Cell of origin
CR	Complete Response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLBCL	Diffuse Large B-Cell Lymphoma
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EZH2	Enhancer of zeste homolog 2

FL	Follicular Lymphoma
GCB	Germinal-Center B-cell-like
GELF	Groupe d'Etude des Lymphomas Folliculaires
HMT	Histone Methyl Transferase
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IRC	Independent Review Committee
ITT	Intent-to-Treat
IWG	International Work Group
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple gated acquisition
NHL	Non-Hodgkin Lymphoma
ORR	Objective Response Rate
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PT	Preferred term
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's

	formula
PFS	Progression-free survival
PK	Pharmacokinetics
POD24	Progression or relapse within 24 months of diagnosis
PR	Partial Response
RP2D	Recommend Phase 2 Dose
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SI	Système International
SOC	System organ class

1 INTRODUCTION

The clinical study, E7438-G000-101, is a Phase 1/2, open-label, multicenter study of tazemetostat. The Phase 1 portion is comprised of dose escalation and expansion parts to establish the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) when tazemetostat is given twice daily (BID) orally on a continuous basis in subjects with histologically and/or cytologically confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in the Phase 1 portion of the study, which is completed, the effect of food on the bioavailability of tazemetostat was evaluated as well as the drug-drug interaction potential as evaluated by the effect of tazemetostat on the pharmacokinetics (PK) of midazolam, a cytochrome P450 (CYP) 3A4 substrate. Phase 2 enrolls subjects with Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL) for the determination of efficacy and safety of tazemetostat monotherapy and of tazemetostat in combination with prednisolone.

This statistical analysis plan (SAP) describes the planned analyses to be included in the Clinical Study Report for the Phase 2 portion of Protocol E7438-G000-101. The efficacy analyses described in Version 2.0 of this SAP were performed for the FL cohorts of WT and MT only for analyses submitted in December 2019. This version of the SAP adds efficacy analyses for the DLBCL cohorts.

This SAP is based on Amendment 13.0 of the protocol, dated 10 August 20121 Any changes made to the planned analyses after this document has been finalized will be noted in the final clinical study report. This SAP was written in accordance with International Council on Harmonisation (ICH) Guideline E9.

Analyses of the Phase 2 PK, pharmacodynamics, biomarker, and pharmacogenomics data will not be covered in this SAP.

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective

- For the Phase 2 portion of the study, the primary objective is to determine the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in subjects with enhancer of zeste homolog 2 (EZH2) gene mutation positive or negative (wild-type) with histologically confirmed DLBCL or FL with relapsed or refractory disease and the ORR of tazemetostat in combination with prednisolone in subjects with EZH2 wild-

type DLBCL. ORR will be assessed by the International Working Group-Non-Hodgkin's Lymphoma (IWG-NHL; Cheson 2007) criteria.

2.1.2 Secondary Objectives

For the Phase 2 portion of the study, the secondary objectives are as follows:

- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on progression-free survival (PFS) based on IWG-NHL (Cheson 2007) criteria
- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on duration of response (DOR) based on IWG-NHL (Cheson 2007) criteria
- To assess the safety and tolerability of tazemetostat monotherapy and tazemetostat in combination with prednisolone;
- To assess the PK profile of tazemetostat monotherapy and tazemetostat in combination with prednisolone (covered in a separate SAP).

2.1.3 Exploratory Objectives

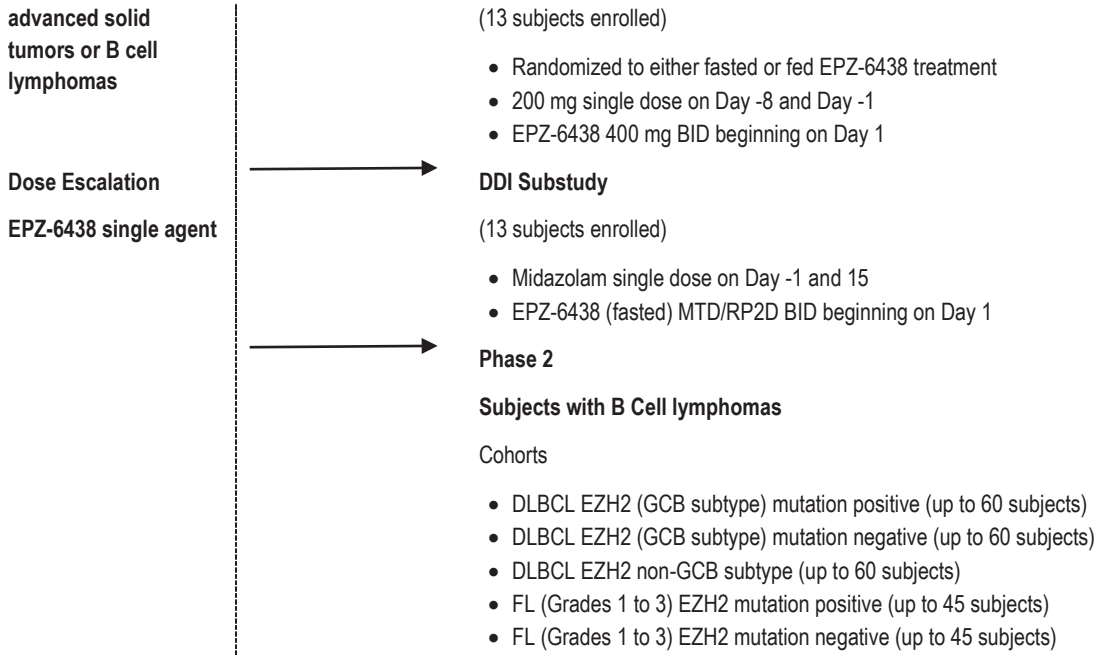
For the Phase 2 portion of the study, the exploratory objectives of the study are as follows:

- To explore the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on overall survival
- To explore the PK and pharmacodynamic relationship of tazemetostat (covered in a separate SAP)
- To identify and investigate biomarkers and their correlation with biological activity for tazemetostat (covered in a separate SAP)
- To explore the effects of tazemetostat on histone H3K27 methylation, target gene expression, and phenotypic markers including those for differentiation, apoptosis, cell proliferation, and changes in the tumor microenvironment (covered in a separate SAP)
- To explore the role of DNA sequence variability on absorption, metabolism, excretion and susceptibility to adverse events of tazemetostat (covered in a separate SAP)

2.2 STUDY DESIGN

The overall study design for both Phases 1 and 2 is displayed in Figure 1.

Figure 1 Schematic of the Study Design



Phase 2 of the study is an open-label, multicenter study of tazemetostat that enrolls subjects with DLBCL (Cohorts 1-3 and 6) and FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat monotherapy (Cohorts 1-5) and of tazemetostat in combination with prednisolone (Cohort 6) with placement determined by centrally confirmed histology, cell of origin, and EZH2 mutation status as shown below.

Table 1 Phase 2 Cohorts

Cohort	Treatment	Description	Planned Enrollment
1	Tazemetostat Monotherapy	DLBCL (GCB subtype) EZH2 mutation positive	60
2	Tazemetostat Monotherapy	DLBCL (GCB subtype) EZH2 wild-type	60
3	Tazemetostat Monotherapy	DLBCL non-GCB subtype	60
4	Tazemetostat Monotherapy	FL (Grades 1 to 3) EZH2 mutation positive	45
5	Tazemetostat Monotherapy	FL (Grades 1 to 3) EZH2 wild-type	45
6	Tazemetostat/Prednisolone Combination	DLBCL GCB or non-GCB subtype EZH2 wild-type	70

DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste- homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like

2.2.1 Number of Patients

Approximately 340 subjects were planned to be enrolled in the Phase 2 portion of the study with 60 subjects planned for each of the 3 DLBCL monotherapy cohorts, 45 for each of the 2 FL cohorts, and 70 for DLBCL combination therapy cohort.

2.2.2 Sample Size Determination

The original study design planned enrollment of up to 30 subjects enrolled in each monotherapy Cohort for Phase 2. The initial assessment of efficacy was to be conducted within each cohort when 10 subjects had been enrolled (stage 1). For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 30% and there is a 2.8% probability of observing no responders among 10 subjects. For each FL cohort, if 1 or zero responders (CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 40% and there is a 4.6% probability of

observing ≤ 1 responder among 10 subjects. Subsequent to the futility analysis in the DLBCL cohorts, the Data Monitoring Committee (DMC) supported a study design change to a modified 2-stage Green-Dahlberg design [Green, 1992] for each cohort.

Up to 70 subjects with DLBCL (GCB or non-GCB, EZH2 wild-type) was to be enrolled in an additional combination therapy cohort (tazemetostat and prednisolone). A 2-stage Green-Dahlberg design was used to terminate enrollment for futility.

For the purpose of calculating an expanded cohort size, a modified 2-stage Green-Dahlberg design was used where the stage 1 futility sample size was set to the original protocol design sample size of 10 subjects per cohort (for Cohorts 1-5) and the stage 1 rejection criteria was set to the original protocol defined rejection criteria (0 for the DLBCL cohorts and 1 for the FL cohorts). Final sample sizes are displayed in Table 2.

For the DLBCL Monotherapy Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.197.
- The probability of stopping under the alternative hypothesis is 0.028.

For the FL Monotherapy Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.376.
- The probability of stopping under the alternative hypothesis is 0.046.

A 2-stage Green-Dahlberg design was used to assess futility in the DLBCL combination therapy cohort. The stage 1 rejection criterion is 6 or fewer responders (CR + PR).

- The probability of early stopping under the null hypothesis is 0.433.
- The probability of stopping under the alternative hypothesis is 0.017.

Table 2 2-Stage Green Dahlberg Design

	Monotherapy					Combination therapy
	DLBCL GCB EZH2 Mutant	**DLBCL GCB EZH2 Wild-Type**	**DLBCL non-GCB**	**FL EZH2 Mutant**	**FL EZH2 Wild-Type**	**DLBCL EZH2 Wild-Type**
Ho: CR + PR	≤15%	≤15%	≤15%	≤20%	≤20%	≤20%
Ha: CR + PR	≥30%	≥30%	≥30%	≥40%	≥40%	≥35%
Stage 1						
n	10	10	10	10	10	35[a]
ORR events for declaring rejection of treatment	0	0	0	≤1	≤1	≤6
Stage 2						
Total n	60	60	60	45	45	70
ORR events for declaring rejection of treatment at end of Stage 2	≤14	≤14	≤14	≤13	≤13	≤19

CR = complete response, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like, Ha = Alternative Hypothesis, Ho = Null Hypothesis, n = sample size, PR = partial response
Note: Approximate alpha=0.025 and power =0.80

2.2.3 Randomization and Blinding Procedures

The Phase 2 portion of the study was not randomized and includes no blinding.

2.2.4 Data Monitoring Committee

An independent Phase 2 DMC performed futility analysis during three DMC meetings. The stopping boundaries detailed in Table 2 were utilized by the DMC to assess the futility of the study. Details governing the independent DMC review are covered in a separate Charter and DMC Reporting Plan.

2.2.5 Efficacy Assessments

Tumor assessments were performed based upon IWG-NHL (Cheson, 2007) criteria at each assessment time point and entered onto the appropriate CRF page. Investigator determined response assessments at each assessment time point were also entered onto the appropriate CRF page. Scans were performed according to guidelines provided by the imaging core laboratory designated for this study. For the FL cohorts only, all tumor assessment scans were sent, as soon as they had been performed, to the imaging core laboratory for quality assessment and an Independent Review Committee (IRC) provided an independent response assessment.

During Screening:

Computed tomography (CT) scans of the chest, and CT or magnetic resonance imaging (MRI) scans of the brain, abdomen, pelvis, and other known sites of disease (as well as photographs of skin lesions that were to be followed as target and nontarget lesions), were performed at Screening. Standard of care scans performed within 28 days before Cycle 1 Day 1 using the protocol-specified parameters could have been used as screening assessments. An ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan was performed. A bone marrow biopsy (including IHC) was to be performed for all subjects with FL and if clinically indicated in subjects with DLBCL, if they were not performed within 42 days of Cycle 1 Day 1.

During the Treatment Phase:

CT scans of the chest, and CT or MRI of the brain (if clinically indicated), abdomen, pelvis, and other known sites of disease were to be performed every 8 weeks (starting from Cycle 1 Day 1 of continuous tazemetostat dosing), or sooner if clinically indicated. If local regulatory authorities mandate less frequent imaging, maximum frequency would be every 12 weeks. Tumor assessments was to be carried out every 8 weeks (or sooner, if clinically indicated) during treatment cycles in the Treatment Phase. For subjects who remain on study drug for 24 weeks or more, radiologic disease assessments were to be performed every 12 weeks. At the first indication of

possible PR and CR, a whole body ^{18}FDG-PET scan was to be performed. At the first indication of CR, a repeat bone marrow biopsy was to be performed if lymphoma involvement in the bone marrow was reported at Screening. Repeat bone marrow biopsies were to be performed if clinically indicated (if progressive disease or relapse is suspected).

After the treatment phase, subjects were to be followed for overall survival every 12 weeks unless they withdraw consent.

2.2.6 Safety Assessments

Safety assessments consisted of monitoring and recording all AEs, regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, echocardiograms/ multiple gated acquisition (MUGA) scans, electrocardiograms (ECGs), and physical examinations.

For details, refer to the Schedule of Visits and Procedures in appendix 1.

2.2.6.1 Laboratory Measurements

For the Phase 2 part of the study, clinical laboratory tests were performed locally. Blood samples were to be collected for clinical laboratory tests at Screening, Day 1 and 15 of every cycle, and the End of Treatment visit. All hematology, blood chemistry (including pregnancy test, where applicable) samples were to be obtained before study drug administration and results reviewed before administration/dispensing of study drug at the beginning of each cycle. If a laboratory abnormality met the criteria to qualify as an AE as described in the protocol and the CRF Completion guidelines, the AE corresponding to the laboratory abnormality was to be recorded on the AE CRF page.

2.2.6.2 Vital Signs and Weight Measurements

Vital signs and body weight (kg) were to be collected at Screening, Day 1 and 15 of Cycles 1 and 2, Day 1 of every cycle starting with Cycle 3, and the End of Treatment visit. Vital sign measurements included systolic and diastolic blood pressure (BP, mmHg), heart rate (HR, beats per minute), and body temperature (°C). Height was to be measured at the Screening visit only. Blood pressure and HR were to be collected after subjects have been sitting for 5 minutes.

2.2.6.3 ECOG Performance Status

An Eastern Cooperative Oncology Group (ECOG) performance status was to be done at Screening, Day 1 of every cycle, and the End of Treatment visit.

2.2.6.4 Physical Examinations

Comprehensive physical examinations were to be performed at Screening and the End of Treatment visit, and symptomatic physical examinations were to be performed on Day 1 and 15 of Cycles 1 and 2 and Day 1 of every cycle starting with Cycle 3. Documentation of the physical examination was to be included in the source documentation at the investigational site. Only changes from screening physical examination findings that meet the definition of an AE were to be recorded on the AE CRF.

2.2.6.5 Electrocardiograms

Electrocardiograms were to be complete, standardized, 12-lead recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format at Screening, Day 1 of every cycle, and the End of Treatment visit. In addition to a rhythm strip, a minimum of 3 full complexes were to be recorded from each lead simultaneously. Subjects were to be in the recumbent position for a period of 5 minutes before the ECG.

If an ECG abnormality met the criteria to qualify as an AE as described in the study protocol and the CRF Completion guidelines, the AE corresponding to the ECG abnormality was to be recorded on the AE CRF page.

2.2.6.6 MUGA Scans and Echocardiograms

MUGA scan or an echocardiogram were to be performed at baseline and as clinically indicated.

2.2.7 Other Assessments

2.2.7.1 Pregnancy Test

A serum β-hCG test and/or urine β-hCG test was to be performed at Screening for all women of child bearing potential. A urine or serum pregnancy test was to be performed before the first tazemetostat dose and prior to dosing on Day 1 of each cycle.

2.2.7.2 Tumor Biopsy at Disease Progression

Tumor biopsy was requested, where medically feasible, at disease progression in subjects who achieved a PR or better with tazemetostat.

2.2.7.3 Bone Marrow Biopsy with IHC

A bone marrow biopsy (including IHC) was to be performed for all subjects with FL and in subjects with DLBCL if clinically indicated or if subject has a history of bone marrow involvement, if these have not been performed within 42 days (an approval is

needed from the Sponsor's medical monitor if the window has been beyond 42 days) of Cycle 1 Day 1. At the first notation of CR, a repeat bone marrow biopsy was to be performed if lymphoma involvement in the bone marrow was reported at Screening.

2.2.7.4 Peripheral Blood Smear/ Bone Marrow Biopsy

If peripheral blood smear morphology assessment was confirmed to be abnormal, the subject was required to undergo bone marrow aspirate/biopsy for cytogenetic/genetic testing to closely monitor the cytogenetic/genetic abnormalities known to be associated with MDS (9del 5q, chr 7, abn,etc.) and MPN (e.g. JAK2 V617F, etc.). If results were abnormal, treatment with tazemetostat was to be paused and after discussion with the Investigator, the dose was to be modified or the drug discontinued.

2.2.7.5 Optional Chest Ultrasound

An optional chest ultrasound could have been performed at screening and every 8 weeks at the Investigator's discretion to monitor for early signs of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia (T-LBL/T-ALL).

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher.

3.1.2 Reporting of Numerical Values

All clinical study data will be presented in patient data listings. Descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) will be calculated for continuous variables.

Frequencies and percentages will be presented by treatment group for categorical and ordinal variables. If there are missing values, the number and percent missing will be presented.

Time-to-event statistics will include the 25th percentile, median, and 75th percentile, provided they are estimable. Two-sided 95% CIs, will be estimated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982)

Means, medians, and confidence intervals will be reported to one decimal place more than the data reported on the CRF or by the laboratory/vendor. Standard deviation

will be reported to two decimal places more than the data reported. Minimum and maximum will be reported to the same number of decimal places as the data reported. P-values will be reported to 3 decimal places.

Start of study treatment will use the date of first dose of tazemetostat for cohorts 1-5 and the first dose of tazemetostat or prednisolone for cohort 6.

3.1.3 Study Day

Study Day will be calculated as follows:

- Assessment date ≥ first dose date: Study Day = (date – first dose date) + 1
- Assessment date < first dose date: Study Day = (date – first dose date)

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

3.1.4 Baseline Value and Change from Baseline

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

Change from baseline will be calculated by subtracting the baseline value from the post-dose value for each subject (i.e., post dose – baseline). Percent change from baseline will be calculated by dividing the change value by the baseline value and multiplying the result by 100% (i.e., [{post dose value – baseline} / baseline] x 100).

3.1.5 Analysis Visits

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

3.1.6 Handling of Missing/Incomplete Values

Unless otherwise explicitly specified, missing data will not be imputed; observed data will be used in the analyses.

3.1.7 Adjustments for Multiplicity

There will be no adjustments for multiplicity.

3.2 Analysis Populations and Subgroups

3.2.1 Definition of Analysis Populations

The Enrolled population will consist of all subjects who sign informed consent and were entered into the electronic case report form (eCRF) for the study and were not screen failed. The Enrolled population will be used for summaries of analysis populations, inclusion and exclusion protocol deviations.

The Intent-to-Treat (ITT) population will include all subjects who receive at least one dose of study treatment. The ITT population will be used for summarizing subject disposition, demographic and baseline characteristics and will be used for the efficacy analysis.

The Safety population will include all subjects who received at least one dose of study drug and have at least 1 post-baseline safety evaluation. The Safety population will be used for all safety analyses.

3.2.2 Definition of Subgroups

Refractory definitions.

Treatment refractory:

- No objective response to prior treatment or PD within 6 months of last dose of prior therapy

Rituximab refractory:

- No objective response to either rituximab monotherapy or rituximab-containing therapy (e.g., R-CHOP)

  OR

- Progressive disease (loss of CR/PR) within 6 months of completion of R-containing therapy.
    - Patient received at least 4 doses of rituximab for monotherapy or 5 cycles of R+chemo

Double refractory:

- No objective response to any rituximab-containing therapy (monotherapy or in combination with chemotherapy)

  AND

- Relapsed within 6 months or refractory to any alkylator-based chemotherapy

- These can be given at the same time. For example, a patient who was relapsed within 6 months or refractory to R-CHOP would be considered “double refractory”.

Early Relapse patients: (POD24)

- Defined as disease progression within 2 years of first-line treatment.
  - Defined from the start date of first line systemic therapy.

Where indicated, presentations of efficacy analyses for FL cohorts will be repeated for subgroups defined by the following parameters:

- Treatment refractory
- Rituximab refractory
- Double refractory
- POD24
- Age group (<65 or >= 65)
- Prior radiation (Yes or No)
- Tumor burden (bulky disease [i.e., tumor > 10 cm in longest diameter or more than 1/3 of chest (as checked by the Investigator on the eCRF)]) (Yes or No)
- Sex (Male or Female)
- Lines of prior therapy (<=2 or >2)
- Time from last prior anticancer therapy to first dose (≤ 1 month or > 1 month)
- Region: North America/Europe/Rest of the World
- GELF (Yes or No)

3.3 Efficacy Endpoints

3.3.1 Primary Efficacy Endpoint

- Objective response rate based on IWG-NHL

3.3.2 Secondary Efficacy Endpoints

- Duration of response based on IWG-NHL

- Progression-free survival based on IWG-NHL

3.3.3 Exploratory Efficacy Endpoints

- Overall survival
- Disease control rate
- Time to first response
- Time to first subsequent therapy

3.4 Safety Analyses

- Adverse events
- Laboratory test results
- Vital signs
- Physical exams
- Electrocardiograms
- MUGA scans and echocardiograms

3.5 Subject Disposition and Evaluability

3.5.1 Subject Disposition

Subject disposition, including reasons for treatment withdrawal and status at last contact, will be summarized and listed based on the ITT population. The number of subjects in each analysis population will be summarized based on the Enrolled population.

3.5.2 Major Protocol Deviations

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

- Violation of inclusion/exclusion criteria
- Prohibited medications, as defined in section 7.3.4.3 of the protocol, while on tazemetostat (inclusive of the first and last days of treatment)
- Failure to follow the radiological imaging procedures and schedule identified for the study which results in more than 1 unevaluable response assessment.

Additional categories may be added during the course of the study but will be determined prior to the database lock.

3.6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented for the ITT population by FL (WT, MT and overall), by DLBCL, and by combined DLBCL and FL.

3.6.1 Demographics

Descriptive statistics will be provided for age (years) at screening, along with percentages for <65 and >= 65 years. Frequencies and percentages will be tabulated for sex, race, ethnicity and region (North America/Europe/Rest of the World).

3.6.2 Baseline Characteristics

The following baseline disease characteristics will be summarized:

- ECOG status (0, 1, or 2)
- Location of primary tumor at diagnosis
- Sum of target lesion diameters at baseline
- Presence of lymph node target lesions at baseline (Yes, No)
- Presence of non-lymph node target lesions at baseline (Yes, No)
- Presence of non-target lesions at baseline (Yes, No)
- Bulky disease (yes or no)
- Any prior combination therapy (yes or no)
- Any prior monotherapy (yes or no)
- Number of prior therapies (categorical by 1, 2, >=3 and descriptive statistics)
- Refractory to rituximab chemotherapy regimen
- Refractory to last therapy (i.e., no objective response or PD after response within 6 months of completion of last therapy)
- Last therapy contains an alkylating agent and is refractory (i.e., no objective response or PD after response within 6 months of completion of therapy)
- POD24 status (yes or no)
- Double refractory status (yes or no)

- FL staging (stage I, II, III and IV)
- Myelosuppression (yes or no) (anemia, neutropenia or thrombocytopenia of grade ≥ 1 based on baseline laboratory data)
- Prior radiation
- Prior stem cell transplant, including type of transplant (a subject with both allogenic and autologous stem cell transplants will be categorized as allogenic)
- Groupe d'Etude des Lymphomas Folliculaires (GELF) criteria (yes or no) GELF is defined as meeting at least one of the following criteria:
    - A target lesion > 7 cm in diameter
    - 3 nodal target lesions > 3 cm diameter each
    - B symptoms at baseline
    - Serum LDH greater than normal
    - Hbg = 10 gm/dl or less
    - Neutrophil count 1500 /mm3 or less
    - Platelets 100,000 /microliter or less

For the calculation of progression date and last date of prior therapy for refractory definitions, partial progression dates and end of therapy dates will be imputed as July 1 of the year when only a year is recorded and as the 15th of the month when only a month and year are recorded. If this imputation yields a date of last progression after the informed consent date, then the partial date of last progression will be imputed as January 1 of the year when only a year is provided and the 1st of the month when only a month and year are provided. Other combinations of missing date elements will be treated as missing values.

3.7 Medical and Surgical History

All relevant medical history conditions will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 18.1) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). Medical history conditions will be tabulated by SOC and PT. Surgical history will be summarized by the MedDRA high-level group term (HLGT) and PT. Listings will include start date and stop date or notation of ongoing for conditions continuing into treatment.

3.8 Prior and Concomitant Medications

Medications will be coded using World Health Organization (WHO) Drug Dictionary (version March 2015). Medications will be summarized and listed by Anatomical Therapeutic Chemical (ATC) level 4 and PT for the ITT population.

3.8.1 Previous Anticancer Therapies

Previous anticancer therapy and radiotherapy will be summarized and listed for the ITT population. The summary for previous anticancer therapies will include:

- Number of regimens (1, 2, 3, 4, or more than 4 prior regimens)
- Therapy setting (Neoadjuvant, Adjuvant, Therapeutic for Advanced/Metastatic Disease, Consolidation, Maintenance, or Unknown); a subject may be counted in multiple categories
- Incidence of prior anticancer therapies by WHO Drug ATC level 4 and PT

The summary for the previous radiotherapy will include:

- Number of prior courses (0, 1, or 2 or more courses)
- Major sites of prior radiotherapy (subdivisions of those sites will be listed); A subject may be counted in multiple categories
- Progression at the site of the most recent radiotherapy (Yes, No, Not Evaluated)

The summary for prior hematopoietic stem cell transplantation will include:

- Incidence of prior hematopoietic stem cell transplantation
- Type of hematopoietic stem cell transplantation (autologous, allogenic)

3.8.2 Other Prior and Concomitant Medications

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

Prior and concomitant medications will be summarized and listed separately. Prohibited medications, as defined in Section 7.3.4.3 of the protocol, will be identified with a '*' in the listing.

Prior and concomitant medications will be defined as follows:

- Prior medications will include medications which started and stopped prior to the first dose of study drug.

- Concomitant medications will include medications taken any time from the start of the first dose of study drug through 30 days following end of study drug administration or until the start of a subsequent anticancer therapy, whichever is earlier. Medications that started prior to the first dose of study drug but continued into treatment are considered both concomitant and prior.

For partial start dates, assume the earliest possible date (i.e., missing day will be set to the first day of the month and missing month will be set to January). For partial end dates, assume the latest possible date (i.e., missing day will be set to the last day of the month and missing month will be set to December). A completely missing start date will be assumed to have started prior to the first dose, and a completely missing end date will be assumed to have ended after the first dose.

3.9 Study Drug Exposure and Compliance

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

3.9.1 Exposure to Study Treatment

The following summaries of study drug exposure will be presented:

- Duration of exposure (weeks) = [(last dose date of tazemetostat – first dose date of tazemetostat) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.
- Total number of cycles of study drug categorized as follows:
  - Cycle 1 (Days 1-28; weeks 1-4)
  - Cycle 2 (Days 29-56; weeks 5-8)
  - Cycle 3 (Days 57-84; weeks 9-12)
  - Cycle 4 (Days 85-112; weeks 13-16)
  - Cycle 5 (Days 113-140; weeks 17-20)
  - Cycle 6 (Days 141-168; weeks 21-24)
  - Cycle 7 (Days 169-196; weeks 25-28)
  - Cycle 8 or more (Day 197 and beyond; week 29 and beyond)
- Total amount of study drug taken (mg)

- Average dose intensity (mg BID/day) where the average dose intensity (mg BID/day) = total amount of study drug taken (mg) / [2 * duration of exposure (days)]
- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs).

Duration of exposure for prednisolone exposure (cohort 6) will be summarized similarly.

3.9.2 Study Drug Compliance

The following summaries of study drug compliance will be presented:

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

3.10 Efficacy Analyses

All efficacy analyses will be summarized by cohort and overall for the ITT population. The primary analysis of the primary and secondary endpoints will be performed using the IRC response assessments for the FL subjects. The investigator response assessments will be analyzed as supportive evidence for the FL subjects. For the DLBCL subjects, IRC assessments were not performed. The DLBCL results will be presented by cohort and overall in analyses based on the investigator response assessments, including best overall response, objective response rate, duration of response, progression-free survival, disease control rate, and time to first response.

The analyses of the primary and secondary efficacy endpoints by IRC will be repeated for the FL subjects for the subgroups defined in Section 3.2.2. The subgroup analysis will also be performed for the exploratory endpoint of overall survival. Subgroups for the investigator assessments for FL subjects will only be displayed in forest plots.

No statistical hypothesis testing for comparison between cohorts will be performed. The issue of statistical multiplicity will not apply to this study, therefore, all analyses will be conducted at the nominal 2-sided alpha 0.05 significance level.

3.10.1 Primary Efficacy Endpoint

Objective response rate (ORR; complete response or partial response [CR or PR]) will be summarized and listed for subjects - in the ITT population. Evaluation of response for the subjects will be based on IWG-NHL (Cheson, 2007) response criteria.

ORR is defined as the percentage of subjects achieving a CR or PR out of the total number of subjects included in the analysis population. The CR or PR must occur prior to PD and the start of any subsequent anticancer therapy. Subjects with not evaluable, unknown or missing best response will be handled as non-responders; i.e. they will be included in the denominator when calculating the ORR.

The summaries of ORR will include number and percentage of subjects in each best overall response (BOR) category: Complete response (CR), Partial response (PR), Stable disease (SD), Progressive disease (PD), and Not Evaluable, Missing, or Unknown.

ORR will also be presented with corresponding 2-sided Clopper–Pearson exact 95% confidence intervals (CIs) for each cohort and overall.

Waterfall plots of the best percentage change from baseline in sum of perpendicular diameters for target lesions for each subject will be provided by cohort using investigator and IRC reviews. Each plot will be color coded for best overall response.

Swim lane plots of subject response over time on treatment will also be provided by cohort using investigator and IRC reviews.

Forest plots will present the ORR and 95% CI by subgroups.

3.10.2 Secondary Efficacy Endpoints

3.10.2.1 Duration of Response

For each subject with a response, duration of response (DOR) is defined as the time (in months) from the date of first response (CR or PR, whichever is first recorded) to objectively documented disease progression or death whichever comes first. For patients with a response and no subsequent objectively documented disease progression or death, censoring rules for DOR will be same as for those PFS as detailed in Table 3. The number (%) of subjects with events and censored, as well the reason for censoring will be provided. DOR will be estimated using the Kaplan-Meier method. Median DOR, first and third quartiles and the associated 2-sided 95% CIs will be estimated using the Brookmeyer-Crowley method for each cohort and overall. Figures displaying Kaplan-Meier curves of DOR by cohort will be provided. Kaplan-Meier estimates and 95% CIs will be presented at 6, 12, and 18months. Forest

plots will present the median DOR and 95% CI by subgroups. In addition, the number and percentage of subjects with duration of response > 6, >12, and >18 months will be presented. A listing of DOR will be provided.

3.10.2.2 Progression-Free Survival

PFS is defined as the time from the date of first dose of study drug to the date of first documentation of disease progression, or death, whichever occurs first and will be presented. Subjects that do not die or progress on study will be censored at the last adequate assessment. Subjects who do not die on study and who do not have a baseline tumor assessment or at least one post-baseline tumor assessment will be censored at the first treatment day. Subjects who begin a new cancer therapy before documented progression will be censored at the date of the last adequate tumor assessment prior to the new cancer therapy, and subjects who progress or die immediately after one missed tumor assessment will be censored at the last adequate assessment prior to the missed assessment (See Table 3 for full details on PFS censoring). Then number (%) of subjects with events and censored, as well as the reason for censoring, will be provided. PFS will be estimated using the Kaplan-Meier method. Median PFS, first and third quartiles and the associated 2-sided 95% CIs will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982) for each cohort and overall. Figures displaying Kaplan-Meier curves of PFS by cohort will be provided. Kaplan-Meier estimates and 95% CIs will be presented at 6, 12, 18, and 24 months. Forest plots will present the median PFS and 95% CI by subgroups. A listing of PFS will also be provided.

Table 3 Assignments for Progression and Censoring Dates for DOR and PFS Analysis

Situation	Date of Event (PD/Death) or Censoring	Outcome: Event (PD/Death) or Censored
No *(or inadequate)* baseline tumor assessments and the subject has not died	Date of Study Day 1	Censored
No post-baseline assessments and the subject has not died	Date of Study Day 1	Censored
No post-baseline disease assessments and death occurred prior to the first planned assessment	Date of death	Event

Situation	Date of Event (PD/Death) or Censoring	Outcome: Event (PD/Death) or Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression (or death) and no new anticancer treatment documented	Date of last 'adequate' assessment of response[2]	Censored
New anticancer treatment started during study treatment and prior to documented disease progression or death).[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy	Censored
New anticancer treatment started after study treatment end and prior to documented disease progression or death).[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy	Censored
Death between two planned assessment visits	Date of death	Event
Death or progression after two missed visits (with 2 week window)	Date of last 'adequate' assessment of response[2] prior to missed assessments	Censored
Alive and without documented disease progression	Date of last 'adequate' assessment of response[2]	Censored
No documented disease progression or death and rolled over into Study 501	Date of last 'adequate' assessment of response[2]	Censored

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

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

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

3.10.3 Concordance

Concordance of the investigator and IRC assessments for BOR andORRwill be summarized by FL cohort and for all FL subjects.

3.10.4 Exploratory Efficacy Endpoints

3.10.4.1 Overall Survival (OS)

Overall survival is the duration (in months) measured from the date of first dose of study drug until the date of death from any cause. Subjects who do not die will be censored at the time of the last contact. The Kaplan-Meier estimate of the 25th percentile, median, and 75th percentile, of survival times will be presented with the corresponding 2-sided 95% CIs for each cohort and overall.

Figures displaying Kaplan-Meier curves of overall survival by cohort and overall will be provided.

The analyses for OS will be repeated for the subgroups defined in Section 3.2.2.

Forest plots will present the median OS time and 95% CI by subgroups.

3.10.4.2 Disease Control Rate (DCR)

DCR at the specified time point (month 12, month 18, and month 24) is defined as the percentage of subjects who achieve either confirmed CR or PR of any duration or who have SD lasting at least the number of months indicated from the start of study drug, according to the IWG-NHL (Cheson, 2007). Subjects with a best response of unknown/non-evaluable response will be handled as not achieving disease control, i.e., they will be included in the denominator when calculating the percentage. Subjects with a time point response of unknown/non-evaluable response on or before the specified time point will still be classified as having disease control as long as there is a response of CR, PR, or SD on or after the specified time point. Disease control rate will be analyzed and summarized in the same manner as ORR except that forest plots by subgroup will not be produced for DCR.

3.10.4.3 Time to First Response

For each subject with a response, the time to first response (months) is defined as time from the date of the first dose of study drug until the date of first response (CR or PR, whichever is first recorded). Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for time to first response.

3.10.4.4 Time to First Subsequent Therapy (TFST)

TFST is defined as the time from the date of first dose of study drug to the date of start of the first subsequent anticancer therapy and will be summarized only for patients who started subsequent anticancer. Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for TFST.

3.11 Safety Analysis

Safety analyses will be performed on the Safety population by FL (WT, MT and overall), by DLBCL (tazemetostat monotherapy, tazemetostat combination therapy, overall) and by combined FL and DLBCL.

3.11.1 Adverse Events

The AE verbatim description (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Adverse events will be coded to the MedDRA lower level term closest to the verbatim term, the associated preferred term (PT) and primary system organ class (SOC). AEs will be graded by severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A treatment-emergent AE (TEAE) is defined as an AE that:

- Emerges during treatment, having been absent at Baseline
- Reemerges during treatment, having been present at Baseline but stopped before treatment, or
- Worsens in severity during treatment relative to baseline, when the AE is continuous.

If there are missing or partial AE start and/or end dates that prevent the AE as being classified as a TEAE, the following imputation rules will be applied:

1. If partial start date imputed to earliest possible date (i.e., missing day set to the first day of the month and missing month set to January) is on or after first dose date, then classify as a TEAE.

2. If partial start date imputed to latest possible date (i.e., missing day set to the last day of the month and missing month set to December) is before first dose date, then classify as not a TEAE.
3. If partial stop date imputed to latest possible date (i.e., missing day set to the last day of the month and missing month set to December) is before first dose date, then classify as not a TEAE.
4. Otherwise, assume the event was a TEAE.

Only those AEs that are treatment-emergent and had a start date within the earlier of 30 days following study drug discontinuation or initiation of subsequent anticancer therapy will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

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

Investigator assessed causality to study drug will be categorized as "not related," "possibly related," or "probably related". For summary purposes, treatment-related TEAEs will include events with relationship to study drug classified as "possibly related" or "probably related". A TEAE with a missing causality will be classified as "possibly related" to study drug. A subject will be counted once at the strongest causality within a SOC and/or PT.

Deaths due to progressive disease were not to be recorded in the AE CRF page for the study. Thus, fatal AEs (i.e., Grade 5 events) will be not be included in TEAE summaries but will be summarized in the summary of deaths.

Events with a missing grade will not be summarized in "by grade" tables. In "by grade" tables, events will be summarized by Grade 3, Grade 4 and Grade 3 or 4. A subject will be counted once at the worst severity grade within a SOC and/or PT.

Adverse events of special interest (AESI) include T-LBL/T-ALL and MDS/AML/MPN and will be assessed by Sponsor pre-defined MedDRA PTs.

AEs will be summarized with a separate table for each of the following:

- TEAEs
- TEAEs of grade 3 or 4
- Treatment-related TEAEs

- Treatment-related TEAEs of grade 3 or 4
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from study
- Serious adverse events (SAEs)
- Treatment-related SAEs
- AESIs

Deaths

- Summary and listing of subjects who died ≤30 days after last dose of study drug, by cause as follows:
  - Any AE (by MedDRA preferred Term)
  - Any treatment related TEAE
  - Progressive Disease
  - Disease under Study
  - Unknown/Other causes
- Summary and listing of subjects who died ≤ 30 days after last dose of study drug with treatment-related TEAEs
- Summary and listing of subjects who died > 30 days after the last dose of study drug with treatment-related AEs

Listings of all AEs, SAEs, AESIs, and TEAEs leading to discontinuation of study drug.

3.11.2 Clinical Laboratory Evaluation

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each post baseline visit and to the end of treatment (defined as the last on-

treatment value) will be summarized by visit using descriptive statistics. The summaries will include all laboratory parameters included in Table 4.

In addition, creatinine clearance will be calculated by the Cockcroft-Gault formula. For males the creatinine clearance in mL/min will be calculated as (140-age) × weight (kg)/[serum creatinine (mg/dL) × 72]. For females, the creatinine clearance in mL/min will be calculated as 0.85 × (140-age) × weight (kg)/[serum creatinine (mg/dL) × 72].

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

- For parameters graded by NCI CTCAE, shift from baseline grade to worst post-baseline grade based on NCI CTCAE v4.03). For laboratory tests with both low and high values, summaries will be provided separately.
- For parameters not graded by NCI CTCAE, shift from baseline to worst post-baseline value that is < 0.25 x LLN or > 2.5 x ULN.

For subjects with a post-baseline parameter that is grade 3 or higher (per NCI CTCAE), all values for that parameter will be listed. Similarly, for parameters not gradable by NCI CTCAE for subjects with a post-baseline parameter value that is < 0.25 x LLN or > 2.5 x ULN, all values for that parameter will be listed.

The number of subjects with potential Hy's Law cases will be summarized, and all chemistry laboratory results will be summarized for any subjects meeting the criteria. Potential Hy's Law cases require a concurrent ALT or AST ≥ 3 × ULN, total bilirubin ≥ 2 × ULN, and ALP < 2 × ULN. To count as concurrent, each of the laboratory parameters must be drawn within +/- 3 days.

Table 4 Laboratory Parameters

Category	Parameter
Hematology	• Hematocrit • Hemoglobin • Red blood cell count (RBC) • Platelet count • White blood cell count (WBC) • Differentials (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	• Bicarbonate

	• Chloride • Potassium • Sodium
Liver Function	• Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Total bilirubin
Renal Function	• Blood urea or blood urea nitrogen (BUN) • Creatinine
Other	• Albumin • Amylase • Calcium • Cholesterol • Creatine phosphokinase (CPK) • Glucose • International Normalized Ratio (INR) • Lactate dehydrogenase (LDH) • Phosphorous • Total protein • Triglycerides • Uric acid

3.11.3 Vital Signs and Other Physical Findings

Weight (kg) as well as vital signs for sitting systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), sitting heart rate (bpm), sitting respiratory rate (breaths/min), and temperature (^{0}C) will be collected and listed. Summaries of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be based on markedly abnormal criteria defined below:

Table 5 Marked Abnormal Vital Signs Criteria

Vital Sign	**Markedly Abnormal Criteria**
Heart rate (bpm)	< 60 bpm > 100 bpm
Temperature (^{0}C)	≤ 35 ^{0}C ≥ 38 ^{0}C
Systolic blood pressure (mmHg)	120-139 mmHg, inclusive (CTCAE grade 1) 140–159 mm Hg, inclusive (CTCAE grade 2)

	≥ 160 mmHg (CTCAE Grade 3)
Diastolic blood pressure (mmHg)	80–89 mmHg, inclusive (CTCAE grade 1) 90–99 mm Hg, inclusive (CTCAE grade 2) ≥ 100 mmHg (CTCAE grade 3)

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

3.11.4 ECG

Electrocardiogram assessments will be performed as specified in the Schedule of Assessments. Time-matched, central-read ECGs were performed to evaluate RR, PR, QRS, QT intervals, QTc, QTc Fridercia (QTcF), QTc Bazett (QTcB), and heart rate (HR) at various time points throughout the study. All 12-lead ECG data will be listed, and changes from baseline will be summarized using descriptive statistics. When triplicates are collected, the averages (as calculated by the central ECG vendor) will be used in the summaries. The number and percentage of subjects with abnormal ECG findings at each visit will be reported.

The following summaries will be provided for 12-lead ECG assessments listed above:

- Quantitative 12-lead ECG measurements: values and changes from baseline (and changes from pre dose) by planned visit
- Investigator overall interpretation of the ECG: counts and percentages of subjects for each category
- Quantitative 12-lead ECG: Shift from baseline to worst post-baseline in QTcF status categorized as markedly abnormal or not (defined in the table below)
- Quantitative 12-lead ECG measurements: Counts and percentages of subjects whose worst-case changes from baseline in QTcF measurements meet markedly abnormal criteria (described in the table below).

Table 6 Markedly Abnormal ECG Criteria

QTcF Measure	Markedly Abnormal Criteria

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

3.11.5 MUGA Scans and Echocardiograms

The results of MUGA scans and echocardiograms at baseline and post-baseline visits will be listed along with the type of assessment (MUGA or echocardiogram).

3.11.6 Concurrent Nonpharmacological Procedures and Palliative Radiotherapy

Concurrent nonpharmacological anticancer procedures noted during survival follow up and palliative radiotherapy will be summarized and listed.

The number and percentage of subjects with anticancer procedures noted during survival follow up and reason for the procedure (pre-existing condition, AE, or other) will be summarized. The incidence (number and percentage) of subjects undergoing each anticancer procedure will also be summarized by MedDRA HLGT and PT.

The number and percentage of subjects receiving concurrent palliative radiotherapy will be summarized overall and by site of palliative radiotherapy.

3.12 CHANGES TO ANALYSES FROM PROTOCOL

- The primary analysis of the primary and secondary efficacy endpoints is based on the data assessed by IRC, which was requested by regulatory agency. As a result, concordance analysis was added for BOR and ORR.
- TEAEs with a missing causality will be assumed to be “possibly related” to study drug.
- Time to first response analysis was added as an exploratory endpoint.
- Disease control rate added as an exploratory endpoint.
- Time to first subsequent therapy added as an exploratory endpoint.

- Section 7.6.1.4 of the protocol indicates that laboratory parameters will be summarized descriptively as actual value and change from baseline, as well as, shifts from baseline (based on low, normal, high categorization) at each visit. To allow for more focused presentation of values most likely to represent a safety concern, laboratory parameters will be summarized as shift from the baseline to the worst post-baseline severity (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] severity grades). When an NCI CTCAE category is undefined for a parameter, a multiple of the nearer normal limit will be used.
- The Full Analysis Set is relabeled as the Intent-to-Treat (ITT) population. Other analysis sets are relabeled as the corresponding populations.
- For vital signs, Section 7.6.1.4 of the protocol specifies summarizing the values and change from baseline for each vital sign by visit. The analysis of vital signs specified in the SAP will only present the number of subjects that have markedly abnormal vital signs as defined in Section 3.11.3 of the SAP.
- For ECGs, markedly abnormal definitions have been added to the SAP, and the number of subjects meeting the markedly abnormal criteria will be summarized.
- A summary of concurrent nonpharmacological anticancer procedures and palliative radiotherapy has been added to track other anticancer therapies given after the first dose of study drug for subjects.

4 References

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5 Appendix

Appendix 1 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	-28 to -1	1 (± 3days)	15 (± 3days)	1 (± 3days)	15[d] (± 3days)		
Procedures/Assessments							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Prior and concomitant medications	Throughout study						
Comprehensive physical examination	X					X	
Symptom directed physical exam		X	X	X			
Pregnancy test[e]	X	X		X			
Body weight	X	X	X	X		X	
Height	X						
Vital signs[f]	X	X	X	X		X	
ECOG performance status	X	X		X		X	
12-lead ECGs[g]	X	X		X		X	
Hematology	X	X	X	X		X	

Appendix 1 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	**-28 to -1**	**1 (± 3days)**	**15 (± 3days)**	**1 (± 3days)**	**15[d] (± 3days)**		
Procedures/Assessments							
Blood chemistry	X	X	X	X	X	X	
Genomic DNA[h]							
PK blood samples[i]		X[i]	X[i]				
PD blood samples[j]		X[j]	X[j]				
PD blood sample for nucleic acid[k]		X		X		X	
Sufficient tumor tissue available[l]	X						
Paired tumor biopsies[m]		X					
Optional tumor biopsy at DP[n]						X	
Tumor assessments: CT (MRI), and assessments of B symptoms[o]	X	Radiologic tumor assessments (IWG-NHL [Cheson 2007] criteria) **must be performed every 8 weeks during Cycles 2-6, and every 12 weeks starting at Cycle 7 and beyond**				X	X
CT or MRI of the brain[p]	Brain scans should be performed if clinically indicated.						
Bone marrow biopsy (with IHC)[q]	X	At first notation of CR if bone marrow involvement at Screening, and if clinically indicated (eg, suspicion of relapse or progressive disease)					
^{18}FDG-PET scan[r]	X	Performed at first notation of possible PR or CR					

Appendix 1 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	-28 to -1	1 (± 3days)	15 (± 3days)	1 (± 3days)	15[d] (± 3days)		
Procedures/Assessments							
AEs/SAEs	Throughout study						
EPZ-6438 administration[e]		Continuous 28-day cycle of EPZ-6438 twice daily. EPZ-6438 can be taken with or without food.					
Survival status and subsequent anticancer therapy						X	X

AE = adverse event, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, CR = complete response, CT = computed tomography, DLBCL = diffuse large B cell lymphoma, DNA = deoxyribonucleic acid, DP = disease progression, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EZH2 = enhancer of zeste homolog 2, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, FL = follicular lymphoma, HR = heart rate, IHC = immunohistochemistry, IWG-NHL = International Working Group-Non-Hodgkin's Lymphoma, MRI = magnetic resonance imaging, PD = pharmacodynamic, PK = pharmacokinetic, SAE = serious adverse event.

a. The Screening Period extends from Day -28 to Day -1, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment, however subjects must continue to meet eligibility criteria prior to first dose of tazemetostat on Cycle 1 Day 1. The screening assessments (except tumor assessment) must be performed within 28 days before the first dose of study drug. Tumor assessment must occur within 28 days for CT or MRI or photographs.

b. Off-treatment assessment may occur at time of treatment discontinuation (e.g., at the visit at which the decision to discontinue treatment occurs) or up to 30 days after the final dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone.

c. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Information on all anticancer therapies will be collected (the sponsor may choose to stop the collection of therapies after the first anticancer treatment following EPZ-6438). This may be done by telephone contact.

d. **Starting at Cycle 3, a Day 15 visit is not required**. On Day 15 of each cycle, subjects will have hematology and blood chemistry samples drawn at a local laboratory and telephone contact with the site to review AEs.

e. A serum pregnancy test (β-hCG) will be performed at Screening for all women of childbearing potential. A urine or serum pregnancy test will be performed predose on Day 1 of each cycle starting at Cycle 2.

f. Vital signs include BP, HR and body temperature. BP and HR will be collected after the subject has been sitting for 5 minutes.

g. 12-Lead ECGs will be collected at the following time points: Screening (triplicate), Cycles 1 and 2 Day 1 (predose and **0.5 – 2 hours post dose immediately before PK sample**), Day 1 of all subsequent cycles (before and after morning dose of study drug administration), and at the Off-Treatment Visit. In case of any alteration or if clinically necessary an echocardiogram and/or cardiac enzymes should be performed.

h. Genomic DNA samples will be collected predose at Screening. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

i. Blood samples for PK analysis will be collected in Cycle 1 on Day 1 at 0.5 to 2 hours and 3 to 6 hours and Day 15 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours; and Cycle 2 on Day 1 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of start of Cycle 2.

j. Blood samples for PD analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Days 1 and 15; and Predose (0 h) on Cycle 2 Day 1. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of the start of Cycle 2.

k. Blood samples for nucleic acid analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Day 1, and Day 1 of every other cycle, and at the off-treatment visit.

l. Subjects will have collection of archived, tumor-biopsy sections for central testing of EZH2 mutation status (all subjects) and confirmation of cell of origin for DLBCL subjects.

m. Paired tumor biopsies (DLBCL cohorts) and/or bone marrow biopsies (FL cohorts) are optional and may be obtained, with appropriate subject consent, from at least 4 to 6 subjects per cohort to examine tissue target inhibition, relevant PD biomarkers, and potential markers of response. Subjects should have the biopsy before administration of the first dose of EPZ-6438 and the second biopsy at the time of first disease assessment. If sufficient tumor exists from archival, this could be considered the predose sample.

n. Tumor biopsy is to be requested, where medically feasible, at disease progression in subjects who achieve a PR or better with EPZ-6438.

o. Tumor assessments include CT scan of the chest, CT or MRI of the neck, abdomen, pelvis, and other areas of known disease or newly suspected disease and should be performed between Day -28 and Day -14 and every 8 weeks, irrespective of treatment delays, during Cycles 1 to 6, and every 12 weeks during Cycle 7 and beyond. If local regulatory authorities mandate less frequent imaging, minimum frequency must be every 12 weeks. The same parameters as the screening scans should be used. A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed at each visit.

p. CT or MRI of the brain should be performed if clinically indicated.

q. A bone marrow biopsy (including IHC) will be performed between Day -28 and Day -4, unless there is a report of bone marrow negative for lymphoma involvement within 42 days before administration of the first dose of study drug. At the first notation of CR, a repeat bone marrow biopsy should be performed if lymphoma involvement in the bone marrow was reported at Screening.

r. ^{18}FDG-PET scan should be performed at Screening and at the first notation of possible PR or CR.

s. On visit days, subjects should not take study drug before evaluations are performed.