SET-101

A PHASE 1/1B, OPEN-LABEL MULTI-CENTER TWO-PART STUDY OF SETD2 INHIBITOR EZM0414 IN SUBJECTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

Protocol Amendment 3.0: 06 July 2022

Protocol Amendment 2.0: 10 February 2022

Protocol Amendment 1.0: 26 July 2021

Original Protocol: 18 June 2021

GCP Statement:	This study is to be performed in full compliance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Epizyme, Inc. (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Epizyme, Inc.

Sponsor's Authorized Officer:

DocuSigned by:
PPD

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Date

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INVESTIGATOR'S AGREEMENT

I have read the SET-101 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	
Document	**Date**
Amendment 3.0	**06 July 2022**
Amendment 2.0	10 February 2022
Amendment 1.0	26 July 2021
Original Protocol	18 June 2021

Amendment 3.0

This amendment is being made to:

- Added an optional step-down dose level in the dose escalation part of the study
- Clarify dose modifications for the three lowest dose levels
- Updates to refine the inclusion and exclusion criteria
- Clarify disease assessments for subjects with MM

In addition, minor editorial, and document formatting revisions (eg, deletion of repeated information in the same sections, addition of abbreviations to tabular footnotes, etc) were made. All changes are visible in the tracked version.

Details of Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale
Section 2 (Synopsis) Section 7.1 (Overall Study Design) Section 7.5.2 (Dose Reduction and Interruptions) Section 7.5.6 (Determination of Sample Size and Criteria for Early Stopping Due to Futility) Section 14.1 (Study Design) Section 14.4 (Statistical Analysis Groups) Section 14.6.1 (DLT Evaluation and MTD Determination)	Added an optional step-down dose level cohort in the dose escalation part of the study	To give the study design more flexibility to adapt based on subject safety.
Section 2 (Synopsis) Section 7.1 (Overall Study Design) Section 14.1 (Study Design)	Removed language regarding “back-filling” dose levels in the dose escalation part of the study	This amendment added an optional step-down dose level. Future dose levels may be added using protocol amendments.

Section # and Name	Description of Change	Brief Rationale
Section 2 (Synopsis) Section 8.1 (Subject Inclusion Criteria)	Removed previous inclusion criteria regarding tumor/bone marrow biopsies.	This information is provided in Section 12 (Translational Research Samples)
Section 2 (Synopsis) Section 8.2 (Subject Exclusion Criteria)	Removed previous exclusion criteria regarding Gilbert's syndrome and ASCT eligibility	This study plans to enroll subjects who meet all of the inclusion criteria and will not exclude subjects based solely on Gilbert's syndrome or ASCT eligibility
Section 2 (Synopsis) Section 8.2 (Subject Exclusion Criteria)	Changed the exclusion criterion from "clinically significant amyloidosis" to "systemic amyloidosis"	To provide a clearer definition of the exclusion criterion.
Section 7.5.2 (Dose Reduction and Interruptions)	Added dose modifications for the three lowest dose levels	To provide more details on how to modify EZM0414 in the event of a treatment-related adverse event
Section 2 (Synopsis) Section 14.9 (Efficacy Analyses)	Update efficacy endpoints to remove overall survival as an endpoint, define duration of response and disease control rate as endpoints, and change ORR to a primary efficacy endpoint.	Efficacy endpoints were updated to better reflect the objectives of this trial.

Details of Non-substantial Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale
Section 2 (Synopsis)	Administrative updates	Updates based on the current study timeline and plan.
Section 2 (Synopsis)	Changed the format of objectives and endpoints from a list to a table	For clarity and to align with Section 6
Section 2 (Synopsis) Section 6 (Trial Objectives and Purpose)	Clarify overall survival is not an endpoint in this study	This study is not designed to capture overall survival. This was previously included as an endpoint as an oversight.

Section # and Name	Description of Change	Brief Rationale
Section 2 (Synopsis) Section 7.1 (Overall Study Design)	Clarification on when safety, tolerability, PK and PD data, as available, will be reviewed.	Previous amendment was not clear that, in addition to the Safety Review Committee review needed before starting new dose levels, safety, tolerability, PK and PD data, as available, will be reviewed after 4 dose levels, after the 600 mg dose level, after the 900 mg dose level, and at the MTD dose level.
Section 2 (Synopsis)	Additional edits can be found in the redline.	Edits to align the synopsis and body text.
Section 7.1 (Overall Study Design)	Moved location of study schema	To present information on the study design in the same order used in the synopsis
Table 8 (Schedule of Assessments for Dose Escalation and Dose Expansion) Section 13.1.3 (Vital Signs) Section 13.1.7 (Electrocardiogram (ECG))	Clarify timing of vital signs and ECGs	To provide more details on the single assessments compared to the serial assessments of vital signs and ECGs.
Section 5.2.6.1 (Multiple Myeloma) Table 8 (Schedule of Assessments for Dose Escalation and Dose Expansion)	Clarified disease assessments for subjects with MM	To provide more details on when and how disease assessments will be conducted.

2. SYNOPSIS

Name of Sponsor/Company: Epizyme, Inc.

Name of Investigational Product: EZM0414

Name of Active Ingredient:
CCI [redacted]

Protocol Number: SET-101	**Country: USA**

Title of Study:
A Phase 1/1b, Open-label Multi-center Two-part Study of SETD2 Inhibitor EZM0414 in Subjects with Relapsed/refractory Multiple Myeloma and Relapsed/refractory Diffuse Large B Cell Lymphoma

Study center(s): Approximately 20 sites in the United States

Studied period (years):	**Phase of development:** 1/1b
Estimated date first patient enrolled: Q2, 2022 Estimated date last patient completed: Q4, 2024	

Objectives:

Objectives	Endpoints
Part 1: Phase 1 Dose Escalation Phase	
Primary	
• To evaluate the safety and maximum tolerated dose (MTD) of EZM0414 when administered as monotherapy in subjects with R/RMM and R/R DLBCL.	• Adverse event assessment according to Common Terminology Criteria for Adverse Events (CTCAE 5.0), physical examination, vital signs (blood pressure, heart rate, respiration rate, and body temperature), 12-lead ECG, clinical laboratory tests (hematology including coagulation profile, serum chemistries, and urinalysis), Eastern Cooperative Oncology Group (ECOG) performance status, concomitant medication monitoring, and dose limiting toxicities (DLT).
Exploratory	
• To investigate target engagement in samples collected before and during treatment with EZM0414. • To determine exploratory biomarkers such as histones and histone methylation, somatic mutations, DNA methylation, DNA alterations such as t(4;14) and others, protein levels, RNA expression, and immune cells in bone	• H3K36me3 in tumor/bone marrow biopsy and blood collected at baseline and during treatment. • Biomarkers such as histones and histone methylation, somatic mutations, DNA methylation and other DNA alterations such as t(4;14) and others, protein levels, RNA expression, immune cells in bone marrow aspirates, tumor biopsies, and blood samples.

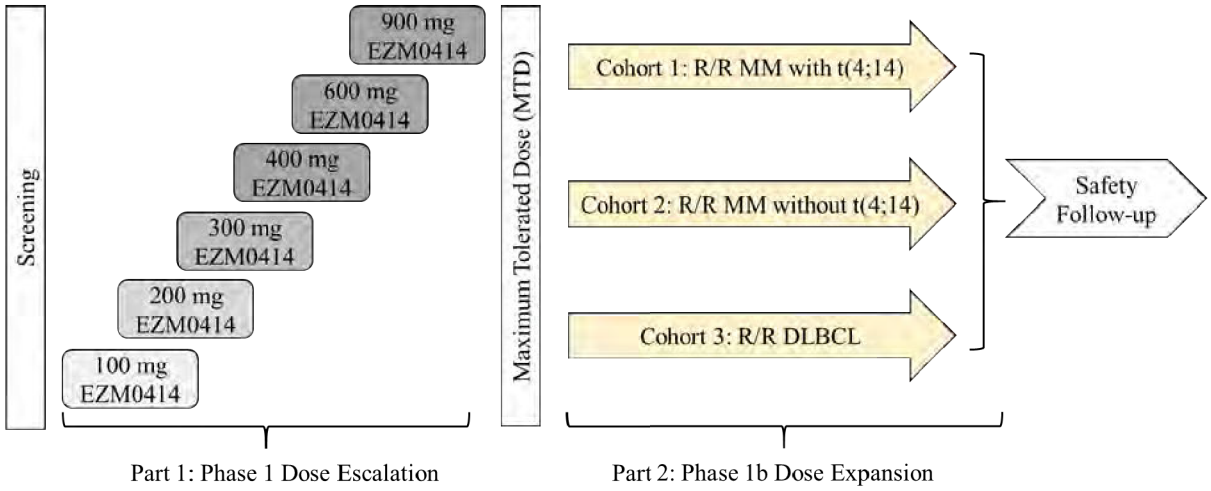
marrow aspirates, tumor/bone marrow biopsies, and blood samples. • To assess pharmacokinetics (PK) of EZM0414 when administered as monotherapy in subjects with R/R MM and R/R DLBCL.	• Pharmacokinetic parameters including but not limited to: AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}: observed maximum plasma concentration; T_{max}: observed time at C_{max}; λ_z: terminal phase elimination rate constant; $t_{1/2}$: terminal elimination half-life.
Part 2: Phase 1b Dose Expansion Phase	
Primary Safety	
• To determine the safety and tolerability of EZM0414 in subjects with R/R MM and R/R DLBCL.	• Adverse event assessment according to CTCAE 5.0, assessment of changes in physical examination, vital signs (blood pressure, heart rate, respiration rate, and body temperature), 12-lead ECG, clinical laboratory tests (hematology including coagulation profile, serum chemistries, and urinalysis), ECOG performance status, and concomitant medication monitoring.
• To establish the recommended Phase 2 dose (RP2D).	• Adverse events, clinical laboratory tests, and pharmacokinetic profile.
Primary Efficacy	
• To determine the efficacy of EZM0414 as demonstrated by the effect on ORR in subjects with R/R MM and R/R DLBCL.	• ORR defined as the proportion of responders as assessed by Investigator per IMWG 2016 guidelines for MM (sCR, CR, VGPR, and PR) or Lugano 2014 guidelines for DLBCL (CR+PR).
Secondary	
• To determine the efficacy of EZM0414 as demonstrated by the effect on ORR, PFS, and DOR in subjects with R/R MM and R/R DLBCL.	• PFS defined as the time from start of treatment until the first documented PD, as assessed by Investigator per IMWG 2016 guidelines for MM or Lugano 2014 guidelines for DLBCL or death due to any cause, whichever occurs first. • DCR defined as the proportion of subjects who have achieved confirmed CR, sCR, PR, VGPR, minimal response, or stable disease (SD) per IMWG 2016 Guidelines for MM or CR, PR, or SD per Lugano 2014 Guidelines for DLBCL since administration of EZM0414 in dose expansion part (including the cycle 1 observations of the subjects who receive EZM0414 at MTD in the dose

	escalation part and are rolled over to the dose expansion part). • DOR defined as the time from initial response to documented progression or death, whichever comes first, as assessed by Investigator per IMWG 2016 guidelines for MM or Lugano 2014 guidelines for DLBCL.
Exploratory	
• To determine H3K36me3 in tumor tissue biopsy and blood samples. • To determine exploratory biomarkers such as histones and histone methylation, somatic mutations, DNA methylation and other DNA alterations such as t(4;14) and others, protein levels, RNA expression, and immune cells in bone marrow aspirates, tumor/bone marrow biopsies, and blood samples. • To determine the pharmacokinetic profile of EZM0414.	• H3K36me3 in tumor/bone marrow biopsy and blood collected at baseline and during treatment. • Biomarkers such as histones and histone methylation, somatic mutations, DNA methylation and other DNA alterations such as t(4;14) and others, protein levels, RNA expression, immune cells in bone marrow aspirates, tumor biopsies, and blood samples. • Pharmacokinetic parameters including but not limited to: AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}: observed maximum plasma concentration; T_{max}: observed time at C_{max}; λ_z: terminal phase elimination rate constant; $t_{1/2}$: terminal elimination half-life, C_{max}/D: maximum observed concentration normalized to the dose; and AUC/D: AUC normalized to the dose.

Study Design:

This is a first-in-human (FIH), 2-part, multi-center, open-label Phase 1/1b safety, tolerability, PK, and efficacy study of oral SETD2 inhibitor, EZM0414, in subjects with R/R MM and R/R DLBCL. The first part of the study will be a Phase 1 dose-escalation designed to evaluate the safety, tolerability, and PK of EZM0414 in subjects with R/R MM and R/R DLBCL. Six dose levels starting at 100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg as well as an optional step-down dose level of 75 mg (if needed) will be tested. The second part of the study is the Phase 1b dose expansion at the MTD designed to evaluate safety and efficacy in subjects with R/R DLBCL and R/R MM with or without select genetic translocation. Dose expansion will enroll subjects in 3 cohorts: Cohort 1 for R/R MM subjects with t(4;14), Cohort 2 for R/R MM subjects without t(4;14), and Cohort 3 for subjects with R/R DLBCL.

Figure 1: Study Schema



NOTE: The subjects who are treated at MTD in Phase 1 dose escalation AND do not experience any DLT will be rolled over to Phase 1b dose expansion until disease progression, occurrence of unacceptable toxicity or withdrawal of consent.

Note: if needed, the Part 1: Phase 1 Dose Escalation may include an optional step-down dose level of 75 mg.
Abbreviations: DLBCL = diffuse large B cell lymphoma; DLT = dose limiting toxicities; MM = multiple myeloma; MTD = maximum tolerated dose; R/R = relapsed/refractory.

Methodology:

Part 1: Phase 1 Safety Dose Escalation

Part 1 is a safety dose escalation to determine the MTD for dose expansion in Part 2 of the study. Bayesian Optimal Interval (BOIN) design will be used to evaluate the safety and tolerability of EZM0414 in subjects with R/R MM and R/R DLBCL. Six dose levels starting at 100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg as well as an optional step-down dose level of 75 mg (if needed) will be tested in this dose escalation part of the study. Safety, tolerability, PK, and PD data will be reviewed, as available, initially after 4 planned dose levels (100 mg, 200 mg, 300 mg, and 400 mg) are evaluable, then again when the 600 mg dose level is evaluable, then again when the 900 mg dose level is evaluable, and lastly when the MTD is determined. Subjects will be enrolled and treated in groups of at least 3 subjects, and up to 36 subjects (at least 3 subjects each with t(4;14) MM, non-t(4;14) MM and DLBCL) will be enrolled in order to evaluate at least 9 subjects for MTD. Successive subjects within a given dose level will follow a staggered dose pattern with at least 48 hours between subjects. Additional daily dose levels and/or dosing schedules (including BID regimen) may be studied based on clinical safety, tolerability, and PK data obtained during this study.

All subjects will be treated with the study drug in cycles of 28 days and the DLTs that occur within the first cycle will be used to determine MTD. Progression to the next dose level will be based upon the dose escalation/de-escalation/elimination rules (See Section 14.1) and Safety Review Committee (SRC) review of the safety and PK data (if available) of the current dose group.

A screening visit will occur within 28 days of signing an informed consent form (ICF). In Cycle 1 (except Day 2 and Day 3), EZM0414 will be administered orally once daily (QD) without food (no food two hours prior and one hour after EZM0414 dose, water is permitted without restrictions) in continuous 28-day cycles. Subjects will continue to receive treatment at the assigned dose level until disease progression, occurrence of unacceptable toxicity, withdrawal of consent, or need for treatment prohibited on this study. No intra-patient dose escalation will be permitted. Dose limiting toxicities (as defined in Table 3) will be assessed during the first treatment cycle and dose modifications for EZM0414 are discussed in Table 4.

Safety assessments will be performed throughout the study and at each study visit. Vital signs including blood pressure, respiration rate, heart rate, and body temperature will be collected according to schedule of assessments (Table 8 and Table 9).

A single 12-lead ECG will be collected at screening and triplicate ECGs 1-minute apart will be collected at all other time points mentioned in Table 8 and Table 9. Subjects should be seated resting for 10 min prior to collection of all study ECGs.

Blood samples will be collected from all subjects for PK analyses at time points mentioned in Table 9.

At time points where vital signs, ECG and PK blood samples are required, the following order of collection is recommended (1) vital signs, (2) ECG (3) Blood sample for PK analyses and biomarker analyses.

Translational samples for research

Bone marrow aspirates and a bone marrow biopsy will be collected at screening or Cycle 1 Day 1 (pre-dose) in subjects with MM. For subjects with MM, a bone marrow biopsy and bone marrow aspirations will be performed on-treatment (Cycle 3 Day 1). In subjects with MM a bone marrow biopsy and bone marrow aspirates will be performed at VGPR. A non-mandatory bone marrow biopsy and bone marrow aspirates can be performed at progression in MM subjects. If a standard of care (SOC) bone marrow will be performed, a bone marrow aspiration will be requested for research in MM subjects. In subjects with DLBCL, archival tissue sample not older than 6 months will be collected. In DLBCL subjects with not enough archival tissue available, an optional fresh biopsy is recommended at screening or Cycle 1 Day 1 (pre-dose). An on-treatment biopsy (Cycle 3 Day 1) will be optional for subjects with DLBCL. An optional tumor biopsy will be taken in subjects with DLBCL at PR. A non-mandatory tumor biopsy at progression can be taken for subjects with DLBCL. Biopsies in patients with DLBCL will be optional and a separate ICF will be provided. Blood samples for exploratory analyses in MM and DLBCL subjects will be collected pre-dose at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1 and after that every other cycle until Cycle 26 and then every 4 Cycles after Cycle 26, at progression, and at any response event. In blood samples and tumor tissue/tumor cells DNA alterations such as mutations, copy number variation (CNV), and other DNA alterations will be assessed, RNA expression will be investigated in tumor tissue/tumor cells and/or blood samples as well as protein expression and methylation status. Different assays such as next-generation sequencing (NGS), fluorescent-in situ hybridization (FISH), immunohistochemistry, and others will be performed to investigate translational research samples.

Assessment of Safety

In the Phase 1 safety portion, a SRC will monitor safety data on an ongoing basis. All dose escalation decisions will be made by the SRC and Sponsor upon review of all available data. Determination of the MTD will be informed by all available data, including the overall tolerability of EZM0414.

Assessment of response

Assessment of response to treatment will be performed according to IMWG 2016 (Kumar, 2016; Appendix 1) consensus criteria in MM subjects and Lugano Classification (Cheson, 2014; Appendix 2) in DLBCL subjects.

In MM: IMWG 2016 consensus criteria that includes serum M-protein, 24-hour urine M-protein, serum free light chain kappa, lambda, and their ratio, bone marrow aspiration (CR) and bone marrow biopsy (sCR). Hence, subjects with MM would need to undergo a bone marrow biopsy or bone marrow aspiration for IMWG response assessment (Kumar, 2016; Appendix 1).

In DLBCL: International Working Group consensus response evaluation criteria in lymphoma, Lugano Classification (Cheson, 2014; Appendix 2). Hence subjects with a previously positive or unknown bone marrow biopsy at baseline would undergo a bone marrow biopsy in suspected CR.

Part 2: Phase 1b Safety and Efficacy Dose Expansion

In the dose expansion phase, Bayesian optimal phase 2 (BOP2) design will be used to evaluate safety and efficacy in subjects with or without select genetic translocation in R/R MM and R/R DLBCL.

In dose expansion part, 3 cohorts of subjects will be enrolled (20 subjects/cohort) and treated:

- Cohort 1: R/R MM with t(4;14)
- Cohort 2: R/R MM without t(4;14)
- Cohort 3: R/R DLBCL

During the treatment period, subjects will receive EZM0414 in continuous 28-day cycles. EZM0414 will be administered orally once daily (QD) without food (nothing to eat two hours prior and one hour after EZM0414 dose, water is permitted as needed). The subjects who receive EZM0414 at MTD and do not have DLT in the dose escalation part of the study will be rolled over to a cohort of this dose expansion part, depending on their condition (R/R MM or R/R DLBCL) and the select genetic translocation for R/R MM. All subjects will continue to receive treatment at the MTD in Phase 1b part until disease progression, occurrence of unacceptable toxicity, withdrawal of consent or need for treatment prohibited on this study. Subjects with R/R MM regardless of t(4;14) status will be enrolled first. Dose modifications for EZM0414 are discussed in Table 4.

Safety assessments will be performed throughout the study and at each study visit. Vital signs including blood pressure, heart rate, respiration rate, and body temperature will be collected according to schedule of assessments (Table 8 and Table 10).

A single 12-lead ECG will be collected at screening and triplicate ECGs, 1-minute apart will be collected at time points mentioned in Table 8 and Table 10.

Blood samples will be collected from all subjects for PK analyses at the time points mentioned in Table 10.

At time points where vital signs, ECG and PK blood samples are required, the following order of collection is recommended 1) vital signs, 2) ECG and 3) blood sample for PK analyses and biomarker analyses.

Assessment of response

Assessment of response to treatment will be performed according to IMWG 2016 consensus criteria (Kumar, 2016; Appendix 1) in MM subjects and Lugano Classification (Cheson, 2014; Appendix 2) in DLBCL subjects. To assess response according to IMWG 2016, subjects with MM will undergo bone marrow aspirates or biopsies to assess CR or stringent CR respectively. To assess complete response according to Lugano Classification, subjects with DLBCL might undergo a bone marrow biopsy. In MM subjects, treatment response will include serum M-protein, 24-hour urine M-protein, serum free light chain kappa, lambda, and their ratio. In DLBCL, imaging will be used to assess response.

Translational samples for research

Bone marrow aspirates and a bone marrow biopsy will be collected from all MM subjects at baseline (at screening or Cycle 1 Day 1 pre-dose), on-treatment (Cycle 3 Day 1) and at VGPR. A non-mandatory bone marrow biopsy and bone marrow aspirates will be taken for subjects with MM at disease progression. If a SOC bone marrow will be performed, a bone marrow aspiration will be requested for research in subjects with MM. In subjects with DLBCL, archival tissue sample not older than 6 months will be collected and if not available, an optional fresh biopsy will be performed at screening or Cycle 1 Day 1 (pre-dose). An optional on-treatment biopsy (Cycle 3 Day 1) and at PR will be performed in DLBCL subjects. Non-mandatory tumor biopsies in subjects with DLBCL at disease progression. All biopsies for subjects with DLBCL will be optional and a separate ICF will be provided. Blood samples will be collected predose at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, after that at every other cycle until Cycle 26 and then every 4 cycles after Cycle 26, at

progression, and at any response event. The translational research samples will be investigated for clones harboring t(4;14) translocation, somatic mutations such as SETD2 or multiple myeloma SET domain (MMSET), expression of H3K36me2, and H3K36me3. Other markers and analysis might be performed as well.

Biomarker results including PD data will be correlated with PK data or outcome to investigate possible differences between subjects who respond to treatment versus those who do not respond.

Sample Size Justification:

Part 1: Phase 1 Safety Dose Escalation

Bayesian optimal interval design (Liu, 2015; Yuan, 2016; Zhou, 2017) will be used to evaluate the safety and tolerability of EZM0414 in subjects with R/R MM and R/R DLBCL. Six dose levels (j=6, ie, starting at 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg) as well as an optional step-down dose level of 75 mg are set forth for investigation. Subjects will be enrolled and treated in groups of at least 3, and up to 36 subjects will be enrolled in order to evaluate at least 9 subjects for MTD. Additional daily dose levels and/or dosing schedules (including BID regimen) may be studied based on clinical and PK data obtained during this study.

Part 2: Phase 1b Safety and Efficacy Dose Expansion

Bayesian optimal phase 2 design (Yuan, 2016; Zhou, 2017)will be applied to the Phase 1b dose expansion part to discover efficacy signals. Twenty subjects per cohort are planned to be enrolled and treated in 3 cohorts: R/R MM subjects with t(4;14), R/R MM subjects without t(4;14) and R/R DLBCL subjects.

Number of Subjects (planned):

Phase 1 dose escalation: up to 36 subjects

Phase 1b dose expansion: up to 60 subjects

Total: approximately 96 subjects

Diagnosis and Main Criteria for Inclusion:

1. Voluntarily provide signed informed consent after review of verbal and written material about the trial and agree to abide with protocol requirements. All study related activities must be carried out after written consent is obtained.
2. Subjects must be ≥18 years of age at the time of signing the ICF.
3. Subjects must have an ECOG status of 0 – 2 (Appendix 3).
4. For **MM**, subjects must have measurable disease by IMWG 2016 criteria (Kumar, 2016; Appendix 1) as defined by at least one of the following:
   - Serum monoclonal protein (M-protein) concentration ≥ 0.5g/dL.
   - Urine M-protein excretion of ≥ 200mg in 24 hours.
   - Serum free light chain concentration ≥10mg/dL with an abnormal (<0.26 or >1.65) κ:λ free light chain ratio.
5. For **DLBCL**, subjects must have measurable disease by Lugano criteria (Cheson, 2014; Appendix 2).
6. **MM** subjects who are relapsed/refractory to immune modulator, proteasome inhibitor and anti-CD38 therapy. Subjects who could not tolerate a protease inhibitor (PI), immunomodulatory agent (IMiDs), and a CD38-directed cytolytic antibody are eligible to participate and R/R MM subjects who are intolerant of established therapies known to provide clinical benefit in multiple myeloma.
7. **DLBCL** subjects who are relapsed or refractory with at least two prior line including treatment with R-CHOP, R-EPOCH, R-hyperCVAD and other standard of care therapies. Lines of therapy could have been discontinued due to completion of therapy, intolerance, or lack of response.

Note: Relapsed disease is defined as progression of disease, after initial response to previous treatment, more than six months after end of treatment. Refractory disease is defined as resistance to treatment due to lack of response or progression of disease during treatment or within six months after end of treatment.

8. For dose expansion cohort 1 and 2 only; subjects must have local t(4;14) test results available for enrollment.
9. At enrollment, subjects should have an estimated life expectancy ≥ 3 months in the opinion of the Investigator.
10. Subjects must have sufficient organ and marrow function as defined below:
    - Hemoglobin ≥8g/ dL
    - Platelets >75x10^9/L (includes transfusion dependent subjects)
    - Absolute neutrophil count (ANC) ≥1000/mm^3. Growth factors within 7 days of screening is not allowed to meet ANC eligibility criteria
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2.5xULN, or if attributed to tumor involvement, AST, and ALT <5x ULN.
    - Bilirubin ≤1.5xULN
    - Creatinine clearance ≥40 ml/min. Estimated creatinine clearance calculated using the Cockcroft-Gault formula
    - Coagulation parameters: prothrombin time/ international normalized ratio (PT/INR) <1.5xULN and activated partial thromboplastin (aPTT) < 1.5xULN.
11. Females must not be breastfeeding or pregnant at screening (as documented by a negative beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study treatment. All female subjects will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutively amenorrheic, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, and/or bilateral oophorectomy, with all surgery completed at least 1 month before the first dosing).
12. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception, beginning at least 14 days prior to study entry, during treatment cycles, and for 30 days after the final dose of study treatment and have a male partner who uses a condom. Highly effective contraception includes:
    - Placement of an intrauterine device.
    - Established hormonal contraceptive methods: oral, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product while enrolled on trial and must continue to use the same contraceptive during the study and for one months after last dose of study drug.
13. Male subjects must either practice complete abstinence **or** agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), during study treatment and for 30 days after the final dose of study treatment.
    Note: Male subjects must not donate semen or sperm from the first dose of study treatment, during study treatment (including during dose interruptions), and for 30 days after the final dose of study treatment.

Diagnosis and Main Criteria for Exclusion:

1. Subjects with plasma cell leukemia defined as a plasma cell count >2000/mm^3.

2. Subjects with Waldenstrom's macroglobulinemia or smoldering MM.
3. Subjects with corrected serum calcium >14mg/dL (>3.5mmol/L) or free ionized calcium >6.5mg/dL (1.6mmol/L).
4. Subjects with known systemic amyloidosis.
5. Subjects who had prior treatment with SETD2 or NSD2 inhibitor.
6. Prior cancer therapy for disease under study within the past 4 weeks or 5 half-lives, whichever is shorter. All prior treatment-related adverse events (AEs) must have resolved to Grade 1 or baseline per NCI CTCAE 5.0.
7. Have known active central nervous system (CNS) or any leptomeningeal metastasis of primary extracranial tumor. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging 4 weeks prior to the first dose of study treatment and any neurologic symptoms have stabilized), have no evidence of new or enlarging brain metastases, and are on stable or tapering doses of steroids for at least 7 days prior to first dose of study treatment.

   Note: Subjects with asymptomatic brain metastases found on screening magnetic resonance imaging (MRI) may be entered into the study without prior radiation therapy to the brain if they do not require immediate surgical or radiation therapy in the opinion of the treating Investigator and in the opinion of a radiation therapy or neurosurgical consultant.
8. Subjects taking medications that are known as strong and moderate cytochrome P450 3A4 (CYP3A4) and P-gp inducers/inhibitors (including St. John's Wort). Subjects taking ARA, H2 blockers and PPIs. Subjects must stop taking such medications and must not take them for the duration of their participation in the study. Washout of minimum 14 days or 5 half-lives (whichever is longer) prior to starting EZM0414 is required.
9. Subjects unwilling to exclude Seville oranges, grapefruit juice, AND grapefruit from their diet and all foods that contain those fruits from time of enrolment to while on study.
10. Have a known active infection with hepatitis B virus (HBV, as measured by positive hepatitis B surface antigen), hepatitis C virus (HCV, as measured by positive hepatitis C antibody). *Exceptions*: Subjects with a history of hepatitis B or C who have normal ALT AND are hepatitis B surface antigen negative and/or have undetectable HCV RNA are eligible.
11. Known to be human immunodeficiency virus (HIV) seropositive.
12. Subjects with active acute or chronic systemic infection requiring systemic treatment, including COVID-19.
13. Has cardiovascular impairment: history of congestive heart failure greater than NYHA Class II, uncontrolled arterial hypertension (ie, systolic blood pressure (BP) >150 mm Hg and/or diastolic BP >110 mm Hg), unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of study drug; or ventricular cardiac arrhythmia requiring medical treatment (Appendix 4).
14. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec or history of long QT syndrome. A history or evidence of current clinically significant uncontrolled arrhythmias. History of additional risk factors for Torsade de Pointes including heart failure, hypokalemia, family history of Long QT Syndrome, and use of concomitant medications that are known to increase the risk of Torsade de Pointes (www.crediblemeds.org).
15. Known left ventricular ejection fraction (LVEF) < 50% by either echocardiogram (ECHO) or multigated acquisition (MUGA).
16. Prior major surgery within 4 weeks of treatment start.
17. Known hypersensitivity to components of the investigational product.
18. Subjects who have received treatment with any unapproved drug product within 4 weeks prior to screening.

19. Current participation in any other interventional clinical study except for follow-up.
20. Subjects with a history of or active malignancy other than disease under study, except for:
    - Cervical carcinoma Stage 1B or less.
    - Surgically treated non-invasive basal cell and squamous cell skin carcinoma.
    - Malignant melanoma with a complete response for more than 10 years.
    - Curable cancer and/or hematologic malignancies diagnoses with a complete response for more than 5 years.
21. Underlying medical/social conditions that in PI opinion will place the subject in significant risk and affect the interpretation of toxicity and adverse events assessments.
22. Inability to take oral medication or known gastrointestinal (GI) disease, GI procedure or medical condition that could interfere with the oral absorption or tolerance of the study drug.

Investigational product, dosage, and mode of administration:

EZM0414 will be administered orally once daily in continuous 28-day cycles. In dose escalation part, patient will not receive EZM0414 on Cycle 1 Day 2 and on Cycle 1 Day 3, all other days will follow daily dosing in cycle 1. Each subject will receive EZM0414 according to the dose level they are enrolled in. Intra-patient dose escalation will not be permitted. During the dose expansion part, subjects in cohorts 1-3 will receive EZM0414 at the MTD orally once daily. EZM0414 will be administered at approximately the same time once daily and without food, (no food two hours prior and one hour after EZM0414 dose, water is permitted without restrictions).

Duration of treatment:

Subjects will be treated continuously until consent withdrawal, unacceptable toxicity, disease progression, or need for treatment prohibited on this study. Each treatment cycle will be of 28-day duration. There will be a 30-day safety follow-up.

Reference therapy, dosage, and mode of administration:

Not applicable

Criteria for evaluation:

Safety: Clinical and laboratory safety will be assessed using NCI CTCAE 5.0 criteria (Appendix 5).

Efficacy: IMWG 2016 will be used to evaluate response in MM subjects (Kumar, 2016; Appendix 1) and Lugano criteria will be used to assess response in DLBCL subjects (Cheson, 2014; Appendix 2).

Pharmacokinetics: AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}: observed maximum plasma concentration; T_{max}: observed time at C_{max}; λz: terminal phase elimination rate constant; $t_{1/2}$: terminal elimination half-life.

Biomarkers: H3K36me3 in tumor/bone marrow biopsy and blood collected at baseline and during treatment. Biomarkers such as histones and histone methylation, somatic mutations, DNA methylation and other DNA alterations such as t(4;14) and others, protein levels, RNA expression, immune cells in bone marrow aspirates, tumor biopsies, and/or blood samples.

Statistical methods:

This is an open-label study and there will be no randomization. Bayesian optimal interval design will be used for the Phase 1 dose escalation part of this study. Subjects with R/R MM or R/R DLBCL will be enrolled to determine MTD based on DLT and safety. The MTD will then be used for the subsequent Phase 1b dose expansion part of the study. In the dose expansion part, BOP2 design will be applied and the endpoints ORR, DOR, and PFS will be used to discover efficacy signals of EZM0414 treatment. The ORR, as the primary efficacy endpoint, will be summarized by cohort and compared with pre-specified boundaries to determine if the study drug is promising or futile at MTD.

The secondary efficacy endpoint of PFS will be analyzed using Kaplan-Meier (KM) methodology. Median values along with two-sided 95% CIs will be calculated. KM based PFS at 6, 12, 18, and 24 months will be estimated and associated two-sided 95% CIs will be provided.

Analyses on DCR will be similar to the ones conducted on the ORR.

DOR will be estimated using KM methodology for subjects who achieve CR, sCR, PR, or VGPR per IMWG 2016 Guidelines for MM or CR or PR per Lugano 2014 Guidelines for DLBCL. Median values along with two-sided 95% CIs will be calculated.

The establishment of RP2D will be achieved based on the totality of the safety, efficacy data, target engagement (pharmacodynamic markers), and pharmacokinetic/pharmacodynamic (PK/PD) relationships.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

5-HT	5-hydroxytryptamine
AE	Adverse event
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin
ASCT	Autologous stem cell transplantation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BNP	Brain natriuretic peptide
BOIN	Bayesian Optimal Interval
BOP2	Bayesian optimal phase 2
BP	Blood pressure
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Total clearance after intravascular dose
C_{max}	Maximum observed plasma drug concentration
CNS	Central nervous system
CNV	Copy number variation
CR	Complete response
CRF	Case report form
CS	Clinically significant
CSR	Clinical study report
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
DCR	Disease Control Rate
DLBCL	Diffuse large B cell lymphoma
DLT	Dose limiting toxicities
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRd	Daratumumab, lenalidomide and dexamethasone
ECG	Electrocardiogram
ECHO	Echocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOT	End of treatment
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FIH	First-in-human
FISH	Fluorescent-in situ hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HMT	Histone methyltransferase
HNSTD	Highest Non-severely Toxic Dose
HTLV-1	Human T-cell lymphotropic virus 1
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
Ig	Immunoglobulin
IMWG	International Myeloma Working Group
ip	Intraperitoneal
IPI	International Prognostic Index
IRB	Institutional review board
ITT	Intent-to-Treat
IUD	Intrauterine device
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter of a lesion
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MMSET	Multiple myeloma SET domain

M-protein	Monoclonal protein
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next-generation sequencing
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PI	Protease inhibitor
pj	pj~binomial
PK	Pharmacokinetics
PPIs	proton pump inhibitors
PR	Partial response
PT	Preferred term
PT/INR	Prothrombin time/international normalized ratio
QSR	Quarterly Safety Review
R	Renal insufficiency
R/R	Relapsed/refractory
RBC	Red blood cell
REB	Research ethics board
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAM	S-adenosyl-methionine
SAP	Statistical analysis plan
sCR	Stringent complete response
SD	Standard deviation
SDi	Shortest perpendicular diameter
SEER	Surveillance, Epidemiology and End Results
SOC	Standard of care
SRC	Safety Review Committee
SSD	Safe Starting Dose
SUSAR	Serious adverse drug reactions
$t_{½}$	Half-life
TEAE	Treatment-emergent adverse events

TGI	Tumor growth inhibition
TK	Toxicokinetics
VGPR	Very good partial response
vs	Versus
WBC	White blood cell

5. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to: United States and international standards of good clinical practice (GCPs), FDA Title 21 Part 312, and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines; applicable government regulations; and institutional research policies and procedures.

5.1. Background

5.1.1. Multiple Myeloma

According to the United States Department of Health, National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) program estimate, 34,920 new cases of multiple myeloma (MM) will be diagnosed in 2021 representing 1.8% of all new cancer case diagnoses (SEER database, NCI: SEER, 2018). Multiple myeloma is a neoplasm of the terminally differentiated clonal plasma cells and is cytogenetically heterogenous disease characterized by an abnormal proliferation of plasma cells in the bone marrow and usually accompanied by excessive production of monoclonal antibodies.

Genetic abnormalities common in MM include hyperdiploidy, chromosomal translocations, deletions, duplications, and genetic mutations. Chromosomal translocations occur between the immunoglobulin heavy chain alleles at chromosome 14q32 and various partner chromosomes (Kuehl, 2002). These abnormalities form the basis for classification and risk stratification of MM subjects. High-risk MM is defined by the presence any of the following chromosomal abnormalities t(4;14), t(14;16), t(14;20), 17p deletion, 1q gain or p53 mutation. Some subjects may present with more than one high-risk abnormality (Kumar, 2018). These chromosomal translocations lead to overexpression of putative oncogenes and favor a pre-malignant state, which can ultimately lead to the plasma cell-derived, post-germinal center malignancy MM (Barwick, 2019). According to the International Myeloma Working Group (IMWG), events that define MM are hypercalcemia (C), renal insufficiency (R), anemia (A) and bone lesions (B), collectively referred to as CRAB features.

National Comprehensive Cancer Network (NCCN) recommended treatment options for subjects with newly diagnosed MM are based on eligibility for autologous stem cell transplant (ASCT). Subjects who are candidates for ASCT, receive induction therapy with bortezomib (Velcade), lenalidomide (Revlimid) and dexamethasone (VRd), transplant followed by maintenance treatment with lenalidomide, and dexamethasone (Rd) based on S0777 study (Durie, 2020; Rajkumar, 2020). SWOG S0777, evaluated a combination of VRd vs Rd in previously untreated MM subjects and showed better progression free survival (PFS) and overall survival (OS) in VRd subjects as compared to Rd subjects. In subjects who are not candidates for ASCT, initial therapy options include VRd or alternatively daratumumab, lenalidomide and dexamethasone (DRd). MAIA study compared daratumumab plus lenalidomide and dexamethasone or lenalidomide and dexamethasone alone in transplant ineligible subjects. MAIA study showed that daratumumab plus lenalidomide and dexamethasone had significant efficacy in this patient population (Facon, 2019). VRd and DRd remain initial therapy options for subjects not eligible for transplant. These regimens are continued for 8-12 cycles for VRd followed by maintenance and until disease progression for DRd.

Additional treatment options include elotuzumab, SLAMF7-directed immunostimulatory antibody, in combination with lenalidomide and dexamethasone for MM after one to three prior therapies; Selinexor, a nuclear export inhibitor, in combination with dexamethasone for relapsed/refractory (R/R) MM after at least four prior therapies; Panobinostat, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone for MM after at least 2 prior regimens. In 2020, multiple new treatment options for MM were approved by the Food and Drug Administration (FDA). Belantamab mafodotin-blmf (Blenrep) was approved for R/R MM subjects who received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD. Isatuximab-irfc (Sarclisa), an anti-CD38 monoclonal antibody was approved for R/R MM, in combination with pomalidomide, and dexamethasone after 2 or more prior therapies, including lenalidomide and a PI. Subcutaneous daratumumab (daratumumab and hyaluronidase-fihj) in combination with other treatments was approved for adults with newly diagnosed MM or R/R MM. The first Chimeric antigen receptor (CAR) T-cell therapy idecabtagene vicleucel (ABCEMA) for was approved for R/R MM after 4 or more lines of prior therapy. Clinical trials are ongoing to investigate novel options such as bispecific antibodies or BiTE.

After initial response, frontline treatment options eventually fail and almost all subjects with MM relapse. Relapsed/refractory MM is treated with combination regimens described above. Development of novel drugs has led to dramatic improvements in MM disease management and outcomes; however, majority of subjects with MM experience multiple remissions and relapses. Each subsequent remission after initial remission is of shorter duration (Kumar, 2017). Multiple myeloma subjects have a 5-year relative survival rate of 55.6% (SEER database, NCI: SEER, 2018). Estimated deaths from MM in 2021 will be 12,410, representing 2% of all cancer related deaths (SEER database, NCI: SEER, 2018). Relapsed/refractory MM continues to remain an incurable disease and the need for targeted therapies to provide novel treatment options to subjects with R/R MM persists.

5.1.2. Diffuse Large B Cell Lymphoma

Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma in the United States. Based on 2014–2018 cases and deaths, the rate of new cases of DLBCL was 5.6 per 100,000 persons per year (SEER database, NCI: SEER, 2017). Diffuse large B cell lymphoma is most frequently diagnosed among people aged 65-74 years old with median age at diagnosis being 66 years old, while 75% of the cases are diagnosed in persons 55 years old and older. Diffuse large B cell lymphoma is an aggressive neoplasm of the mature B cells and usually presents as asymptomatic disease with either nodal or extranodal lesions.

Diffuse large B cell lymphoma is a clinically and genetically heterogeneous disease and based on cell of origin, can be classified into germinal center B-cell subtype (GCB-DLBCL), or activated B cell subtype (ABC-DLBCL). Detailed genetic analysis have identified five distinct clusters of the DLBCL subsets based on recurrent mutations, somatic copy number alterations and structural variants (Chapuy, 2018). These molecular signatures define genetic complexity and heterogeneity present in DLBCL that can be potentially targeted to develop novel treatment options. In the clinic, treatment decisions are made using the International Prognostic Index (IPI) to categorize prognosis in aggressive lymphomas based on five clinical factors: age, number of extranodal sites, performance status, disease stage at diagnosis, and LDH levels.

NCCN recommended frontline chemoimmunotherapy treatment is combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) which leads to cure in 50-60% of the subjects (Liu, 2019). R-CHOP may be combined with involved field radiation therapy (IFRT). Other regimens for advanced disease are combination of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) or dose dense R-CHOP-14. Subjects who have refractory disease or who experience relapse are candidates for salvage therapy followed by ASCT, if eligible. If ineligible for ASCT, treatment with chemotherapy is considered based on IPI. Second-line regimens for high dose chemotherapy include the following (which may be given with or without rituximab): DHAP (dexamethasone, cytarabine, cisplatin), ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), GemOx (gemcitabine and oxaliplatin), ICE (ifosfamide, carboplatin, etoposide), and MINE (mitoxantrone, ifosfamide, mesna, etoposide). Relapsed/refractory DLBCL subjects have poor outcomes in subsequent therapy, shorter duration between each line of treatment and very few subjects achieve remission. Recent FDA approvals for R/R DLBCL include Selinexor after at least 2 lines of systemic therapy. Tafasitamab-cxix, a CD19-directed cytolytic antibody, in combination with lenalidomide for R/R DLBCL subjects not eligible for ASCT. Polatuzumab, is a CD79b-directed antibody–drug conjugate, in combination with bendamustine and a rituximab product for R/R DLBCL after at least 2 prior therapies. Anti-CD19 directed CAR-T cell therapies include axicabtagene ciloleucel and tisagenlecleucel for adults with R/R DLBCL after two or more lines of systemic therapy. Clinical trials are ongoing to develop antibody drug conjugates, immunotherapies, and targeted therapies to provide better outcome for R/R DLBCL subjects.

The 5-year relative survival rate for DLBCL subjects is 63.9%, however the stage of the disease at diagnosis has a strong influence on survival rate with 73.6 % in stage I subjects and 53.2% in stage IV subjects. (SEER database, NCI: SEER, 2017). Based on 2014–2018 cases and deaths, the death rate was 1.8 per 100,000 persons per year (NCI: SEER, 2017). Thus, medically unmet need for better and novel treatments for subjects with R/R DLBCL is high.

5.2. Investigational Product

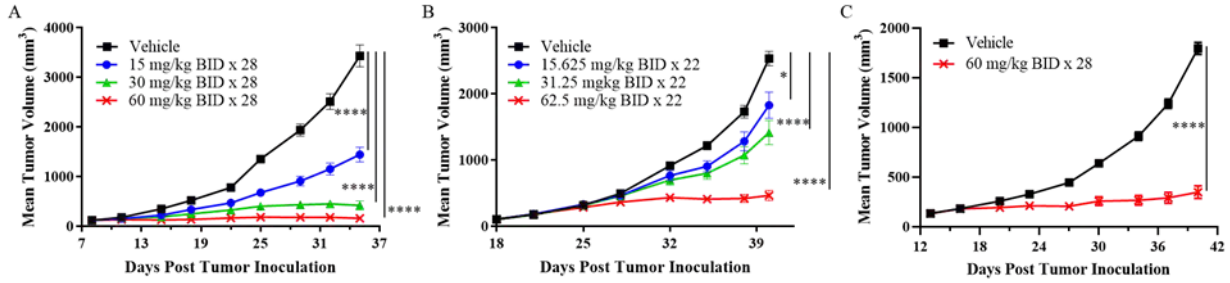
5.2.1. EZM0414

EZM0414 (also referred to as PH-EPZ-055-RS2-300, EPZ040414, or EPZ- 040414) is a potent and selective, orally bioavailable small molecule inhibitor of histone methyltransferase (HMT) Su(var)3-9, Enhancer of zeste, Trithorax domain containing 2 (SETD2), also known as KMT3A. Inhibition of SETD2 is expected to lead to decreased growth of MM tumors. In preclinical studies, inhibition of SETD2 by EZM0414 has demonstrated anti-proliferative activity in vitro in a panel of MM cell lines, with increased activity in the t(4;14) subset, and in vivo tumor growth inhibition (TGI) in multiple cell line-derived MM xenograft models (Figure 2). In addition, in vitro and in vivo EZM0414 treatment led to tumor growth inhibitory effects in DLBCL model systems (Figure 2). Therefore, EZM0414 is expected to have activity in t(4;14) as well as non-t(4;14) R/R MM and R/R DLBCL patient populations.

EZM0414 is orally bioavailable and formulated as tablets. Nonclinical safety studies completed in dogs and rats show EZM0414 is tolerated as evidence by the demonstration of no medical limiting clinical observations or clinical pathology findings. In GLP 28-day toxicity studies, animals were administered EZM0414 orally once daily for 28 consecutive days. The Safe

Starting Dose (SSD) in the planned FIH study with EZM0414 was determined based on the lowest human equivalent dose (HED) established in the most sensitive species. The dog was determined to be the most sensitive species; therefore, using the Highest Non-severely Toxic Dose (HNSTD) and the HED established for dogs, the SSD in a first-in-human (FIH) study with EZM0414 is 100 mg/60 kg patient.

Figure 2: Tumor Volume in MM and DLBCL Xenograft Models



(A) KMS-11 human t(4;14) MM xenograft model, (B) MM.1S human non-t(4;14) MM xenograft model, and (C) TMD8 human DLBCL xenograft model. Tumor volume was measured twice a week and mean tumor volumes were plotted over time. Data represent the mean ± SEM (n=10, KMS-11, and MM.1S or n=8, TMD8). * p <0.1 and **** p<0.0001 versus vehicle control at the end of the respective studies. p values were determined by one-way ANOVA followed by Tukey's multiple comparison test.
Abbreviations: ANOVA = analysis of variance; EZM0414 = EPZ-040414-6 (KMS-11); EZM0414 = EPZ-040414-4 (MM.1S); EPZ-040414-5 (TMD8); SEM = standard error of the mean.
Source: EPZ-040414-PH-0009, EPZ-040414-PH-0004, EPZ-040414-PH-0008.

5.2.2. EZM0414 Mechanism of Action

EZM0414 (also referred to as PH-EPZ-055-RS2-300, EPZ040414, or EPZ-040414 in the nonclinical reports, but referred to as EZM0414 hereafter) is a potent and selective, orally bioavailable small molecule inhibitor of the enzymatic activity of histone methyltransferase (HMT) Su(var)3-9, Enhancer of zeste, Trithorax domain containing 2 (SETD2), also known as KMT3A. SETD2 catalyzes the S-(5′-Adenosyl)-L-methionine (SAM)-dependent deposition of the third or final methyl group onto the di-methylated state of lysine 36 of histone H3 (H3K36me2) yielding the tri-methylated state of lysine 36 of histone H3 (H3K36me3) (Sun, 2005). With the exception of PRDM9, which is expressed primarily in germ cells, SETD2 is the only known HMT capable of catalyzing H3K36me3 in vivo (Grey, 2017; Diagouraga, 2018). SETD2 also has been implicated in the methylation of non-histone proteins, including p53, STAT1 and α-tubulin (Carvalho, 2014; Park, 2016). It has several biological roles including transcriptional regulation and RNA splicing, DNA damage repair, and immune cell development and differentiation (Licht, 2017).

5.2.3. Nonclinical Experience

EZM0414 is being developed as a potential treatment for adult patients with R/R MM specifically those with the (4;14) chromosomal translocation and R/R DLBCL. Studies in both t(4;14) and non-t(4;14) MM cell lines demonstrated marked anti-proliferative activity in response to EZM0414. Studies in DLBCL cells exhibited a wide range of sensitivity to EZM0414. In vivo, in 28-day studies using xenograft models, SCID mice bearing human MM

and DLBCL cell line-derived xenografts exhibited TGI and dose-dependent reductions in H3K36me3 levels.

5.2.3.1. Nonclinical Pharmacology

Cell-free in vitro experiments demonstrated potent inhibition of SETD2 methyltransferase activity. EZM0414 inhibited SETD2 enzymatic activity with a half maximal inhibitory concentration (IC50) of 18.3 ± 8.1 nmol/L with at least 11000 fold selectivity over 13 other related HMTs. The SETD2 IC_{50} value was dependent on substrate concentration, with a maximal intrinsic potency, as determined by inhibition constant (K_i), of 12.9 ± 1.5 nmol/L. Further, the mechanism of EZM0414 inhibition of SETD2 was mixed uncompetitive with respect to S-adenosyl-methionine (SAM) and noncompetitive with respect to peptide, suggesting EZM0414's potency cannot be abated by accumulating or high substrate concentrations in a cellular context. These results show that EZM0414 is a potent and selective inhibitor of SETD2 methyltransferase activity.

5.2.3.2. Nonclinical Pharmacokinetics

EZM0414 possesses favorable ADME properties with good probability to achieve efficacious exposure levels in humans. EZM0414 exhibited low to moderate CL and moderate to large V_{ss} in mice, rats, dogs, and monkeys. EZM0414 displays good oral absorption in preclinical species (F: 56% to 100%) and is a substrate for P-gp as detected by Caco-2 cells (ER: 7 at 1 µM); however, intrinsically, it is a highly permeable compound. EZM0414 is primarily metabolized by CYP3A enzymes and has negligible renal excretion. Metabolite identification conducted in vitro (hepatocytes), and ex vivo (rats and dogs) showed mainly oxidation followed by dehydrogenation or N-dealkylation on the piperazine moiety and indole moiety, with no unique human metabolites identified. Additionally, no metabolite was observed in sufficient quantities (> 10% EZM0414 plasma exposure) to require monitoring.

5.2.3.3. Drug-Drug Interaction

EZM0414 has a low potential of DDIs as a perpetrator. The IC_{50} of EZM0414 toward seven human CYP isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D, CYP3A) evaluated was ≥100 µmol/L except for CYP2C8 (IC_{50} = 6.80 µmol/L), and preincubation did not intensify the inhibitory potency for the majority of the CYPs except for CYP3A (IC_{50} was reduced from >100 µmol/L to 60.2 and 28.0 µmol/L with midazolam and testosterone as CYP3A substrates, respectively). EZM0414 may be a low CYP inducer, especially of CYP3A4; however, induction was observed based on mRNA levels only, whereas CYP activity was not induced. With respect to drug transporters, preliminary studies indicated the potential of EZM0414 to inhibit P-gp and breast cancer resistance protein (BCRP); (IC_{50} = 45.7 and 30.3 µmol/L, respectively). With respect to the potential of EZM0414 as victim in DDI scenarios, hepatic metabolism was predominantly mediated by CYP3A isozymes, rendering EZM0414 susceptible to concomitant drugs that are strong CYP3A modulators.

5.2.3.4. Nonclinical Pharmacodynamics

Secondary pharmacology and PD studies did not reveal significant potential for off-target toxicity. Two G-protein coupled receptors (GPCRs) that were targeted by EZM0414 included the DRD_2 and the $5\text{-}HT_{1B}$ receptors. The anticipated margin of exposure at the projected human

efficacious $C_{max,u}$ would be approximately 16- to 35-fold for the DRD_2 receptor and approximately 4- to 9-fold for the $5\text{-}HT_{1B}$ receptor, suggesting a low potential for adverse effects clinically.

Two stand-alone CV safety pharmacology studies were performed in dogs as a result of the data obtained in the hERG and CiPA screening studies. Consistent findings between these studies included decreases in arterial and pulse pressure, possibly related to the decrease in systolic pressure. This was accompanied by a compensatory increase in heart rate. An increase in QTc was also observed at the same dose levels but was not considered clinically significant as it did not rise to the 10% threshold of concern. Although plasma concentration was not assessed directly, the GLP CV study was conducted at the same doses as the initial 28-day dog toxicity study using the same batch of API. Utilizing the $C_{max,u}$ values at equivalent doses in 28-day toxicity study, the CV effects observed in the GLP CV study began at approximately 1.2- to 2.5-fold (50 mg/kg dose level) and were observed up to 3- to 6.6-fold (200 mg/kg dose level) the predicted human efficacious $C_{max,u}$ (0.4 µmol/L for a 120mg/60kg dose of EZM0414). Of interest, there were no ECG effects observed in the 28- day follow-up toxicity study in dogs.

Central nervous system and respiratory safety pharmacology endpoints were included on the 28-day rat study. Motor function effects and a reduced respiration rate were observed at the high dose (7- to 15-fold the predicted human efficacious $C_{max,u}$), minute volume was reduced at ≥75 mg/kg (≥ approximately 3- to 6.5-fold the predicted human efficacious $C_{max,u}$), and tidal volume was reduced at all doses (0.2- to 0.5-fold the predicted human efficacious $C_{max,u}$) at the end of exposure and into recovery. While these effects were considered drug-related, based on magnitude they were not considered adverse.

5.2.3.5. Preclinical Safety

The nonclinical safety profile of EZM0414 was evaluated in Sprague Dawley rats and Beagle dogs. In all studies, EZM0414 was delivered by oral gavage to simulate the oral route of administration proposed for the phase 1 clinical trials. The toxicity studies included a single escalating dose study in dogs, 7-day repeat-dose toxicity studies in rats and dogs, and 28-day GLP studies with 28-day recovery phases in rats (1 study) and dogs (2 studies, initial and follow-up). GLP genetic toxicity assessments were conducted to assess the mutagenicity potential of EZM0414. In addition, a thorough investigation was conducted to evaluate the differences in toxicity observed in the 7-day (non-GLP) and 28-day (GLP) repeat-dose toxicity studies in dogs, including additional single- and repeat-dose pharmacokinetic studies in rat and dog.

Following repeat dosing of EZM0414 in rats and dogs, the primary target systems include the respiratory, immunology, coagulation, hepatic, kidney, and reproductive organs. Reduction in respiratory rate, tidal, and minute volume was seen in the 28-day GLP rat study, as well as depressed respiratory function during week 4 (males and females) and the recovery period (high dose males). Effects on lymphoid cellularity, particularly in the thymus and occasionally on germinal centers, were noted throughout the immune system in rats and dogs. Additionally, there were reproducible changes in the erythron and coagulation parameters in both species. Reproductive changes were evident in rats of both sexes in the 28-day rat study and in male dogs only in the follow-up 28-day dog study. At higher dose levels, there also was toxicity to the liver and gastrointestinal tract (rats and dogs), and the adrenal gland and skeletal muscle (rat). All

EZM0414-related effects, with the exception of reproductive effects, which minimally persisted through the recovery period, were reversible. A review of the literature suggests that the changes in the hematopoietic/immune system and the reproductive system of both sexes as well as those observed in the skeletal muscle of the rat may be the result of on-target pharmacology.

The nonclinical safety profile of EZM0414 has been well characterized through the conduct of secondary pharmacology and PD studies, genetic toxicology, safety pharmacology, and repeat-dose toxicity and TK studies in rats and dogs. Based on the available data, a potential clinical starting dose of 111 mg could be employed and is based on 1/6 of the HNSTD (20 mg/kg/day) in the dog, the more sensitive nonclinical species tested (Table 2). This approach is in line with the guidance provided by ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, and the accompanying Q&A document. A starting dose of 100 mg has been proposed and is supported by the data. Therefore, the nonclinical toxicology studies are considered adequate for supporting the proposed first-in-human study.

These data support the clinical development plans for EZM0414 for the treatment of R/R MM and R/R DLBCL in adult patients.

5.2.3.6. Preclinical Efficacy

Preclinical efficacy studies with EZM0414 support the hypothesis that there is dependency on SETD2 for MM and DLBCL growth and survival, particularly in t(4;14) MM, and that SETD2 inhibition leads to tumor cell growth inhibition. Oral administration of EZM0414 demonstrated significant antitumor activity in one t(4;14) MM, two non-t(4;14) MM, and four DLBCL cell line-derived xenograft models, with tumor regressions/growth stasis and dose-dependent TGI observable starting at 4 to 7 days of dosing initiation (Figure 2). In all models with more than one treatment group, the effects observed were dose-dependent and correlated well with reductions in tumor H3K36me3 levels, demonstrating on-target inhibition of SETD2 methyltransferase activity in vivo.

5.2.3.7. Rationale for the Use of EZM0414 to Treat Multiple Myeloma and Diffuse Large B Cell Lymphoma

Data regarding the role of SETD2 in tumorigenesis demonstrates a variety of context-dependent mechanisms. While SETD2 may function as a classical tumor suppressor in the context of certain solid tumors, this is not true for SETD2's role in the development of hematological malignancies. Several studies suggest that heterozygous loss of SETD2 acts to drive leukemogenesis, whereas homozygous loss slows disease progression. This suggests that complete loss of SETD2 is profoundly deleterious and provides strong rationale for use of SETD2 inhibitors against these hematological tumors (Hart, 2015; Shi, 2015; Wang, 2015; Tzelepis, 2016; Skucha, 2019).

Importantly, several epigenetic mutations and dependencies have been identified in B-cell malignancies, including MM and DLBCL, providing therapeutic rationale for epigenetic inhibitors in these tumor types. As in the case of leukemia, SETD2 loss of function mutations found to date in DLBCL are also always heterozygous, suggesting that a similar haploinsufficient tumor suppressor role for SETD2 and therapeutic potential of SETD2 inhibition may also exist in the setting of B-cell malignancies (Reddy, 2017).

In addition, SETD2 dependency also could manifest in other B cell malignancies where perturbation of H3K36 methylation plays a key role, including Histone H1 mutations and in the setting of (4;14) chromosomal translocations present in high-risk MM (Barwick, 2019; Yusufova, 2020). The (4;14) chromosomal translocation results in juxtaposition of IgH control elements with two genes on chromosome 4, fibroblast growth factor receptor 3 (FGFR3) and multiple myeloma SET domain (MMSET) (Chesi, 1997; Richelda, 1997; Chesi, 1998). MMSET, also known as WHSC1 or NSD2, is an HMT that catalyzes H3K36me1 and me2 formation and extensive scientific work has led to general agreement that high MMSET is the key factor in t(4;14) MM pathogenesis. MMSET has therefore been long recognized as a potential therapeutic target in t(4;14) MM; yet it has eluded drug discovery efforts to date (Lauring, 2008; Marango, 2008; Brito, 2009; Kuo, 2011; Martinez-Garcia, 2011). However, since the (4;14) translocation results in high levels of the H3K36me2 substrate for SETD2, inhibiting SETD2 offers promise for targeting the underlying oncogenic mechanism driven by MMSET overexpression in t(4;14) MM subjects.

Based on the in vitro and in vivo pharmacology studies EZM0414 shows selective and potent inhibitory activity for SETD2. In vitro studies show that EZM0414 reduces H3K36me3 levels and inhibits proliferation of MM and DLBCL cell lines in a dose-dependent manner. In vivo MM and DLBCL cell line-derived xenograft models demonstrated significant tumor growth inhibition by EZM0414. Nonclinical safety studies completed in dogs and rats show EZM0414 is tolerated as evidenced by no medically limiting clinical observations or clinical pathology findings. These results, coupled with the need for novel treatment options for R/R MM and R/R DLBCL, provide proof of concept for clinical exploration of EZM0414 in these B-cell malignancies.

5.2.4. Clinical Experience

This first-in-human study is being conducted to study the safety and efficacy of EZM0414 in R/R MM and R/R DLBCL subjects based on the results observed in pre-clinical studies supported by the mechanism of action. Details of currently approved therapies and novel agents in clinical trials are presented in Section 5.1.1 and Section 5.1.2.

5.2.5. Rationale for Starting Dose and Dosing Schedule

The nonclinical safety profile of EZM0414 has been well characterized through the conduct of secondary pharmacology and PD studies, genetic toxicology, safety pharmacology, and repeat-dose toxicity and TK studies in rats and dogs. Based on the available data, a potential clinical starting dose of 111 mg could be employed and is based on 1/6 of the HNSTD (20 mg/kg/day) in the dog, the more sensitive nonclinical species tested (Table 2). This approach is in line with the guidance provided by ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, and the accompanying Q&A document. A starting dose of 100 mg has been proposed and is supported by the data. Therefore, the nonclinical toxicology studies are considered adequate for supporting the proposed first-in-human study.

These data support the clinical development plans for EZM0414 for the treatment of R/R MM and R/R DLBCL in adult patients.

Table 2: Predicted Safe Starting Dose in Humans for EZM0414 Based on HED Relative to the Dog HNSTD

Species	Duration	Route	STD_{10}/HNSTD (mg/kg/day)	HED[a] (mg/day)	Supported FIH Starting Dose	STD10/HNSTD AUC0-t (ng•h/mL)
Rat	4 weeks	Oral	150	1452	145 mg	769,500[b]
Dog	4 weeks	Oral	20	667	111 mg	72,900[b]

FIH = first-in-human; HED = human equivalent dose; HNSTD = highest non-severely toxic dose; STD_{10} = severely toxic dose in 10% of animals.
[a] HED was calculated by dividing the STD10 by 6.2 for rats and the HNSTD by 1.8 for dogs and then multiplying by average body weight of 60 kg.
[b] Day 28; males and females combined.

5.2.6. Assessment of Response

All baseline local tumor assessments are to be performed within 28 days prior to the start of study treatment. Tumor response assessments at screening and during the trial will include whole body positron emission tomography-computed tomography (PET-CT), ^{18}FDG-PET for PET avid disease OR contrast enhanced computed tomography (CT) of the neck, chest, abdomen and pelvis, and other applicable sites for PET non-avid disease. Radiologic disease assessments will occur as per Table 8.

5.2.6.1. Multiple Myeloma

Response will be assessed at every cycle using the IMWG 2016 consensus criteria that includes serum monoclonal protein (M-protein), 24-hour urine M-protein, serum free light chain kappa, lambda, and their ratio, bone marrow aspiration (CR), and bone marrow biopsy (sCR). Hence, subjects with MM would need to undergo a bone marrow biopsy or bone marrow aspiration for IMWG response assessment (Kumar, 2016; Appendix 1). If minimal residual disease (MRD) assessment or any molecular tumor assessments is performed as standard of care during the trial the results of these assessments will be shared with the sponsor.

5.2.6.2. Diffuse Large B Cell Lymphoma

A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed every 8 weeks at clinic visits. Response will be assessed using 2014 Lugano classification (Cheson, 2014; Appendix 2). Hence subjects with a previously positive or unknown bone marrow biopsy at baseline would undergo a bone marrow biopsy in suspected CR.

5.3. Conclusion

Based on the available nonclinical data presented in Section 5.2, the potential risks include cardiovascular, respiratory, immunology, gastrointestinal, hematologic, hepatic, renal, and reproductive systems.

Clinical subjects meeting protocol inclusion and exclusion criteria will be monitored rigorously for early signs of any of the potential risks noted in the nonclinical toxicology studies by

physician-performed history and physical examination as well as monitoring safety laboratory studies of the blood, urine, and serial time point-specific electrocardiogram (ECG).

Epizyme's assessment of the potential benefit:risk ratio is expected to be positive in human subjects with R/R MM and R/R DLBCL.

6. TRIAL OBJECTIVES AND PURPOSE

Objectives	Endpoints
Part 1: Phase 1 Dose Escalation Phase	
Primary	
• To evaluate the safety and maximum tolerated dose (MTD) of EZM0414 when administered as monotherapy in subjects with R/RMM and R/R DLBCL.	• Adverse event assessment according to Common Terminology Criteria for Adverse Events (CTCAE 5.0), physical examination, vital signs (blood pressure, heart rate, respiration rate, and body temperature), 12-lead ECG, clinical laboratory tests (hematology including coagulation profile, serum chemistries, and urinalysis), ECOG performance status, concomitant medication monitoring, and dose limiting toxicities (DLT).
Exploratory	
• To investigate target engagement in samples collected before and during treatment with EZM0414. • To determine exploratory biomarkers such as histones and histone methylation, somatic mutations, DNA methylation, DNA alterations such as t(4;14) and others, protein levels, RNA expression, and immune cells in bone marrow aspirates, tumor/bone marrow biopsies, and blood samples. • To assess pharmacokinetics (PK) of EZM0414 when administered as monotherapy in subjects with R/R MM and R/R DLBCL.	• H3K36me3 in tumor/bone marrow biopsy and blood collected at baseline and during treatment. • Biomarkers such as histones and histone methylation, somatic mutations, DNA methylation and other DNA alterations such as t(4;14) and others, protein levels, RNA expression, immune cells in bone marrow aspirates, tumor biopsies, and blood samples. • Pharmacokinetic parameters including but not limited to: AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}: observed maximum plasma concentration; T_{max}: observed time at C_{max}; λ_z: terminal phase elimination rate constant; $t_{1/2}$: terminal elimination half-life.

Objectives	Endpoints
Part 2: Phase 1b Dose Expansion Phase	
Primary Safety	
• To determine the safety and tolerability of EZM0414 in subjects with R/R MM and R/R DLBCL.	• Adverse event assessment according to CTCAE 5.0, assessment of changes in physical examination, vital signs (blood pressure, heart rate, respiration rate, and body temperature), 12-lead ECG, clinical laboratory tests (hematology including coagulation profile, serum chemistries, and urinalysis), ECOG performance status, and concomitant medication monitoring.
• To establish the recommended Phase 2 dose (RP2D).	• Adverse events, clinical laboratory tests, and pharmacokinetic profile.
Primary Efficacy	
• To determine the efficacy of EZM0414 as demonstrated by the effect on ORR in subjects with R/R MM and R/R DLBCL.	• ORR defined as the proportion of responders as assessed by Investigator per IMWG 2016 guidelines for MM (sCR, CR, VGPR, and PR) or Lugano 2014 guidelines for DLBCL (CR+PR).
Secondary	
• To determine the efficacy of EZM0414 as demonstrated by the effect on ORR, PFS, and DOR in subjects with R/R MM and R/R DLBCL.	• PFS defined as the time from start of treatment until the first documented PD, as assessed by Investigator per IMWG 2016 guidelines for MM or Lugano 2014 guidelines for DLBCL or death due to any cause, whichever occurs first. • DCR defined as the proportion of subjects who have achieved confirmed CR, sCR, PR, VGPR, minimal response or stable disease (SD) per IMWG 2016 Guidelines for MM or CR, PR, or SD per Lugano 2014 Guidelines for DLBCL since administration of EZM0414 in dose expansion part (including the cycle 1 observations of the subjects who receive EZM0414 at MTD in the dose scalation

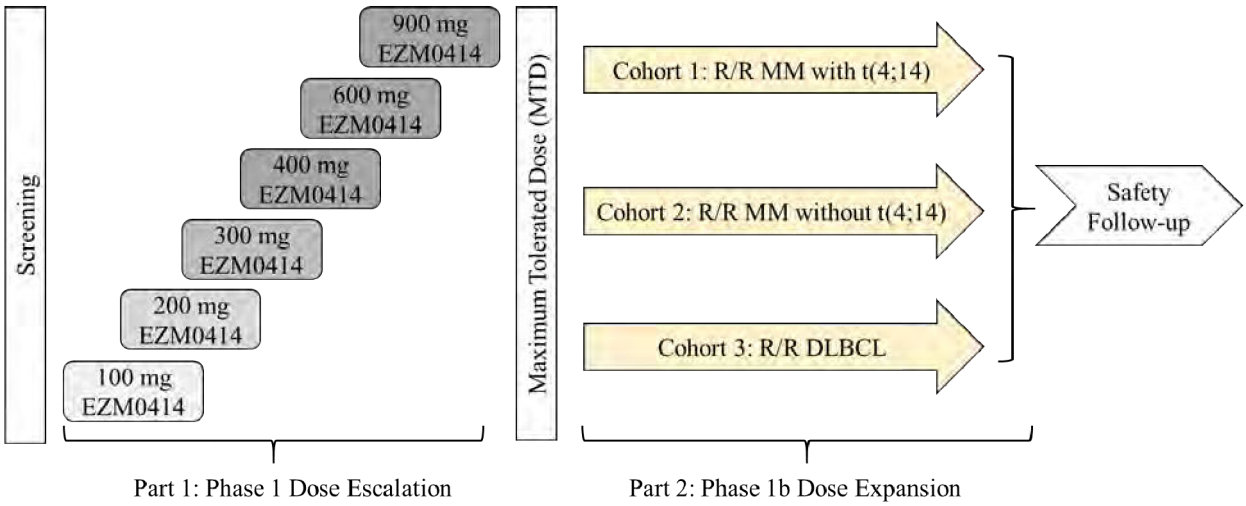
Objectives	Endpoints
	part and are rolled over to the dose expansion part). • DOR defined as the time from initial CR or PR to documented progression or death, whichever comes first, as assessed by Investigator per IMWG 2016 guidelines for MM or Lugano 2014 guidelines for DLBCL.
Exploratory	
• To determine H3K36me3 in tumor tissue biopsy and blood samples. • To determine exploratory biomarkers such as histones and histone methylation, somatic mutations, DNA methylation and other DNA alterations such as t(4;14) and others, protein levels, RNA expression, and immune cells in bone marrow aspirates, tumor/bone marrow biopsies, and blood samples. • To determine the pharmacokinetic profile of EZM0414.	• H3K36me3 in tumor/bone marrow biopsy and blood collected at baseline and during treatment. • Biomarkers such as histones and histone methylation, somatic mutations, DNA methylation and other DNA alterations such as t(4;14) and others, protein levels, RNA expression, immune cells in bone marrow aspirates, tumor biopsies, and blood samples. • Pharmacokinetic parameters including but not limited to: AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}: observed maximum plasma concentration; T_{max}: observed time at C_{max}; λ_z: terminal phase elimination rate constant; $t_{1/2}$: terminal elimination half-life, C_{max}/D: maximum observed concentration normalized to the dose; and AUC/D: AUC normalized to the dose.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a FIH, 2-part, multi-center, open-label Phase 1/1b safety, tolerability, PK, and efficacy study of oral SETD2 inhibitor, EZM0414, in subjects with R/R MM and R/R DLBCL. The first part of the study will be a Phase 1 dose-escalation designed to evaluate the safety, tolerability, and PK of EZM0414 in subjects with R/R MM and R/R DLBCL. Six dose levels starting at 100 mg, and then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg as well as an optional step-down dose level of 75 mg (if needed) will be tested. The second part of the study is the Phase 1b dose expansion at the MTD designed to evaluate safety and efficacy in subjects with R/R DLBCL and R/R MM with or without select genetic translocation. Dose expansion will enroll subjects in 3 cohorts: Cohort 1 for R/R MM subjects with t(4;14), Cohort 2 for R/R MM subjects without t(4;14), and Cohort 3 for subjects with R/R DLBCL.

Figure 3: Study Schema



NOTE: The subjects who are treated at MTD in Phase 1 dose escalation AND do not experience any DLT will be rolled over to Phase 1b dose expansion until disease progression, occurrence of unacceptable toxicity or withdrawal of consent.

Note: if needed, the Part 1: Phase 1 Dose Escalation may include an optional step-down dose level of 75 mg.
Abbreviations: DLBCL = diffuse large B cell lymphoma; DLT = dose limiting toxicities; MM = multiple myeloma; MTD = maximum tolerated dose; R/R = relapsed/refractory.

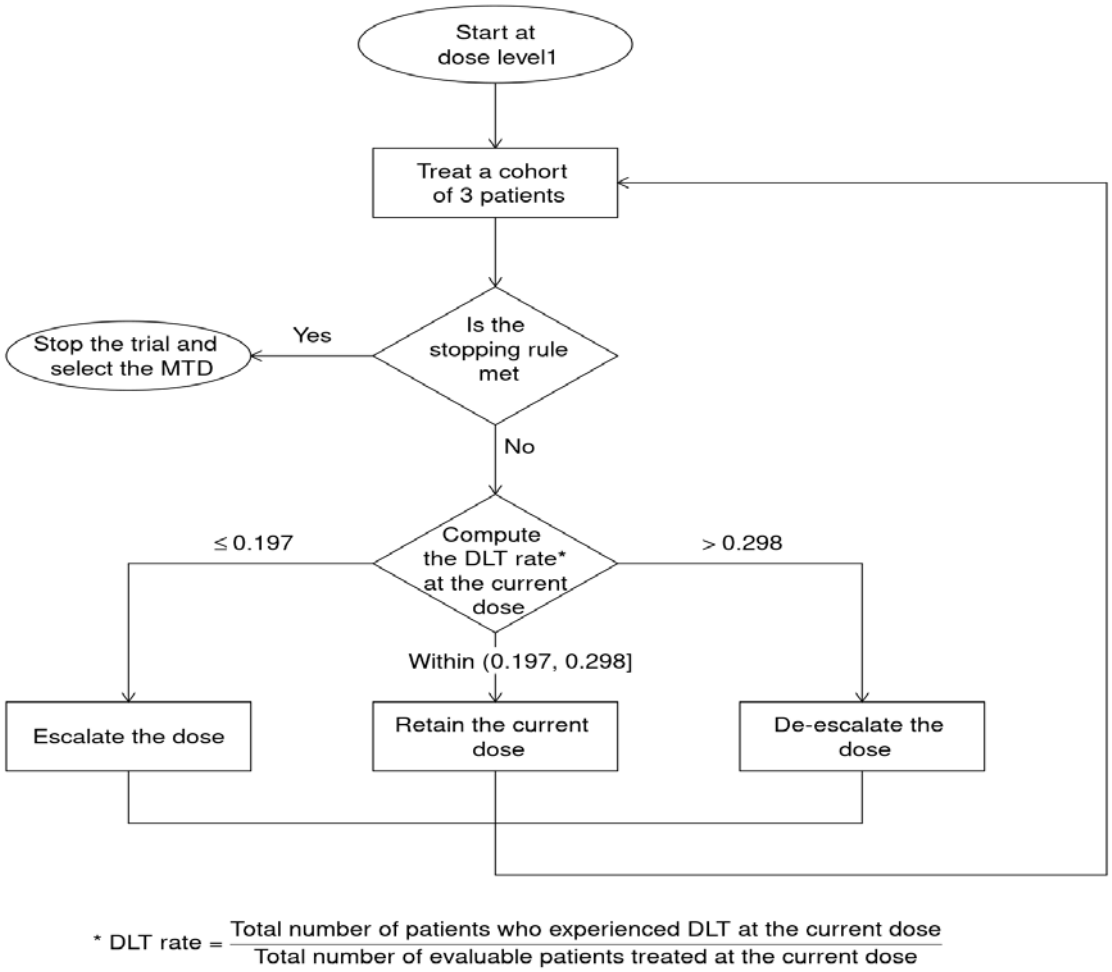
Part 1: Phase 1 Safety Dose Escalation

Part 1 is a safety dose escalation to determine the MTD for dose expansion in Part 2 of the study. Bayesian optimal interval design will be used to evaluate the safety and tolerability of EZM0414 in subjects with R/R MM and R/R DLBCL. Six dose levels starting at 100 mg, and then 200 mg, 300 mg, 400 mg, 600 mg, and 900 as well as an optional step-down dose level of 75 mg (if needed) will be tested in this dose escalation part of the study. Safety, tolerability, PK, and PD data will be reviewed, as available, initially after 4 planned dose levels (100 mg, 200 mg, 300 mg, and 400 mg) are evaluable, then again when the 600 mg dose level is evaluable, then again when the 900 mg dose level is evaluable, and lastly when the MTD is determined. Subjects will be enrolled and treated in groups of at least 3 subjects, and up to 36 subjects (at least 3 subjects each with t(4;14) MM, non-t(4;14) MM and DLBCL) will be enrolled in order to evaluate at

least 9 subjects for MTD. Successive subjects within a given dose level will follow a staggered dose pattern with at least 48 hours between subjects. Additional daily dose levels and/or dosing schedules (including BID regimen) may be studied based on clinical safety, tolerability, and PK data obtained during this study.

All subjects will be treated with the study drug in cycles of 28 days and the DLTs that occur within the first cycle will be used to determine MTD. Progression to the next dose level will be based upon the dose escalation/de-escalation/elimination rules (See Section 14.1) and SRC review of the safety and PK data (if available) of the current dose group.

Figure 4: Flowchart for Trial Conduct Using the BOIN design



$$* \text{ DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of evaluable patients treated at the current dose}}$$

A screening visit will occur within 28 days of signing an informed consent form (ICF). In Cycle 1 (except Day 2 and Day 3), EZM0414 will be administered orally once daily (QD) without food (no food two hours prior and one hour after EZM0414 dose, water is permitted without restrictions) in continuous 28-day cycles. Subjects will continue to receive treatment at the assigned dose level until disease progression, occurrence of unacceptable toxicity, withdrawal of consent, or need for treatment prohibited on this study. No intra-patient dose escalation will be permitted. DLT (as defined in Table 3) will be assessed during the first treatment cycle. Dose modifications for EZM0414 are discussed in Table 4.

Safety assessments will be performed throughout the study and at each study visit. Vital signs including blood pressure, respiration rate, heart rate, and temperature will be collected according to schedule of assessments (Table 8 and Table 9).

A single 12-lead ECG will be collected at screening and triplicate ECGs 1-minute apart will be collected at all other time points mentioned in Table 8 and Table 9. Subjects should be rested in a sitting position for 10 min prior to collection of all study ECGs.

Blood samples will be collected from all subjects for PK analyses at time points mentioned in Table 9.

At time points where vital signs, ECG and PK blood samples are required, the following order of collection is recommended (1) vital signs, (2) ECG (3) Blood sample for PK analyses and biomarker analyses.

Translational samples for research

Tumor samples in MM subjects: Bone marrow aspirates and a bone marrow biopsy will be collected at screening or Cycle 1 Day 1 (pre-dose) in subjects with MM. For subjects with MM, a bone marrow biopsy and bone marrow aspirations will be performed on-treatment (Cycle 3 Day 1). In subjects with MM a bone marrow biopsy and bone marrow aspirates will be performed at VGPR. A non-mandatory bone marrow biopsy and bone marrow aspirates can be performed at progression in MM subjects. If a standard of care (SOC) bone marrow will be performed, a bone marrow aspiration will be requested for research in MM subjects.

Tumor samples in DLBCL subjects: In subjects with DLBCL, archival tissue sample not older than 6 months will be collected. In DLBCL subjects with not enough archival tissue available, an optional fresh biopsy is recommended at screening or Cycle 1 Day 1 (pre-dose). An on-treatment biopsy (Cycle 3 Day 1) will be optional for subjects with DLBCL. An optional tumor biopsy will be taken in subjects with DLBCL at PR. A non-mandatory tumor biopsy can be performed at progression in DLBC subjects. Biopsies in patients with DLBCL will be optional and a separate ICF will be provided.

Blood samples for biomarker analyses in MM and DLBCL subjects: Blood samples for exploratory analyses will be collected pre-dose at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1 and after that every other cycle until Cycle 26 and then every 4 Cycles after Cycle 26, at progression, and at any response event.

Blood samples, tissue samples and bone marrow aspirates for biomarker analyses in MM and DLBCL subjects: In blood samples and tumor tissue/bone marrow aspirates/tumor cells DNA alterations such as mutations, copy number variation (CNV), and other DNA alterations will be assessed, RNA expression will be investigated in tumor tissue/bone marrow aspirates/tumor cells and/or blood samples (eg circulating tumor cells [CTCs] in the PBMC fraction/in PBMCs and/or the buffy coat) as well as protein expression and methylation status. Different assays such as next-generation sequencing (NGS), fluorescent-in situ hybridization (FISH), immunohistochemistry, and others will be performed to investigate translational research samples.

Assessment of Safety

In the Phase 1 safety portion, a Safety Review Committee (SRC) will monitor safety data on an ongoing basis. All dose escalation decisions will be made by the SRC upon review of all

available data. Determination of the MTD will be informed by all available data, including the overall tolerability of EZM0414.

Assessment of response

Assessment of response to treatment will be performed according to IMWG 2016 (Kumar, 2016; Appendix 1) consensus criteria in MM subjects and Lugano Classification (Cheson, 2014; Appendix 2) in DLBCL subjects.

In MM: IMWG 2016 consensus criteria that includes serum M-protein, 24-hour urine M-protein, serum free light chain kappa, lambda, and their ratio, bone marrow aspiration (complete response) and bone marrow biopsy (stringent complete response). Hence, subjects with MM would need to undergo a bone marrow biopsy or bone marrow aspiration for IMWG response assessment (Kumar, 2016; Appendix 1).

In DLBCL: International Working Group consensus response evaluation criteria in lymphoma, Lugano Classification (Cheson, 2014; Appendix 2). Hence subjects with a previously positive or unknown bone marrow biopsy at baseline would undergo a bone marrow biopsy in suspected CR.

Part 2: Phase 1b Safety and Efficacy Dose Expansion

In the dose expansion phase, Bayesian optimal phase 2 (BOP2) design will be used to evaluate safety and efficacy in subjects with or without select genetic translocation in R/R MM and R/R DLBCL.

In the dose expansion part, 60 subjects will be enrolled (20 subjects/cohort) and treated:

- Cohort 1: R/R MM with t(4;14)
- Cohort 2: R/R MM without t(4;14)
- Cohort 3: R/R DLBCL

During the treatment period, subjects will receive EZM0414 in continuous 28-day cycles. EZM0414 will be administered orally once daily (QD) without food (nothing to eat two hours prior and one hour after EZM0414 dose, water is permitted as needed). The subjects who receive EZM0414 at MTD and do not have DLT in the dose escalation part of the study will be rolled over to a cohort of this dose expansion part, depending on their condition (R/R MM or R/R DLBCL) and the select genetic translocation for R/R MM. All subjects will continue to receive treatment at the MTD in Phase 1b part until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent, or need for treatment prohibited on this study. Subjects with R/R MM regardless of t(4;14) status will be enrolled first. Dose modifications for EZM0414 are discussed in Table 4.

Safety assessments will be performed throughout the study and at each study visit. Vital signs including blood pressure, heart rate, respiration rate, and temperature will be collected according to schedule of assessments (Table 8 and Table 10).

A single 12-lead ECG will be collected at screening and triplicate ECGs, 1-minute apart will be collected at time points mentioned in Table 8 and Table 10.

Blood samples will be collected from all subjects for PK analyses at the time points mentioned in Table 10.

At time points where vital signs, ECG and PK blood samples are required, the following order of collection is recommended 1) vital signs, 2) ECG and 3) blood sample for PK analyses and biomarker analyses.

Assessment of response

Assessment of response to treatment will be performed according to IMWG 2016 consensus criteria (Kumar, 2016; Appendix 1) in MM subjects and Lugano Classification (Cheson, 2014; Appendix 2) in DLBCL subjects. To assess response according to IMWG 2016, subjects with MM will undergo bone marrow aspirates or biopsies to assess CR or stringent CR. respectively. To assess complete response according to Lugano Classification, subjects with DLBCL might undergo a bone marrow biopsy. In MM subjects, treatment response will include serum M-protein, 24-hour urine M-protein, serum free light chain kappa, lambda, and their ratio. In DLBCL, imaging will be used to assess response.

Translational samples for research

Tumor samples in MM subjects: Bone marrow aspirates and a bone marrow biopsy will be collected from all MM subjects at baseline (at screening or Cycle 1 Day 1 pre-dose), on-treatment (Cycle 3 Day 1) and at VGPR. A non-mandatory bone marrow biopsy and bone marrow aspirates will be taken for subjects with MM at disease progression. If a SOC bone marrow will be performed, a bone marrow aspiration will be requested for research in subjects with MM.

Tumor samples in DLBCL subjects: In subjects with DLBCL, archival tissue sample not older than 6 months will be collected and if not available, an optional fresh biopsy will be performed at screening or Cycle 1 Day 1 (pre-dose). An optional on-treatment biopsy (Cycle 3 Day 1) and at PR will be performed in DLBCL subjects. Non-mandatory tumor biopsies in subjects with DLBCL will be taken at disease progression. All biopsies for subjects with DLBCL will be optional and a separate ICF will be provided.

Blood samples for biomarker analyses in MM and DLBCL subjects: Blood samples will be collected predose at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, after that at every other cycle until Cycle 26 and then every 4 cycles after Cycle 26, at progression, and at any response event.

Blood samples, tissue samples and bone marrow aspirates for biomarker analyses in MM and DLBCL subjects: In blood samples and tumor tissue/bone marrow aspirates/tumor cells DNA alterations such as mutations, copy number variation (CNV), and other DNA alterations will be assessed, RNA expression will be investigated in tumor tissue/bone marrow aspirates/tumor cells and/or blood samples (eg circulating tumor cells [CTCs] in the PBMC fraction/in PBMCs and/or the buffy coat) as well as protein expression and methylation status. Different assays such as next-generation sequencing (NGS), fluorescent-in situ hybridization (FISH), immunohistochemistry, and others will be performed to investigate translational research samples.

The translational research samples will be investigated for clones harboring t(4;14) translocation, somatic mutations such as SETD2, multiple myeloma SET domain (MMSET), expression of H3K36me2, and H3K36me3. Other markers and analysis might be performed as well.

Biomarker results including PD data will be correlated with PK data or outcome to investigate possible differences between subjects who respond to treatment versus those who do not respond.

7.2. Number of Subjects

Phase 1 dose escalation: up to 36 subjects.

Phase 1b dose expansion: up to 60 subjects.

Total: approximately 96 subjects.

7.3. Treatment Assignment

After obtaining written informed consent, subjects with R/R MM and R/R DLBCL will be screened according to the exclusion and inclusion criteria. Subjects who meet all selection criteria will receive a unique subject number upon enrollment in the study. Subject numbers will be allocated sequentially in the order in which subjects are enrolled. The Investigator or designee will enter the corresponding subject number in each subject's electronic case report form (eCRF).

In part 1, subjects will be administered EZM0414 based on the dose level they are enrolled in. Six dose levels starting at100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg as well as an optional step-down dose level of 75 mg (if needed) will be tested in this dose escalation part of the study.

In part 2, subjects will be enrolled and treated with EZM0414 at the MTD in 3 cohorts:

- Cohort 1: R/R MM with t(4;14)
- Cohort 2: R/R MM without t(4;14)
- Cohort 3: R/R DLBCL

All subjects in this study will receive EZM0414 as monotherapy orally once daily (QD) in 28-day cycles.

7.4. Duration of Treatment

Subjects will be treated continuously until consent withdrawal, unacceptable toxicity, disease progression, or need for treatment prohibited on this study. Each treatment cycle will be of 28-day duration. There will be a 30-day safety follow-up.

7.5. Dose Adjustment Criteria

7.5.1. Dose Limiting Toxicities

Any adverse event (AE) which meets the criteria of a DLT as assessed by the Investigator and warrants action as per Table 3, will be reviewed by the Safety Review Committee (SRC). No intra-patient dose reduction will be permitted in Cycle 1 of dose escalation. For subjects who require a dose interruption due to a DLT during cycle 1, the treatment will be restarted once the toxicity resolves to Grade ≤1 or baseline. However, an interruption in the administration of EZM0414, for more than 14 days will be discussed with the Sponsor's or Designee Medical

Monitor before treatment can be resumed. The DLT evaluable subjects will consist of dose escalation dose level subjects who received at least 80% of planned study treatment during cycle 1. If a subject is non evaluable, this subject will be replaced by a new subject.

Safety assessments will be performed throughout the study and at each visit. DLT period is 28 days of cycle 1 of the dose escalation part. AEs that are clearly and incontrovertibly due to the underlying disease or extraneous causes will not be considered as DLTs. All of the AEs of specified grades as listed in Table 3 will be classified as DLTs. Events will be assessed as DLTs according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0), as shown in Table 3 (Appendix 5). When a subject is assessed to be experiencing a DLT, study treatment will be interrupted and DLTs will be managed by concomitant medication (as appropriate), treatment discontinuation, or a combination of these. All dose escalation decisions will be made by the SRC and Sponsor upon review of all available data. Determination of the MTD will be informed by all available data, including the overall tolerability of EZM0414.

Table 3: Dose Limiting Toxicities

Toxicity Category	Dose-Limiting Toxicity/CTCAE (version 5.0) Grade
Hematological toxicity	• Grade 4 neutropenia lasting more than 5 days • Grade 3 febrile neutropenia (ANC <1.0 x 10^9/L fever ≥ 38.4°C or ≥ 38°C for 1 hour) • Grade 3 thrombocytopenia with clinically significant bleeding • Grade 4 thrombocytopenia • Grade 4 Anemia unexplained by underlying disease
Other non-hematological toxicity	• Any other non-hematologic toxicity ≥ 3 except: – Alopecia – Grade 3 nausea/vomiting or diarrhea for less than 3 days with adequate antiemetic and other supportive care – Grade 3 fatigue for less than one week – Grade 3 or higher isolated electrolyte abnormalities that last up to 3 days, are not clinically complicated, and resolve spontaneously, or respond to conventional medical interventions – Grade 3 or higher amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis – Grade 3 tumor lysis syndrome (TLS) that lasts up to 3 days, is not clinically complicated, and resolves spontaneously, or responds to conventional medical interventions. • Any patient meeting Hy's Law Criteria without alternate explanation, concurrent values of: – ALT or AST elevation of >3xULN, and – TBL elevation of >2xULN, and – Absence of initial findings of cholestasis (ie, absence of elevation of ALP to >2xULN)

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group (ECOG); TBL = total bilirubin; ULN = upper limit of normal
Note: ALT is also referred to as serum glutamic pyruvic transaminase (SGPT); AST is also referred to as serum glutamic oxaloacetic transaminase (SGOT)

7.5.2. Dose Reductions and Interruptions

EZM0414 dose adjustments/reductions and interruptions will be allowed. However, an interruption in the administration of EZM0414, for more than **14 days** must be discussed with the Sponsor's or Designee 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 study drug, dose interruption and reduction for subjects who experience study drug-related toxicity will be in accordance with the Dose Modifications Instructions in Table 4.

For subjects who require dose interruption due to study drug-related toxicity, the treatment may restart once the toxicity has resolved to Grade ≤ 1 or baseline according to the Dose Modifications Instructions in Table 4. If clinically appropriate thereafter re-escalation can be considered in consultation with the Sponsor's Medical Monitor.

Based up on physical exam and respiration rate, follow-up examination should be performed as clinically indicated. For continuation of treatment for cycle 2 and beyond, subjects must meet the following retreatment criteria:

- Platelet count must be ≥50 × 10^9/L, include transfusion dependent subjects
- Absolute neutrophil count (ANC) must be ≥1.0 × 10^9/L if no lymphoma infiltration of bone marrow **OR** ANC must be ≥0.75 × 10^9/L with bone marrow infiltration, and
- Any Grade 3 or higher toxicity must have resolved to Grade 1 or baseline, unless otherwise noted.

The suggested dose reductions for the three lowest dose levels are as follows based on the dose reduction increments included in Table 4:

- Starting dose: 100 mg QD EZM0414
  - 1st dose reduction 75 mg
  - 2nd dose reduction: 50 mg
- Step down dose (if needed): 75 mg QD EZM0414: 1st dose reduction 50 mg and 2nd dose reduction: 25 mg
- Starting dose: 200 mg QD EZM0414
  - 1st dose reduction 150 mg
  - 2nd dose reduction: 100 mg
- Starting dose: 300 mg QD EZM0414
  - 1st dose reduction 200 mg
  - 2nd dose reduction: 100 mg

All final decisions on dose reductions in response to drug-related AEs should be made after discussion with the Sponsor's Medical Monitor.

Table 4: Dose Modifications Instructions for Grade 1 – Grade 4 study drug-related Adverse Events*

Toxicity[a]	During Therapy	Approximate Study Drug Dose Adjustment[b]
Excluding fatigue, alopecia, nausea, vomiting, or diarrhea not receiving adequate medical treatment. For management of QTcF prolongation please refer to Section 7.5.3, AST/ALT elevations please refer to Table 5, creatinine elevations please refer to Table 6, and INR elevations please refer to Table 7.		
Grade 1		
All occurrences	Continue study drug	Maintain dose level
Grade 2[c]		
Toxicity	**During therapy**	**Approximate Study Drug Dose Adjustment[b]**
1st occurrence	Monitor as clinically indicated	Maintain dose level
2nd occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline[b]	Maintain dose level
3rd occurrence		Restart at one lower dose level
4th occurrence	Discontinue study drug	Not applicable
Grade 3[c,d]		
Toxicity	**During therapy**	**Approximate Study Drug Dose Adjustment[b]**
1st occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline[b]	Restart at one lower dose level
2nd occurrence		Restart at second lower dose level
3rd occurrence	Discontinue study drug	Not applicable
Grade 4		
Any occurrence	Discontinue study drug	Not applicable

AST = aspartate aminotransferase; ALT = alanine aminotransferase; INR = international normalized ratio
* Subjects diagnosed with a Covid-19 positive PCR test will be discontinued from treatment.
[a] The term occurrences applies to same AE term and not any AE term.
[b] An interruption of any study drug for more than 14 days due to any toxicity must be discussed with the Sponsor's or Designee Medical Monitor before treatment can be resumed.
[c] Excluding Grade 2 and 3 anemia: Subjects are allowed to continue study drug at their current dose level with transfusion per Investigator discretion.
[d] Use of growth factors (G-CSF, GM-CSF) is permitted as per ASCO and ESMO guidelines

7.5.3. Safety Management Guidelines

Investigation: QTcF prolongation

The QTcF is the QT interval corrected for heart rate according Fridericia's formula (QTcF). For eligibility and withdrawal, subjects QTcF value will be used. For purposes of data analysis, QTcF values will be used.

If QTcF >500 msec or QTcF prolongation >60 msec from baseline is observed at any point during the study treatment and confirmed, the below guidance must be followed:

1. Assess the quality of the ECG recording and the QT value and repeat if needed.
2. Interrupt study treatment until confirmed resolution of QTcF and as per dose reduction guidelines in Table 4.
3. Determine the serum electrolyte levels (in particular hypokalemia hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication use for other causes for QT prolongation (refer to qtdrugs.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation (e.g., concomitant use of CYP3A4 inhibitors).
5. Check study drug dosing diary and treatment compliance.
6. Increased ECG safety monitoring is recommended during or in-between subsequent visits.

Table 5: Investigation: Hepatic

Liver function elevation management: Elevations in AST and/ or ALT			
Grade 1	All occurrences	Continue study drug	Maintain dose level
Grade 2	1st occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Maintain dose level
	2nd occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Maintain dose level
	3rd occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Restart at one lower dose level
	4th occurrence	Discontinue study drug	Not applicable
Grade 3	1st occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Maintain dose level
	2nd occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Restart at one lower dose level
	3rd occurrence	Discontinue study drug	Not applicable
Grade 4	Any occurrence	Discontinue study drug	Not applicable

Table 6: Investigation: Renal

Creatinine elevation management:			
Grade 1	All occurrences	Continue study drug	Maintain dose level
Grade 2	1st occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Maintain dose level
	2nd occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Restart at one lower dose level
	3rd occurrence	Discontinue study drug	Not applicable
Grade 3	1st occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Restart at one lower dose level
	2nd occurrence	Discontinue study drug	Not applicable

Grade 4	Any occurrence	Discontinue study drug	Not applicable

Table 7: Investigation: Coagulation

INR management:			
Grade 1	All occurrences	Continue study drug	Maintain dose level
Grade 2	1st occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Maintain dose level
	2nd occurrence	Interrupt study drug until resolved to Grade ≤1 or baseline	Restart at one lower dose level
	3rd occurrence	Discontinue study drug	Not applicable
Grade ≥3	Any occurrence	Discontinue study drug	Complete safety assessments as clinically indicated

7.5.4. Safety Stopping Rules

Monitoring of all toxicity will be routinely performed by the SET-101 Safety Review Committee (SRC), composed of SET-101 investigators, Epizyme Medical Directors and Pharmacovigilance. Unacceptable toxicity is defined as those treatment-emergent adverse events that are at least possibly related to study drug, are of CTCAE Grade 4 or 5, and for which no other cause is identified.

For unacceptable toxicities: If there are more than 25% (of the total number of subjects treated within the safety population [MM and DLBCL]) study drug withdrawals due to treatment related grade 4 or 5 toxicity at any point during the study, the SRC will escalate the safety findings to an ad hoc Epizyme Quarterly Safety Review (QSR) committee meeting. The QSR committee, an internal cross functional scientific and medical review board, will determine the final action for study SET-101. The decision will be communicated to investigators and health authorities, as applicable.

For treatment related deaths: the SRC will also perform ongoing assessment and monitoring during routine data review meetings. All treatment-related deaths will trigger an ad hoc QSR meeting for full evaluation and decision with regard to continuing study SET-101.

7.5.5. Post-Treatment Monitoring for Hematologic Second Primary Malignancy

Post treatment monitoring as clinically indicated will be performed for those subjects who 1) do not enroll in a new clinical study, 2) do not withdraw consent and 3) do not begin a new anti-neoplastic therapy. Monitoring will include a complete blood count with at least an automated differential or peripheral blood smear.

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

This is a FIH study. The objective of this study is to evaluate the safety, tolerability, and PK of EZM0414 in order to determine MTD in Phase 1 part, and safety, tolerability, PK, and efficacy to determine RP2D in Phase 1b part.

This is an open-label study and there will be no randomization. Subjects will be enrolled based on their conditions.

The sample size of Phase 1 part is determined based on number of doses to be tested using BOIN design and there is no formal sample size estimation for the Phase 1b part of the study.

The study will enroll approximately 96 subjects, of which up to 36 subjects will be enrolled in Phase 1 dose escalation part and 60 subjects (20 subjects/cohort) will be enrolled in Phase 1b dose expansion part. There will be 6 dose levels (starting at 100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg) as well as an optional step-down dose level of 75 mg (if needed) to be tested in Phase 1 dose escalation part to determine MTD, and additional daily dose levels and/or dosing schedules (including BID regimen) may be studied based on clinical and pharmacokinetic data obtained during this study. The sample size will therefore be adjusted accordingly. There will be 3 cohorts for the dose expansion part: 20 R/R MM subjects with t(4;14), 20 R/R MM subjects without t(4;14) and 20 R/R DLBCL subjects.

The subjects who are treated at MTD in Phase 1 dose escalation part and do not experience any DLT will continue to receive the treatment beyond cycle 1 (be rolled over to the dose expansion part) until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent, or need for treatment prohibited on this study.

There will be 3 looks performed in Phase 1b part when the data of 10, 15, and 20 subjects of a cohort have been available. The cohort will be terminated earlier if deemed futile by SRC and the study team.

7.6. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study for medical reasons or for any other reason at any time. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The institutional review board (IRB)/independent ethics committee (IEC) should also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted in Section 18.3.

Table 8: Schedule of Assessments for Dose Escalation and Dose Expansion

Assessment	Screening	Cycle 1							Cycle 2				Cycle 3 and Cycle 4		Cycle 5+	EOT[a]	Safety Follow up[b]
Study day (window)	**-28 to -1**	1[c]	**2**	**3**	**4**	**8 (±3D)**	**15 (±3D)**	**22 (±3D)**	**1 (±3D)**	**2**	**8 (±3D)**	**15 (±3D)**	**1 (±3D)**	**15 (±3D)**	**1 (±3D)**		**30 (±3D)**
Informed Consent	X																
Eligibility Criteria	X	X															
Demographics	X																
Medical History	X																
Physical Exam (Complete)	X	X														X	X
Physical Exam (Symptom-directed)						X	X	X	X			X	X	X	X		
Height (screening only) and body weight	X	X							X				X		X	X	X
Vital Signs	X	X	X	X[d]	X[d]	X	X	X	X		X	X	X	X	X	X	X
ECOG	X	X							X				X		X	X	X
12-lead ECG[e]	X	X	X			X	X	X	X	X	X	X	X		X[e]	X	
Disease assessment for DLBCL subjects [f]	X												C3 only		Cycle 5, 7, 9 etc	X	
Adverse Events	X																

Assessment	**Screening**	**Cycle 1**							**Cycle 2**				**Cycle 3 and Cycle 4**		**Cycle 5+**	**EOT**[a]	**Safety Follow up**[b]
Study day (window)	**-28 to -1**	1[c]	**2**	**3**	**4**	**8 (±3D)**	**15 (±3D)**	**22 (±3D)**	**1 (±3D)**	**2**	**8 (±3D)**	**15 (±3D)**	**1 (±3D)**	**15 (±3D)**	**1 (±3D)**		**30 (±3D)**
Concomitant medications	X																
Hematology[g,*]	X	X				X	X	X	X		X	X	X	X	X	X	X
Blood chemistry[h]	X	X				X	X	X	X		X	X	X	X	X	X	X
Coagulation test[i]	X	X				X	X	X	X		X	X	X	X	X	X	X
Pregnancy test[j]	X	X							X				X		X	X	X
Urinalysis	X	X							X				X		X	X	X
EZM0414 oral administration		Continuous oral administration in 28-day cycles per escalation schedule or expansion. In dose escalation: EZM0414 will be administered on C1D1 but will not be administered on C1D2 and C1D3. C1D4, C1D15 and C2D2 dose will be administered after PK sample collection. In dose expansion: C1D2 and C2D2 dose will be administered after PK sample collection.															
Bone marrow aspirates and bone marrow biopsy[k]	X[l]	X[l]											X[m]		X[m]		
Serum β2 microglobulin (MM subjects only)	X															X	
Serum M-protein serum (MM only)	X	X							X				X		X	X	
24-hour urine sample for M-	X	X							X				X		X	X	

Assessment	Screening	Cycle 1							Cycle 2				Cycle 3 and Cycle 4		Cycle 5+	EOT[a]	Safety Follow up[b]
Study day (window)	**-28 to -1**	1[c]	**2**	**3**	**4**	**8 (±3D)**	**15 (±3D)**	**22 (±3D)**	**1 (±3D)**	**2**	**8 (±3D)**	**15 (±3D)**	**1 (±3D)**	**15 (±3D)**	**1 (±3D)**		**30 (±3D)**
protein (MM only)																	
Serum free light-chain assay (MM only)	X	X							X				X		X	X	
MM Disease assessment by IMWG		X							X				X		X	X	
Skeletal survey (MM only)[n]	X	As clinically indicated and per the local standard of care for imaging (X-ray or MRI). The same methodology used at Screening should be used throughout the study for comparison purposes.															
CT or PET/CT for extramedullary soft tissue plasmacytoma (MM only)	X												X (Cycle 3 only)		X[o]		
Whole blood for exploratory analysis[p]		X					X		X				X		X		
Tumor tissue (DLBCL only)[q]	X	X											X (cycle 3 only)		X (optional)		
PK		Please refer to Table 9 for dose escalation PK and Table 10 for dose expansion PK collection schedule														X	

Abbreviations: aPTT = activated partial thromboplastin; BNP = brain natriuretic peptide; C = Cycle; CR = complete response; CT = computed tomography; D = Day; DLBCL = diffuse large B cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group status; EOT = end of treatment; FDG = fluorodeoxyglucose; IMWG = International Myeloma Working Group; INR = international normalized ratio; MM = multiple myeloma; M-protein =

Assessment	Screening	Cycle 1							Cycle 2				Cycle 3 and Cycle 4		Cycle 5+	EOT[a]	Safety Follow up[b]
Study day (window)	**-28 to -1**	1[c]	**2**	**3**	**4**	**8 (±3D)**	**15 (±3D)**	**22 (±3D)**	**1 (±3D)**	**2**	**8 (±3D)**	**15 (±3D)**	**1 (±3D)**	**15 (±3D)**	**1 (±3D)**		**30 (±3D)**
monoclonal protein; PK = pharmacokinetics; PT = prothrombin time; sCR = stringent complete response complete response; VGPR = very good partial response																	

[a] End of treatment visit should be completed within 7 days of the last dose of study drug. This visit may be completed at a scheduled visit when a decision to discontinue treatment is made.

[b] 30-day safety follow-up should be completed 30 (±3) days after last dose of study drug or before start of a new anti-cancer therapy, whichever occurs first.

[c] Cycle 1 Day 1 hematology, serum chemistries, coagulation and urinalysis may be performed on Cycle 1 Day -1.

[d] Only in Part 1 dose escalation.

[e] Collect single ECG at screening and triplicate ECGs at all other timepoints. ECGs during Cycle 1 and Cycle 2 are per Table 9 (dose escalation) and Table 10 (dose expansion). Triplicate ECGs will also be collected at pre-dose (within 30 min of dose) and 2-hours post (± 10min) on Day 1 of every odd cycle starting at Cycle 3 Day 1, and at end of treatment.

[f] Radiologic disease assessments at screening and every 8 weeks ±7 days. PET/CT whole body for FDG avid disease OR contrast enhanced CT of neck, chest, abdomen, and pelvis for subjects with non-FDG avid disease. Use the same modality for disease assessment through the study for each patient.

[g] Hematology assessments will include red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count, peripheral blood smear, and reticulocyte count.
* Post treatment monitoring as clinically indicated will be performed for those subjects who 1) do not enroll in a new clinical study, 2) do not withdraw consent and 3) do not begin a new anti-neoplastic therapy. Monitoring will include a complete blood count with at least an automated differential or peripheral blood smear.

[h] Blood chemistry assessments will include sodium, potassium, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, calcium, glucose, total creatine kinase, total bilirubin, lactic dehydrogenase, creatinine, total protein, bicarbonate, phosphorus, magnesium, uric acid, amylase, lipase, cardiac markers- BNP, and Troponin.

[i] Coagulation tests include aPTT, PT/INR, and fibrinogen.

[j] Serum pregnancy test at screening and serum/urine pregnancy test at all other visits. Cycle 1 Day 1 pregnancy test does not need to be repeated if screening test performed within 72 hours of Cycle 1 Day 1.

[k] Subjects with MM: Bone marrow aspirations and a bone marrow biopsy will be taken at screening/baseline (pre-dose), Cycle 3 Day 1, VGPR for translational studies. Bone marrow aspirates and bone marrow biopsies will be taken at CR and sCR to assess response according to IMWG 2016 criteria as per local institutional practice. If a SOC bone marrow will be performed a bone marrow aspiration will be taken for research in subjects with MM. A non-mandatory bone marrow biopsy and bone marrow aspirates can be taken at progression for research.

[l] MM: Bone marrow aspirates and bone marrow biopsy are taken either at screening/baseline or at Cycle 1 Day1 (predose).

[m] Translational research samples will be collected at Cycle 3 Day 1, VGPR and progression. A bone marrow aspirate will be collected for research if SOC biopsy will be performed for CR or sCR for MM. SOC samples will be taken at CR and sCR to assess ORR.

[n] Skeletal surveys for sites that do not have CT/PET-CT capabilities.

[o] Perform CT or PET/CT at screening, Cycle 3 Day 1 (±7 days) and then starting at cycle 6, every 3 cycles (±7 days) or sooner if clinically indicated.

[p] Whole blood will be collected for: Plasma and CTC in the PBMC fraction, PBMCs and/or buffy coat at Cycle 1 Day1 (pre-dose), Cycle 1 Day 15 (pre-dose), Cycle 2 Day 1 (pre-dose), Cycle 3 Day 1 (pre-dose), progression, or any response. After Cycle 3 Day 1 every other cycle until Cycle 26 and then every 4 Cycles after Cycle 26. For exact sample collections see quick chart (Laboratory manual).

[q] DLBCL subjects: Archival tissue or an optional fresh biopsy can be taken in subjects with DLBCL. An optional biopsy can be taken at PR. A non-mandatory biopsy can be taken at progression. An optional biopsy can be taken on-treatment at Cycle 3 Day 1.
Subjects with DLBCL: Bone marrow biopsy at suspected complete response if bone marrow status was unknown or positive at study entry. Bone marrow aspirate will be taken at CR if at baseline bone marrow status was unknown or positive.

Table 9: PK, Vitals and ECG schedule for Phase 1 (dose escalation)

		C1D1	C1D2	C1D3	C1D4	C1D8	C1D15	C1D22	C2D1	C2D2	C2D8	C2D15	Day 1 of Odd cycles (C3, C5, C7 etc.)
PK	Pre-dose (within 30 min)	X					X		X				X
	30min (±5min)	X							X				
	60min (±5min)	X							X				
	90min (±5min)	X							X				X
	3hr (±10min)	X							X				
	6hr (±10min)	X							X				
	10hr (±60min)	X							X				
	24hr (±60min)		X[a]							X[b]			
	48hr (±2hr)			X[a]									
	72hr (±2hr)				X[b]								
Vital signs	Pre-dose (within 30 min)	X							X				
	30min (±10min)	X							X				
	1hr (±10min)	X							X				
	2hr (±10min)	X							X				
	4hr (±10min)	X							X				
	6hr (±30min)	X							X				
Triplicate ECGs	Pre-dose (within 30 min)	X				X	X	X	X		X	X	X
	30min (±5min)	X							X				
	1hr (±5min)	X							X				
	2hr (±10min)	X				X	X	X	X		X	X	X
	4hr (±10min)	X							X				
	6hr (±30min)	X							X				

		C1D1	C1D2	C1D3	C1D4	C1D8	C1D15	C1D22	C2D1	C2D2	C2D8	C2D15	Day 1 of Odd cycles (C3, C5, C7 etc.)
	24hr (±60min)		X							X[b]			

C = Cycle; D = Day; ECG = electrocardiogram; PK = pharmacokinetics

[a] Skip dosing with EZM0414 on C1D2 and C1D3.

[b] PK sample must be collected prior to dosing with EZM0414 on C1D4 and C2D2. ECG must be collected prior to dosing with EZM0414 on Cycle 2 Day 2.

Table 10: PK, Vitals and ECG Schedule for Phase 1b (dose expansion)

		C1D1	C1D2	C2D1	C2D2	Day 1 of Odd cycles (C3, C5, C7, etc)
PK	Pre-dose (within 30 min)	X		X		X
	30min (±5min)	X		X		
	60min (±5min)	X		X		
	90min (±5min)	X		X		X
	3hr (±10min)	X		X		
	6hr (±10min)	X		X		
	10hr (±60min)	X		X		
	24hr (±60min)		X[a]		X[a]	
Vital signs	Pre-dose (within 30min)	X		X		
	30min (±10min)	X		X		
	1hr (±10min)	X		X		
	2hr (±10min)	X		X		
	4hr (±20min)	X		X		
	6hr (±30min)	X		X		
Triplicate ECGs	Pre-dose (within 30 min)	X		X		
	30min (±5min)	X		X		
	1hr (±5min)	X		X		
	2hr (±10min)	X		X		
	4hr (±10min)	X		X		
	6hr (±30min)	X		X		
	24hr (±60min)		X[a]		X[a]	

C = Cycle; D = Day; ECG = electrocardiogram; PK = pharmacokinetics

[a] PK and ECG must be collected prior to dosing on C1D2 and C2D2.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

To be eligible for inclusion in the trial, the subject has to meet all inclusion criteria and must not violate any of the exclusion criteria. Deviations to the protocol inclusion and exclusion criteria will not be allowed. If there is a question about eligibility, the investigator should consult with the sponsor's medical monitor.

Investigators should ensure that all study enrolment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, he or she should be excluded from participation in the study.

8.1. Subject Inclusion Criteria

1. Voluntarily provide signed informed consent after review of verbal and written material about the trial and agree to abide with protocol requirements. All study related activities must be carried out after written consent is obtained.
2. Subjects must be ≥18 years of age at the time of signing the ICF.
3. Subjects must have an ECOG status of 0 – 2 (Appendix 3).
4. For **MM**, subjects must have measurable disease by IMWG 2016 criteria (Kumar, 2016; Appendix 1) as defined by at least one of the following:
   - Serum monoclonal protein (M-protein) concentration ≥ 0.5g/dL.
   - Urine M-protein excretion of ≥ 200mg in 24 hours.
   - Serum free light chain concentration ≥10mg/dL with an abnormal (<0.26 or >1.65) κ:λ free light chain ratio.
5. For **DLBCL**, subjects must have measurable disease by Lugano criteria (Cheson, 2014; Appendix 2).
6. **MM** subjects who are relapsed/refractory to immune modulator, proteasome inhibitor and anti-CD38 therapy. Subjects who could not tolerate a PI, IMiDs, and a CD38-directed cytolytic antibody are eligible to participate and R/R MM subjects who are intolerant of established therapies known to provide clinical benefit in multiple myeloma.
7. **DLBCL** subjects who are relapsed or refractory with at least two prior line including treatment with R-CHOP, R-EPOCH, R-hyperCVAD and other standard of care therapies. Lines of therapy could have been discontinued due to completion of therapy, intolerance, or lack of response.

   Note: Relapsed disease is defined as progression of disease, after initial response to previous treatment, more than six months after end of treatment. Refractory disease is defined as resistance to treatment due to lack of response or progression of disease during treatment or within six months after end of treatment.
8. For dose expansion cohort 1 and 2 only; subjects must have local t(4;14) test results available for enrollment.

9. At enrollment, subjects should have an estimated life expectancy ≥ 3 months in the opinion of the Investigator.
10. Subjects must have sufficient organ and marrow function as defined below:
    - Hemoglobin ≥8g/ dL
    - Platelets >75x10^9/L (includes transfusion dependent subjects)
    - ANC≥1000/mm^3. Growth factors within 7 days of screening is not allowed to meet ANC eligibility criteria
    - AST and ALT <2.5xULN, or if attributed to tumor involvement, AST, and ALT <5x ULN
    - Bilirubin ≤1.5xULN
    - Creatinine clearance ≥40 ml/min. Estimated creatinine clearance calculated using the Cockcroft-Gault formula
    - Coagulation parameters: prothrombin time/ international normalized ratio (PT/INR) <1.5xULN and activated partial thromboplastin (aPTT) < 1.5xULN.
11. Females must not be breastfeeding or pregnant at screening (as documented by a negative beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study treatment. All female subjects will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutively amenorrheic, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, and/or bilateral oophorectomy, with all surgery completed at least 1 month before first dosing).
12. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception, beginning at least 14 days prior to study entry, during treatment cycles, and for 30 days after the final dose of study treatment and have a male partner who uses a condom. Highly effective contraception includes:
    - Placement of an intrauterine device.
    - Established hormonal contraceptive methods: oral, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product while enrolled on trial and must continue to use the same contraceptive during the study and for one months after last dose of study drug.
13. Male subjects must either practice complete abstinence **or** agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), during study treatment and for 30 days after the final dose of study treatment.
    Note: Male subjects must not donate semen or sperm from the first dose of study treatment, during study treatment (including during dose interruptions), and for 30 days after the final dose of study treatment.

8.2. Subject Exclusion Criteria

1. Subjects with plasma cell leukemia defined as a plasma cell count >2000/mm^3.
2. Subjects with Waldenstrom's macroglobulinemia or smoldering MM.
3. Subjects with corrected serum calcium >14mg/dL (>3.5mmol/L) or free ionized calcium >6.5mg/dL (1.6mmol/L).
4. Subjects with known systemic amyloidosis.
5. Subjects who had prior treatment with SETD2 or NSD2 inhibitor.
6. Prior cancer therapy for disease under study within the past 4 weeks or 5 half-lives, whichever is shorter. All prior treatment-related AEs must have resolved to Grade 1 or baseline per NCI CTCAE 5.0.
7. Have known active central nervous system (CNS) or any leptomeningeal metastasis of primary extracranial tumor. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging 4 weeks prior to the first dose of study treatment and any neurologic symptoms have stabilized), have no evidence of new or enlarging brain metastases, and are on stable or tapering doses of steroids for at least 7 days prior to first dose of study treatment.

   Note: Subjects with asymptomatic brain metastases found on screening MRI may be entered into the study without prior radiation therapy to the brain if they do not require immediate surgical or radiation therapy in the opinion of the treating Investigator and in the opinion of a radiation therapy or neurosurgical consultant.
8. Subjects taking medications that are known as strong and moderate CYP3A4 and P-gp inducers/inhibitors (including St. John's Wort). Subjects taking ARA, H2 blockers and PPIs. Subjects must stop taking such medications and must not take them for the duration of their participation in the study. Washout of minimum 14 days or 5 half-lives (whichever is longer) prior to starting EZM0414 is required.
9. Subjects unwilling to exclude Seville oranges, grapefruit juice, AND grapefruit from their diet and all foods that contain those fruits from time of enrolment to while on study.
10. Have a known active infection with hepatitis B virus (HBV, as measured by positive hepatitis B surface antigen), hepatitis C virus (HCV, as measured by positive hepatitis C antibody).
    Exceptions: Subjects with a history of hepatitis B or C who have normal ALT AND are hepatitis B surface antigen negative and/or have undetectable HCV RNA are eligible.
11. Known to be human immunodeficiency virus (HIV) seropositive.
12. Subjects with active acute or chronic systemic infection requiring systemic treatment, including COVID-19.
13. Has cardiovascular impairment: history of congestive heart failure greater than NYHA Class II, uncontrolled arterial hypertension (ie, systolic blood pressure (BP) >150 mm Hg and/or diastolic BP >110 mm Hg), unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of study drug; or ventricular cardiac arrhythmia requiring medical treatment (Appendix 4).

14. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec or history of long QT syndrome. A history or evidence of current clinically significant uncontrolled arrhythmias. History of additional risk factors for Torsade de Pointes including heart failure, hypokalemia, family history of Long QT Syndrome, and use of concomitant medications that are known to increase the risk of Torsade de Pointes (www.crediblemeds.org).
15. Known left ventricular ejection fraction (LVEF) < 50% by either echocardiogram (ECHO) or multigated acquisition (MUGA).
16. Prior major surgery within 4 weeks of treatment start.
17. Known hypersensitivity to components of the investigational product.
18. Subjects who have received treatment with any unapproved drug product within 4 weeks prior to screening.
19. Current participation in any other interventional clinical study except for follow-up.
20. Subjects with a history of or active malignancy other than disease under study, except for:
    - Cervical carcinoma Stage 1B or less.
    - Surgically treated non-invasive basal cell and squamous cell skin carcinoma.
    - Malignant melanoma with a complete response for more than 10 years.
    - Curable cancer and/or hematologic malignancies diagnoses with a complete response for more than 5 years.
21. Underlying medical/social conditions that in PI opinion will place the subject in significant risk and affect the interpretation of toxicity and adverse events assessments.
22. Inability to take oral medication or known gastrointestinal (GI) disease, GI procedure or medical condition that could interfere with the oral absorption or tolerance of the study drug.

8.3. Subject Withdrawal Criteria

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

Subjects (or legally authorized representatives) can decline to continue receiving any study treatment and/or other protocol-required procedures at any time during the study but can continue participation in the study (eg, for follow-up information). If this occurs, the Investigator is to discuss with the subject (or legally authorized representatives) appropriate processes for discontinuation and the options for procedures that may continue such as collection of data, including endpoints and AEs. The Investigator must document the agreement in the procedures that the subject will continue with and the level of follow-up that is agreed to by the subject (eg,

in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records.) If a subject voluntarily withdraws from the study, the investigator should attempt to contact the subject to determine the reason(s).

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

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

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

A description of the investigational product/study drug is provided in Table 11.

Table 11: Investigational Product/Study Drug

	Investigational Product/Study Drug
Product Name:	EZM0414
Dosage Form:	Immediate-release Tablet
Unit Dose	25 mg or 200 mg
Route of Administration	Oral
Physical Description	25 mg: White to off-white, round, biconvex, coated tablets 200 mg: White to off-white, capsule-shaped, biconvex, coated tablets
Manufacturer	Pharmaron Beijing, Co., Ltd.

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

Definitions, reporting, and management of overdose, misuse, abuse, and medication errors are presented below and refer to EZM0414.

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

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

All instances of special situations are to be reported using the special situations form regardless of presence or absence of an associated AE. Refer to Section 13.6 for detailed instructions on how to handle the reporting of special situations.

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

9.3. Concomitant Medications

Unless clinically indicated, subjects should avoid taking additional non-study medications that may interfere with study treatments. Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded in the CRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Details of prohibited medications are detailed in Table 12 and Appendix 6.

Table 12: Prohibited Medications

Unless stated otherwise, these medications are prohibited from the time that subjects enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anti-cancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy, or any other novel agent for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. Palliative radiotherapy may be used for the treatment of pain, provided the Investigator does not consider these are indicative of clinical progression. Study treatment should be discontinued a minimum of 3 days before a patient undergoes palliative radiotherapy, and study treatment restarted within 4 weeks (provided any bone marrow toxicity has recovered).
Herbal medications and supplements	Should not be given concomitantly unless agreed by the Sponsor. This is due to their potential to modulate CYP3A4 or activity of other enzymes which are not well characterized (see also below), and further details in Appendix 6.
Concomitant medications known to significantly modulate CYP3A4 activity	The principal enzyme for metabolizing EZM0414 is CYP3A4/5. Subjects should avoid concomitant medications and foods known to significantly modulate CYP3A4/5 activity (potent/moderate inhibitors or inducers of CYP3A4). The required washout period prior to starting study treatment is

	minimum 14 days or 5 half-lives (whichever is longer). See Appendix 6.
Concomitant medications known to significantly modulate P-gp activity	EZM0414 is also P-gp substrates. Co-administration of P-gp inhibitors or inducers may affect exposure to EZM0414, and it is recommended that these are not co-administered with EZM0414. See Appendix 6.
Concomitant medications known to significantly alter gastric pH	EZM0414 has pH-dependent solubility. The EZM0414 has potential interact with gastric pH-dependent acid-reducing agents, such as antacids, histamine H2-receptor antagonists (H2 blockers), and proton pump inhibitors (PPIs).
Live virus and bacterial vaccines	Prohibited whilst the patient is receiving study medication and during the 30-day follow-up period.
Anti-cancer therapy like chemotherapy, immunotherapy, hormonal therapy, radiotherapy (except palliative), biological therapy, and other novel agents	Not permitted whilst the patient is receiving study medication.

CYP = Cytochrome P450; P-gp = P-glycoprotein

9.4. Treatment Compliance

Compliance for doses taken outside of the clinic may be assessed by a count of the tablets returned to the study trial site and accounted for by the subject diary.

9.5. Randomization and Blinding

Not applicable.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug Packaging and Labeling

25 mg: Thirty (30) EZM0414 tablets in individually labelled 45 mL heat sealed HDPE bottles with child resistant, tamper-evident polypropylene screw cap, containing a desiccant cartridge.

200 mg: Thirty (30) EZM0414 tablets in individually labelled 75 mL heat sealed HDPE bottles with child resistant, tamper-evident polypropylene screw cap, containing a desiccant cartridge.

10.2. Study Drug Storage

Do not store above 30°C (86°F), Store in original package.

10.3. Study Drug Preparation

EZM0414 drug product is formulated as 25 mg and 200 mg immediate-release film-coated tablets.

10.4. Administration

EZM0414 tablets are intended for oral administration only. Study drug tablets should be swallowed whole and may not be crushed. EZM0414 will be administered at approximately the same time each day and should be taken on an empty stomach with nothing to eat two hours prior and one hour after the EZM0414 dose. Water may be consumed at will.

Missed or vomited dose: If a dose is missed (ie, not within 6 hours of the scheduled dosing time), do not take the dose. Resume dose administration at the next scheduled dose. If a subject vomits after EZM0414 administration, do not take an additional dose. Resume dose administration at the next scheduled dose.

All doses of study drug administered, missed, and vomited (as applicable) are to be recorded in the eCRF.

10.5. Study Drug Accountability

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

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page signed and dated by the Investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC/REB for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required) and the import license (if required)

- An Investigator-signed and dated Form Food and Drug Administration (FDA) 1572 (or Investigator ICH GCP Statement for ex-US sites), a signed and dated curriculum vitae for the Principal Investigator (PI) including a copy of the PI's current medical license (required in the US) or medical registration number on curriculum vitae
- Financial disclosure form for the PI listed on Form FDA 1572/Investigator ICH GCP Statement
- A signed and dated clinical trials agreement.

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

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

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor or a representative of any national health authority. All used and unused study drugs provided by the Sponsor, including empty containers, are to be returned to the Investigator by the subject then potentially to the Sponsor's designated contractor or depot by the conclusion of the study, unless approval is given by the Sponsor for destruction of supplies and containers at the investigational site. Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by the Sponsor's personnel, study drugs that are to be returned to the Sponsor's approved contract vendor must be boxed and sealed and shipped back to the Sponsor's approved contract vendor following all local regulatory requirements.

Study drug accountability will be reviewed during investigational site visits and at the completion of the study.

10.6. Study Drug Handling and Disposal

Study drugs will be stored in accordance with the labeled storage conditions. Refer to the pharmacy manual for details.

All study drug will be supplied to the PI (or a designated pharmacist) by the Sponsor except in the US. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug label. The Investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug

in a drug accountability log, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. Once study drug has been received by the investigational site, the assigned clinical research associate will review these documents along with all other study conduct documents at appropriate intervals during investigational site visits.

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

11. PHARMACOKINETIC ASSESSMENTS

Blood samples (4 mL) will be obtained for the determination of EZM0414 concentration according to the schedule of assessments presented in Table 8, Table 9, and Table 10. The date and time of collection of each sample will be recorded.

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterization of the plasma concentration-time profiles. The timing of later PK samples will be reassessed based on emerging PK data and the desire to characterize 80% of the AUC in all subjects. The total number of samples and the total volume of blood taken from each patient will not exceed than that of planned collection.

If a patient misses any doses of EZM0414 within 3 days of PK sampling, please contact the Epizyme PK representative as to any effect on the changes required on the timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and radiologic assessments should continue to be performed as per study plan, relative to baseline assessments. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterization of metabolites, if consent for this exploratory research has been obtained.

In dose escalation, a screening visit will occur within 28 days of signing an ICF. Subjects will visit the clinical study unit on an out-patient basis from day 1 to day 4, day 8, day 15 and day 22 in cycle 1. Prior to dosing on cycle 1 day 1, subject eligibility will be reconfirmed. A single oral dose of EZM0414 will be administered on day 1. Blood samples for PK analysis will be obtained predose (0 hour), 0.5, 1, 1.5, 3, 6, 10, 24, 48 and 72 hours postdose. The subjects will not be dosed on cycle 1 day 2 and cycle 1 day 3. After the 72-hour PK sample collection conducted on day 4 and the subjects will receive EZM0414 tablets to be taken once daily from day 4 to day 28. Subjects will return to the clinical study unit on an out-patient basis on day 8, day 15, and day 22 for safety monitoring and PK blood sample on cycle 1 day 15. On day 29, subjects will return to out-patient clinic for Cycle 2 Day 1 safety assessment and in clinic administration of EZM0414. Blood samples for PK analysis will be obtained predose (0 hour), 0.5, 1, 1.5, 3, 6, 10 and 24-hours postdose. 24-hour post PK sample will be collected prior to cycle 2 day 2 dose of EZM0414. Vital signs and ECGs will be collected as indicated in Table 9. Subjects will dose with EZM0414 once daily after Cycle 2 Day 1 (Table 8).

In dose expansion, a screening visit will occur within 28 days before day 1 and after signing an informed consent form (ICF). Subjects will visit the clinical study unit on an out-patient basis from day 1 to day 2, day 8, day 15, and day 22 in cycle 1. Prior to dosing on cycle 1 day 1, subject eligibility will be reconfirmed. A single oral dose of EZM0414 will be administered on day 1. Blood samples for PK analysis will be obtained predose (0 hour), 0.5, 1, 1.5, 3, 6, 10, and 24 hours postdose. After the 24-hour PK sample collection conducted on cycle 1 day 2, subjects will receive EZM0414 tablets to be taken once daily from day 2 to day 28. Subjects will return to the clinical study unit on an out-patient basis on day 8, day 15, and day 22 for safety monitoring. On day 29, subjects will return to out-patient clinic for Cycle 2 Day 1 safety assessment and in clinic administration of EZM0414. Blood samples for PK analysis will be obtained predose (0 hour), 0.5, 1, 1.5, 3, 6, 10 and 24 hours postdose. 24-hour post PK sample will be collected prior

to cycle 2 day 2 dose of EZM0414. Vital signs and ECGs will be collected as indicated in Table 10. Subjects will dose with EZM0414 once daily after Cycle 2 Day 1 (Table 8).

11.1. PK Window for Specific PK Timepoints

Unless a specific range is specified, a 5-minute window will be allowed for samples taken up to 1-hour post-dose; a 10 minute window for samples taken between 2-9 hours; a 1 hour window for samples taken between 10-24 hours post-dose, and a 2 hour window between 25-72 hours.

11.2. Determination of Drug Concentration in PK Samples

Samples for determination of EZM0414 concentrations in plasma will be analyzed by Charles River Laboratories, Inc., on behalf of Epizyme, using appropriate bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (ie, EZM0414) at the time of receipt by the bioanalytical laboratory will be analyzed.

In addition, the PK samples may be subjected to further analyses in order to investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report (CSR).

11.3. Storage and Destruction of Pharmacokinetic Samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

12. TRANSLATIONAL RESEARCH SAMPLES

12.1. Tumor Sampling

12.1.1. Archival Tumor, Tumor Biopsy and Bone Marrow Aspirates

Multiple myeloma subjects will undergo a bone marrow biopsy and bone marrow aspirate at screening or Cycle 1 Day 1. All MM subjects will undergo an on-treatment bone marrow biopsy and bone marrow aspirates at Cycle 3 Day 1 and at VGPR. A non-mandatory bone marrow biopsy and bone marrow aspirates can be taken at progression. If a SOC bone marrow will be performed, a bone marrow aspiration will be requested for research as well.

For subjects with DLBCL, unstained slides containing tumor tissue are required (>90% tumor cellularity and min. 5x5mm of tumor area). The archival tissue should not be older than 6 months prior to study enrollment. For subjects without sufficient archival tissue, an optional fresh biopsy is recommended at screening or Cycle 1 day 1 (pre-dose). DLBCL subjects can undergo an optional on-treatment biopsy at Cycle 3 Day 1. Subjects can also have an optional biopsy at PR and at progression. Tumor biopsies should be taken from the same lesion (non-target lesion).

A non-mandatory tumor biopsy for R/R DLBCL subjects can be taken at progression. A bone marrow biopsy and non-mandatory bone marrow aspirations for R/R MM subjects can be taken at progression.

No biopsies, bone marrow aspirates or blood samples can be taken under this study for research under another IRB protocol (eg, institutional IRB protocol of the site to take research samples).

12.1.2. Blood Samples

Subjects will have pre-dose blood draws at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1 and after that day 1 of every other cycle until Cycle 26 and then day 1 of every 4 cycles after Cycle 26, at progression, and at any response event. The blood samples will be processed for plasma and PBMC and/or buffy coat. We expect that circulating tumor cells (CTC) will be collected/within in the PBMC fraction.

12.2. Sample Analysis

For R/R MM subjects central confirmatory testing will be performed for t(4;14) but for study entry, local testing will be accepted. The t(4;14) translocation will be assessed at different time points (eg, baseline, on-treatment). Our preclinical data indicated an increased activity in t(4;14) (Section 5.2.3). Therefore changes (decrease, increase) in the t(4;14) cell clone population during the disease course in heavily pretreated R/R MM subjects (most likely genomically very complex) will be assessed.

SETD2 catalyzed the tri-methylation of H3K36 using di-methylated H3K36 as a substrate. It is expected that EZM0414 will inhibit this process and therefore a decrease in tri-methylated H3K36 (H3K36me3) levels. Hence, the assessment of H3K36me3 is the key pharmacodynamic (PD) marker in this study and will be assessed in the tumor tissue/tumor cell and/or blood (eg, PBMCs, plasma). Tumor tissue/tumor cells will be investigated for somatic mutations such as SETD2, MMSET and others that might be of interest. To assess target engagement, expression of H3K36me3 and additional histone and histone methylation markers will be assessed in tumor

tissue/tumor cells as well as in blood (eg, PBMCs, plasma). The relationship between the PD marker H3K36me3 and plasma PK will be of special interest in this study.

It is described that SETD2 and MMSET can harbor gene mutations and/or CNV. Therefore, somatic mutations that will occur in these 2 genes will be assess in our cohort and correlated with the outcome. Certain mutations could impact responsiveness to EZM0414 such as certain SETD2 truncating mutations (no SET domain) or activating MMSET(NDS2) mutations. Therefore, mutation and CNV analysis will be performed in tumor tissue/tumor cells and/or blood (eg, CTC in the PBMC fraction).

Additional analysis to assess protein and/or RNA expression might be performed on tumor tissue/tumor cells, the tumor microenvironment, PBMCs, buffy coat or from the plasma to better understand mechanism of action, tumor changes, and responsiveness. More extended DNA and other analysis might follow (eg, methylation, mutations, CNV, clonal analysis, and others) for the same reason.

12.3. Future Use of Research Samples

Not all of the tissue, bone marrow aspirates and blood components obtained during this study may be required for the tests that are part of the clinical trial. Following the conclusion of the study, the samples may be used for additional research. These samples will be held for a maximum of 15 years. This research will help to understand disease subtypes, drug response and toxicity, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done according to the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 2006) and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMA/CHMP/PGxWP/201914/2006). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the Sponsor will destroy the samples as described in this FDA guidance. The Sponsor will notify the Investigator in writing that the samples have been destroyed. The Sponsor reserves the right to destroy the biosamples for any reason during the storage period without further notice. Selected de-identified trial and sample data will be uploaded to Epizyme’s sample tracking system.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Unless stated otherwise, all assessments should be performed, and results reviewed before administration of EZM0414 to start a new cycle.

13.1.1. Demographic/Medical History

Demographic information will be collected at the Screening Visit. Standard demography parameters will include age, gender, and race/ethnicity (recorded in accordance with prevailing regulations). The screening visit will occur within 28 days prior to the first dose of study drug to confirm that the subjects meet the selection criteria for the study. The assessments to be conducted at screening are provided in Table 8 (Schedule of Assessments for Dose Escalation and Dose Expansion). Medical and surgical histories will be obtained at the Screening Visit, along with a record of prior concomitant medications and/or procedures. Significant findings before the start of study drug will be recorded on the Medical History and Current Medical Conditions eCRF. A standard of-care clinical examination for MM and lymphoma, including assessment of B symptoms, will also be performed at the screening visit and at all disease assessments.

13.1.2. Prior and Concomitant Medications

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

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

13.1.3. Vital Signs

Vital signs will be performed after the subject is seated for 5 minutes and will include the following:

- Blood pressure
- Respiration rate
- Heart rate
- Temperature

Vitals signs will be collected at screening. Serial vital signs will be collected at pre-dose, 30 minutes, 60 minutes, 2 hours, 4 hours, and 6 hours post oral dose of EZM0414 on Cycle 1 Day 1 (Table 9 and Table 10); pre-dose, 30 minutes, 60 minutes, 2 hours, 4 hours, and 6 hours post oral dose of EZM0414 on Cycle 2 Day 1. One set of vital signs will be collected at day 1 of each cycle, at end of treatment and at follow-up visit (Table 8). Vital signs will be documented in source documents and captured in the relevant eCRF. Any clinically significant changes noted by

the Investigator should be reported as an AE. Timing window allowances can be found in respective tables for serial and one-time vitals.

At time points where vital signs, ECG and PK blood samples are required, the following order of collection is recommended 1) vital signs, 2) ECG and 3) PK blood sample.

13.1.4. Weight and Height

Height measurement is required at screening only.

Body weight will be measured at screening, Cycle 1 Day 1, day 1 of each new cycle, at the end of study treatment and at follow-up (Table 8).

13.1.5. Eastern Cooperative Oncology Group Performance Status

An ECOG performance status assessment will be completed at the visits designated in the Study Design and Schedule of Assessments (Table 8). The ECOG performance scale will be used (Appendix 3).

13.1.6. Physical Examination

A complete physical examination is required at screening, on Cycle 1 Day 1, end of treatment, and at safety follow-up. A symptom-directed physical examination is required at Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 3 Day 15, Cycle 4 Day 1, Cycle 4 Day 15, day 1 of each new cycle thereafter.

A complete physical examination of all body systems must be performed at screening 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

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 (eg, not noted at screening) occurs from the initial EZM0414 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 in Table 8.

It is unknown if EZM0414 will react with exposure to sunlight. Subjects should be advised to take measures to avoid UV exposure including tanning beds. Use sunscreen, protective clothing, and sunglasses whenever outside.

13.1.7. Electrocardiogram (ECG)

Single ECG will be collected at screening. Subjects should be seated resting for 10 minutes prior to collection of all study ECGs.

Triplicate ECGs one-minute apart will be collected at pre-dose, 30 minutes, 60 minutes, 2 hours, 4 hours, and 6 hours post oral dose of EZM0414 on Cycle 1 Day 1, 24 hours post oral dose on Cycle 1 Day 2. On Cycle 2 Day 1 pre-dose, 30 minutes, 60 minutes, 2 hours, 4 hours, and 6 hours post oral dose of EZM0414, and 24 hours post oral dose on Cycle 2 Day 2. Triplicate ECGs will be collected pre-dose and 2 hours post on Day 1 of every odd cycle starting at Cycle 3 Day 1, and at end of treatment visit (Table 8). Machine read ECGs should be reviewed by the Investigator within 24 hours. ECGs will be read by a Central Reader within 72 business hours.

At time points where vital signs, ECG and PK blood samples are required, the following order of collection is recommended 1) vital signs, 2) ECG and 3) PK blood sample.

13.1.8. Laboratory Assessments

Safety laboratory testing at screening and during study will be performed at local labs according to institutional 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 EZM0414 exposure will be recorded in the eCRF as an AE if clinically significant per investigator.

Specific clinical laboratory tests for hematology including coagulation profile, serum chemistries, urinalysis, and viral serology are detailed in Appendix 7.

13.1.8.1. Hematology

Hematology tests will be performed during screening, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 1, Cycle 2 Day 8, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 3 Day 15, Cycle 4 Day 1, Cycle 4 Day 15, and day 1 of each new cycle thereafter, at the end of study, and at follow-up (Table 8).

13.1.8.2. Blood Chemistry

Blood chemistry tests will be performed during screening, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 1, Cycle 2 Day 8, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 3 Day 15, Cycle 4 Day 1, Cycle 4 Day 15, and day 1 of each new cycle thereafter, at the end of study, and at follow-up (Table 8).

13.1.8.3. Coagulation Test

Coagulation test will be performed during screening, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 1, Cycle 2 Day 8, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 3 Day 15, Cycle 4 Day 1, Cycle 4 Day 15, and day 1 of each new cycle thereafter, at the end of study, and at follow-up (Table 8).

13.1.8.4. Urinalysis

Urinalysis will be performed during screening, Cycle 1 Day 1, day 1 of each new cycle thereafter, at the end of study, and at follow-up (Table 8).

13.1.8.5. Creatinine Clearance

Creatinine clearance will be calculated by Cockcroft-Gault formula (Appendix 8) and must be ≥40 ml/min at enrollment.

13.1.8.6. Virus Serology

Viral serology testing, if indicated per eligibility criteria, will be performed at screening for HBV, HCV, HIV, and human T-cell lymphotropic virus 1 (HTLV-1).

13.1.8.7. Pregnancy Screen

In women of childbearing potential, a serum pregnancy test is required at screening and serum/urine pregnancy test at time points indicated in Table 8. Cycle 1 Day 1 pregnancy test does not need to be repeated if screening test is performed within 72 hours of Cycle 1 Day 1.

13.1.8.7.1. Definition of Childbearing Potential: Female Subjects

A female subject is considered of childbearing potential if she:

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

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

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

13.1.8.7.2. 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.

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

- Has a documented successful vasectomy (with medically confirmed azoospermia). However, even with a successful vasectomy, male subjects must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a pregnant female or FCBP from first dose of study drug, during study treatment (including during dose interruptions), and for 30 days after study drug discontinuation.

13.1.8.7.3. Prevention

Female Subjects

Females of childbearing potential (FCBP) enrolled must either practice complete abstinence or agree to use two reliable methods of contraception simultaneously. This includes **ONE** highly effective method of contraception and **ONE** additional effective contraceptive method. Contraception must begin at least 14 days prior to first dose of study drug, continue during study treatment (including during dose interruptions), and for 30 days after study drug discontinuation. Female subjects must also refrain from breastfeeding for 30 days following last dose of study drug. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (ovulation inhibitory combined [estrogen and progesterone] birth control pills or intravaginal/transdermal system, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel])
  - Partner's vasectomy (if medically confirmed [azoospermia] and sole sexual partner)
- Examples of additional effective methods:
  - Male latex or synthetic condom
  - Diaphragm
  - Cervical Cap

If the above contraception methods are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject.

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

Male Subjects

Male subjects must either practice complete abstinence or agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), during sexual

contact with a pregnant female or FCBP from first dose of study drug, during study treatment (including during dose interruptions), and for 30 days after study drug discontinuation.

Note: Male subjects must not donate semen or sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 30 days after study drug discontinuation.

13.1.8.8. Bone Marrow Assessments

Bone marrow biopsy and aspirate performed as per institutional practice are to be evaluated histologically for plasma cells percentage and monoclonality and determination of other cells in the marrow (Table 8). An aspirate is to be evaluated by flowcytometry as per institutional guidelines to characterize myeloma cells. These results will be reported on the eCRF.

13.1.8.9. IgA, IgM, IgG (M-protein Serum, for MM Subjects Only)

A blood sample will be drawn for protein electrophoresis for quantification of M-protein. Subsequent Ig identification will be done by immunofixation (Table 8).

13.1.8.10. M-protein (24-hour Urine, for MM Subjects Only)

Twenty hour-hour urine will be collected for urine protein electrophoresis and quantitation of M-protein (not total protein alone) and for immunofixation (Table 8).

13.1.8.11. Serum Free Light Chain Ratio (MM Subjects Only)

A blood sample will be drawn for quantification of free light chain (Table 8).

13.2. Adverse Events

13.2.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a subject 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. This includes any newly occurring event or previous condition that has increased in severity or frequency after the ICF is signed.

Worsening of a pretreatment event, after initiation of the study drug, must be recorded as a new AE. For example, if a subject experience a mild intermittent dyspepsia prior to dosing of study drug, but the dyspepsia becomes severe and/or more frequent after the first dose of study drug, a new AE of worsening dyspepsia (with the appropriate date of onset) should be recorded in the eCRF.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was screened in the study and progression of underlying disease are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier than planned).

“Lack of efficacy” or “failure of an expected pharmacological action” per se is not to be reported as an AE. However, any signs and symptoms and/or clinical sequelae resulting from “lack of

efficacy" will be reported as an AE and assessed for seriousness accordingly if it meets the definition of an AE.

Diagnostic and therapeutic procedures must not be reported as AE verbatim terms. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an AE.

Elective surgeries or procedures must not be reported as AEs but must be documented on the appropriate eCRF page.

Each AE must be assessed immediately to determine if it meets the definition of serious (Section 13.2.2). If an SAE occurs, expedited reporting must follow local and international regulations, as appropriate. Refer to Section 13.2.5 (assessment of severity) for additional details.

13.2.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose meets any of the following:

- Results in death (regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of study drug)
- Is life-threatening (an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe).

  Note: Life-threatening AE or life-threatening suspected adverse reaction: An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Requires in-subject hospitalization or prolongation of hospitalization
- Results in persistent or significant disability or 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 (eg, sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed in the definition.
- All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Epizyme, Inc.

13.2.3. Disease-Related Events

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

Note: Disease progression should not be reported as an SAE term in and of itself. Report the SAE term that is untoward in the context of disease progression.

13.2.4. Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs must be assessed and those assessed as clinically significant by the treating clinician must be documented as an AE. When possible, a clinical diagnosis for the study assessment must be provided rather than the abnormal test results alone (eg, urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself may be listed as the AE (eg, bacteria in urine or decreased hemoglobin).

The abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Worsening, from baseline, concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention is required
- A change in the dose of study drug, if study drug is withheld, or discontinued from study drug occurs.

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant must be made by the Investigator.

13.2.5. Assessment of Severity

The Investigator must determine and record the severity of all AEs. Adverse events will be graded on a 5-point scale according to CTCAE Version 5.0 (Appendix 5). Investigators will collect all CTCAE grades for AEs (for both increasing and decreasing severity). All AEs reported using CTCAE classification and graded as 4 or 5 are to be considered SAE. Every effort must be made by the Investigator to categorize each AE according to its severity. In the event that an AE is not covered by the CTCAE scale, the assessment of severity will be determined by using the CTCAE general guidelines presented in Table 13.

Table 13: Assessment of Severity per Common Terminology Criteria for Adverse Events General Guidelines

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental 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 ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADLs 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"). Refer to Section 13.2.2 for the definition of an SAE.

All AEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on the appropriate eCRF forms provided by Epizyme, Inc.

13.2.6. Relationship to Study Drug

A qualified Investigator must make the determination of relationship to EZM0414 for each AE. The Investigator should decide whether, in his or her medical judgment there is a reasonable possibility that the event may have been caused by EZM0414.

- 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 study drug
- 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.

Investigators must also systematically assess the causal relationship of AEs to the IP using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the IP):

- **Probable:** A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the IP, and there is a reasonable response on withdrawal.
- **Possible:** A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the IP.
- **Unlikely:** A causal relationship is improbable, and another documented cause of the AE is most plausible.
- **Unrelated:** A causal relationship can be definitively excluded, and another documented cause of the AE is most plausible.

13.2.7. Test Abnormalities

13.2.7.1. Laboratory Abnormalities

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

A clinical laboratory AE is any laboratory value that is considered clinically significant (CS) 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 CSR. If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (eg, anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded as concomitant medications).

If, at the end of the treatment, there are pathological laboratory values which were not present at baseline, further laboratory evaluations should be performed until the values return to within reference range or until a plausible explanation (ie, concomitant disease) is found.

13.2.7.2. Other Test Abnormalities

Other safety assessments (eg, 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 in accordance with the definitions provided in Section 13.2.1 and Section 13.2.2 respectively.

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

13.3. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be collected from the time the subject

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

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Subjects who experience death while on treatment or within 30 days of study drug discontinuation ('deaths on study' hereafter) will have a Grade 5 SAE reported in electronic data capture (EDC) system and an SAE form submitted UNLESS the only known cause of death is progressive disease. Attempts should be made to specify a cause of death. However, if progressive disease or the indication of the study is the only known cause of death, the death is not untoward and should be recorded on the Death eCRF as progression of disease is a key efficacy criterion.

All deaths on study, regardless of cause, or if meeting the criteria for a reportable SAE will be reported on the Death eCRF.

Should a pregnancy occur, it must be reported and recorded on Epizyme, Inc.'s pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should reported as AEs but recorded as planned procedures within the eCRF.

13.4. Reporting Serious Adverse Events

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.

If an AE is considered serious, the AE page/screen of the eCRF must be completed.

For each SAE, the Investigator will provide information on severity, start, and stop dates, relationship to IP, action taken regarding IP, and outcome.

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/IEC, and Investigators.

Any AE that is both unexpected is at least possible related per investigator and meets the definition of a SAE would be considered an SUSAR.

An Investigator who receives an Investigator safety report describing a SUSAR or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

13.5. Reporting of Pregnancy

Pregnancy will not be considered an SAE. However, any pregnancy occurring in a female subject, or a female partner of a male subject should be reported to Epizyme. 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 SET-101 Pregnancy Report Form. A Pregnancy Report Form should be completed and submitted by email as is done for SAE.

The pregnant female subject must be withdrawn from the study treatment.

Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks postpartum. It is the responsibility of the Investigator to obtain all pregnancy outcome information, and information regarding the health status of the baby. Submit this information to the Sponsor or its designee as is done for paper SAE forms.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE and assessed for seriousness per usual. Spontaneous abortions must be reported as SAE under “medically significant”.

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

The Investigator also must attempt to collect and report to the Sponsor or its designee pregnancy information on any female partner of male study subjects who become pregnant while the subject is enrolled in the study.

13.6. Reporting of Special Situations

Report the special situation(s) of overdose, misuse, abuse, and/or medication error (described in Section 9.2) using one of the following sets of instructions according to whether the special situation occurred without any associated AEs, with an associated AE, or with an associated SAE:

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

- Report to Epizyme using a Special Situations Form following the procedures for reporting SAE (Section 13.4).

Special situation(s) with an associated AE:

- Enter the event on the AE eCRF and mark the SAE field, “no”. Serious adverse events related narrative fields should not be completed.
- Report to Epizyme using a Special Situations Form following the procedures for reporting SAE (Section 13.4).

Special situation(s) with an associated SAE:

- Complete the AE eCRF per protocol for the associated SAE term ONLY (Special situations are not adverse event terms in and of themselves); complete eCRF SAE fields.
- Report to Epizyme using a paper Special Situations Form following the procedures for reporting SAE (Section 13.4).

13.6.1. Study Drug Overdose, Misuse, Abuse, or Medication Error without an Adverse Event

Overdose and medication errors with no clinical consequences, need to be reported in the same manner. The report must indicate that there was no associated AE with the overdose or medication error.

14. STATISTICS

14.1. Study Design and Sample Size Justification

This study is a first-in-human, 2-part, multi-center, open-label Phase 1/1b safety, tolerability, PK, and efficacy study of oral SETD2 inhibitor, EZM0414, in subjects with R/R MM and R/R DLBCL. The first part of the study will be Phase 1 dose escalation designed to evaluate safety, tolerability, and PK of EZM0414 in subjects with R/R MM and R/R DLBCL. The second part of the study is the Phase 1b dose expansion designed to evaluate safety and efficacy at MTD in subjects with R/R DLBCL, or R/R MM with or without select genetic translocation. The dose expansion part will enroll subjects in 3 cohorts: Cohort 1 for R/R MM subjects with t(4;14), cohort 2 for R/R MM subjects without t(4;14) and Cohort 3 for subjects with R/R DLBCL.

Part 1: In the dose escalation Phase 1 part, subjects diagnosed with R/R MM or R/R DLBCL will receive EZM0414 as monotherapy orally once daily (QD) in 28-day cycles according to the escalation schedule Table 14 below.

Table 14: Total Daily Dose and Respective Dose Level

Dose Level	Total Daily Dose (mg)
-1 (optional)	75
1	100
2	200
3	300
4	400
5	600
6	900

Additional daily dose levels and/or dosing schedules (including BID regimen) may be studied based on clinical and pharmacokinetic data obtained during this study.

Bayesian optimal interval design (Liu, 2015; Yuan, 2016; Zhou, 2017) will be used for this dose escalation part. Similar numbers of subjects with R/R MM or R/R DLBCL will be enrolled to determine MTD. The target toxicity rate (ϕ_T) for the MTD is set at **0.25** for both R/R MM and R/R DLBCL. The maximum number of subjects for determination of MTD is 9. A total of 6 dose levels ($j = 6$, ie, starting at100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg) as well as an optional step-down dose level of 75 mg will be investigated. We will enroll and treat subjects in groups of at least 3, and up to 36 subjects will be enrolled in this dose-escalation part of the study in order to evaluate at least 9 subjects for MTD. Dose limiting toxicities are defined in Section 7.5.1, and only those DLTs that occur within the first cycle will be used for safety assessment. The BOIN design uses the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is ≥ 0.298, de-escalate the dose to the next lower dose level;

- otherwise, stay at the current dose.

For the purpose of overdose control, the current dose j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.25 \text{ data}) > 0.8$ and at least 3 subjects have been treated at the current dose level j, where p_j is the true DLT rate of dose level $j, j = 1,\cdots, 6$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0,1)$, where y_j is the number of subjects experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cut-off 0.8 is chosen to be consistent with the common practice when the target DLT rate ≤1/6, a dose with 2/3 subjects experienced DLT is eliminated. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 15, which will be used to conduct the trial.

Table 15: Dose Escalation/de-escalation Rule for the BOIN Design

Target Toxicity Rate	Pr (pj > target toxicity rate | data)	Actions	The number of evaluable patients at the current dose								
			1	2	3	4	5	6	7	8	9
0.25	0.8	Escalate if # of DLT ≤	0	0	0	0	0	1	1	1	1
		De-escalate if # of DLT ≥	1	1	1	2	2	2	3	3	3
		Eliminate if # of DLT ≥	NA	NA	2	2	2	3	3	3	4

BOIN = Bayesian Optimal Interval Design; DLT = Dose Limiting Toxicity; NA = Not Applicable
* When none of the actions (ie, escalate, de-escalate, or eliminate) is triggered, stay at the current dose for treating the next group of subjects. Note that "# of DLT" is the number of subjects with at least 1 DLT, and "NA" means that a dose cannot be eliminated before treating 3 evaluable subjects.

Maximum tolerated dose will be determined based on isotonic regression as specified in Liu and Yuan (2015). When the isotonic estimate of toxicity rate $\tilde{p}_{j^*}$ is closest to pre-set target DLT rate (ϕ_T=0.25 for this study). If there are ties for $\tilde{p}_{j^*}$ the higher dose with $\tilde{p}_{j^*}$ < the target toxicity rate will be selected as MTD. Alternatively, the lower dose with $\tilde{p}_{j^*} > \phi_T$ will be selected.

Part 2: Bayesian Optimal Phase 2 Design (BOP2)

Justification for response rates that will be considered futile

Based on previous publications and scientific review (in the table below), the response rate of 20-35% for R/R MM and 25-45% for R/R DLBCL has been used in the SET-101 protocol. For R/R MM, an objective response rate of 20-35% has been reported for monotherapies (Richardson, 2009; Siegel, 2012; Lonial, 2020). For R/R DLBCL, an objective response rate of 25-45% has been reported for monotherapies (Mondello, 2016; Davids, 2017; Kalakonda, 2020) that are not CAR-T or bi-specifics and are not known to cause cytokine release syndromes.

Study	ORR	Number of Subjects
R/R MM		
Carfilzomib (Siegel et al 2012)	23.7% (95% CI, 18.7-29.4)	257
Lenalidomide (Richardson et al 2009)	26% (95% CI, 25.7-26.5)	222
Belantamab mafodotin (Lonial et al, 2020)	34% (97.5% CI, 23.9-46.0)	99

Study	ORR	Number of Subjects
R/R DLBCL		
Venetoclax (Davids et al 2017)	22%	41
Selinexor (Kalakonda et al 2020)	28% (95% CI, 20.7-37.0)	127
Lenalidomide (Mondello et al 2016)	37%	123

Using meta-analysis with fixed effect model for 3 MM studies, the lower 95% CI is 22.5%. Therefore, 20% response rate was selected that will be considered futile. Using meta-analysis with fixed effect model for 3 DLBCL studies, the lower 95% CI is 25.6%. Therefore, 25% response rate was selected that will be considered futile in this proof of concept Phase 1b dose expansion part of the study.

In the dose expansion part of the study, the following cohorts of subjects will receive EZM0414 monotherapy at MTD orally once daily (QD) in 28-day cycles:

- Cohort 1: R/R MM with t(4;14) translocation
- Cohort 2: R/R MM without t(4;14) translocation
- Cohort 3: R/R DLBCL

Subjects treated at MTD in Phase 1 dose escalation part of the study will continue to receive the treatment beyond cycle 1 (be rolled over to this dose expansion part) until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent, or need for treatment prohibited on this study.

Bayesian optimal phase 2 design (Yuan, 2016; Zhou, 2017) will be applied to the Phase 1b dose expansion part to discover efficacy signals. Twenty (20) subjects/cohort are planned to be enrolled and 3 looks will be performed when the data of 10, 15 and 20 subjects have been available. The cohort will be terminated if deemed futile.

For R/R MM

There will be 2 cohorts of R/R MM subjects enrolled in this part of the study. They are with and without t(4;14), respectively. Relapsed/refractory MM subjects treated at MTD in the dose escalation part will be rolled over to either Cohort-1 R/R MM with t(4;14) or Cohort-2 R/R MM without t(4;14) depending on their translocation status.

For either of these 2 cohorts let n_M denote the interim sample size and N_M denote the maximum sample size. Also let p_{Meff} denote the objective response rate (ORR) and define the null hypothesis. $H_0: p_{Meff} \leq 0.2$, under which the treatment is deemed as unacceptable. We will stop enrolling subjects and claim that the treatment is futile if

$$Pr(p_{Meff} > 0.2|data) < \lambda_M \left(\frac{n_M}{N_M}\right)^{\alpha_M}$$

where λ_M=0.84 and α_M=1 are design parameters optimized to maximize power under the alternative hypothesis $H_1: p_{Meff} = 0.35$, (ie, the probability of correctly claiming that the treatment is acceptable under H_1), while controlling the type I error rate (ie, the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.084. This optimization is performed assuming a vague prior Beta (0.2, 0.8) for p_{Meff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.571 under H_1:

Table 16: Optimized Stopping Boundaries for R/R MM Cohort

Sample size for interim looks	Stop if # Response ≤
10	1
15	3
20	6

ORR = Objective response rate; R/R = Relapsed/refractory; MM = Multiple myeloma.
H_0: ORR (Futile)=0.2; H_1: ORR (Promising)=0.35; Type I Error Rate=0.1

Based on Table 16, futility assessments will be conducted for each R/R MM cohort when response assessment data become available (ie, minimum 5 cycles or if all subjects progressed) in the first 10 enrolled subjects, and again in the first 15 enrolled subjects. Enrolment will not cease during the assessment periods. When the response assessment data are available for the total number of 20 subjects, we reject the null hypothesis for the cohort and conclude that the treatment is promising (go) if the number of responses is more than 6 (>6); otherwise, we conclude that the treatment is futile (no-go). The go/no-go criteria in Table 16 are non-binding.

For R/R DLBCL

One cohort of 20 subjects with R/R DLBCL will be enrolled in the dose expansion part of the study following BOP2 design. The subjects with R/R DLBCL treated at MTD in the dose escalation part of the study will be rolled over to this dose expansion part until disease progression, occurrence of unacceptable toxicity or withdrawal of consent occurred.

Let n_D denote the interim sample size and N_D denote the maximum sample size for this cohort. Also let p_{Deff} denote the ORR and define the null hypothesis $H_0: p_{Deff} \leq 0.25$, under which the treatment is deemed as futile. We will stop enrolling subjects and claim that the treatment is unacceptable if

$$Pr(p_{Deff} > 0.25 | data) < \lambda_D \left(\frac{n_D}{N_D}\right)^{\alpha_D},$$

where λ_D=0.82 and α_D=0.51 are design parameters optimized to maximize power under the alternative hypothesis $H_1: p_{Deff} = 0.4$, (ie, the probability of correctly claiming that the treatment is acceptable under H_1), while controlling the type I error rate (ie, the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.093. This optimization is performed assuming a vague prior Beta (0.25, 0.75) for p_{Deff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.555 under H_1:

Table 17: Optimized Stopping Boundaries for R/R DLBCL Cohort

Sample size for interim looks	Stop if # Response ≤
10	2
15	4
20	7

ORR = Objective response rate; R/R = Relapsed/refractory; DLBCL = diffuse large B cell lymphoma
H_0: ORR (Futile)=0.25; H_1: ORR (Promising)=0.4; Type I Error Rate=0.1

Based on Table 17, futility assessments will be conducted when response assessment data become available (ie, minimum 5 cycles or if all subjects progressed) in the first 10 enrolled subjects, and again in the first 15 enrolled subjects. Enrolment will not cease during the assessment periods. When the total number of subjects reaches the maximum sample size of 20, we reject the null hypothesis and conclude that the treatment is acceptable (go) if the number of responses is more than 7 (>7); otherwise, we conclude that the treatment is unacceptable (no-go). The go/no-go criteria in Table 17 are non-binding.

14.2. General Consideration for Statistical Analysis

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

In general, the data from Phase 1 dose escalation part and Phase 1b dose expansion part will be analyzed separately except the efficacy data from the subjects who receive the study drug at MTD in dose escalation part and are rolled over to the dose expansion part. Their efficacy data in Phase 1 part will be integrated in Phase 1b efficacy data analysis unless otherwise specified.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

14.3. Analysis Populations

Safety Population: Safety analyses will be composed of all subjects who receive at least 1 dose of the study drug in Phase 1 (dose escalation part) or Phase 1b (dose expansion part).

Dose-limiting toxicity (DLT) Evaluable Population: The DLT evaluable population will consist of dose escalation dose level subjects in the Safety Population who received at least 80% of planned study treatment during cycle 1.

Intent-to-Treat (ITT) Population (Phase 1b Dose Expansion Portion): The ITT Population is defined as all subjects enrolled in corresponding cohorts of Phase 1b part, regardless of their adherence with the entry criteria, the treatment they actually received, and subsequent withdrawal from treatment or deviation from the protocol. The ITT Population includes the subjects who received the study treatment at MTD in Phase 1, dose escalation part and are rolled over to the corresponding cohorts of the Phase 1b, dose expansion part.

PK Analysis Population: will include all subjects in the Safety Analysis population who have sufficient post-dose blood sample collected to allow estimation of the PK parameters.

14.4. Statistical Analysis Groups

The Safety Population, DLT Population and PK Analysis Population of Phase 1 part (dose escalation) of the study will be categorized to 6 dose groups (starting at 100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg) as well as an optional step-down dose level of 75 mg. In addition, 2 summary groups for R/R MM and R/R DLBCL will be created regardless of the dose levels and an overall group will also be created including all Phase 1 subjects for DLT and safety data analysis.

Similarly the Safety Population, PK Analysis Population, and ITT Population of Phase 1b portion (dose expansion) will be categorized to 3 groups according to the cohorts for relevant data analysis. ITT Population will include the subjects who receive EZM0414 at MTD in the dose escalation part of the study and are rolled over to the dose expansion part. In addition the cohorts of R/R MM with and without t(4;14) will be combined to form a R/R MM group and all 3 cohorts will be combined to form an overall group for summary statistics presentation.

14.5. Interim Looks During the Phase 1b Dose Expansion Portion of the Trial and the Final Analysis

There will be 2 interim looks in the dose expansion part of the trial when the data from 10 and 15 subjects of the cohort are available. A final analysis will be conducted when all data collection is completed, and database is locked. All ORR data from both the dose escalation part and the dose expansion part will be analyzed in this final analysis.

14.6. Safety Analyses

Safety of EZM0414 including DLT for the Phase 1 dose escalation part and all safety events data in both Phase 1 and Phase 1b dose expansion part.

DLT evaluation will be performed based on the DLT Population (Section 14.3) and the other safety analysis will be conducted on the Safety Population.

In general safety parameters will be summarized by the analysis group (see Section 14.4) according to the different phases of the trial. These parameters will consist of the incidence of deaths, adverse events, serious adverse events (SAE), adverse events leading to discontinuation, adverse events leading to dose modification, ECOG, ECGs, physical examination, vital signs, and specific laboratory abnormalities (worst grade).

14.6.1. DLT Evaluation and MTD Determination

Dose limiting toxicities occurred in the first cycle of the study treatment in the dose escalation part will be specifically reported by the dose level group (see Section 14.4) on DLT Population. A listing will be generated presenting the detailed information including the sequential order of these DLTs. The DLTs that lead to the determination if the dose levels starting at 100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg QD as well as an optional step-down dose level of 75 mg QD are safe and tolerable, as well as the determination of MTD for the Dose Expansion part will be evaluated and described in the CSR (not included in any statistical analysis output).

14.6.2. Adverse Events

Treatment-emergent adverse events (TEAE) is defined as AEs that started or worsened in severity on or after the date of the first dose of the study drug through 30 days after the end of treatment.

The reported AE term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of the database lock. The severity of each AE and abnormal laboratory tests will be graded by the site investigator based on version 5.0 of the NCI CTCAE. If a severity grading scale does not exist for an AE, the investigator will classify the severity as mild, moderate, severe, life-threatening/debilitating, or fatal based on the criteria described in the study protocol. The causal relationship between the occurrence of an AE and study drug will be judged by the investigator as “probable”, “possible”, “unlikely”, or “unrelated”.

Incidence of TEAEs will be summarized for all analysis groups (see Section 14.4) in dose escalation part and cohort groups in dose expansion part, and by MedDRA system organ class (SOC) and preferred term (PT) within each SOC. Overall incidence will also be presented for each part. TEAEs will also be summarized by severity, and by relationship to study intervention. If a subject experience repeat episodes of the same AE (as defined by the MedDRA SOC and PT), then the event with the highest reported severity grade and the strongest causal relationship (“related”) to study drug will be used for purposes of the incidence tabulations.

All AEs including TEAEs will be presented in study phase specific listings (Phase 1 dose escalation part and Phase 1b dose expansion part).

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each group (the analysis groups in dose escalation part or cohort groups in dose expansion part). Subject data listings of all AEs leading to discontinuation from study drug will also be provided for the phases.

Serious adverse events will be summarized as for TEAE, ie, by the analysis group, SOC and PT, and by severity and relationship to the study drug. All SAEs will also be presented in listings.

14.6.3. Deaths

Deaths will be summarized by phase (Phase 1, dose escalation portion or Phase 1b, dose expansion portion) and group (see group definitions in Section 14.4) as follows:

- Summary of subjects who died during treatment and till 30 days after last dose of study drug
- Summary of subjects who died during treatment and till 30 days after last dose of study drug with treatment-related TEAEs
- Summary of subjects who died after 30 days after the last dose of study drug with treatment-related AEs.

Listings will be created to present detailed death related information including date, cause of the death and AE/TEAE related to the death, etc.

14.6.4. Laboratory Abnormalities

Abnormal clinical laboratory values will be noted as either high or low based on the normal ranges for each laboratory parameter. Changes from pre-treatment in laboratory parameters will be summarized.

14.6.5. Other Safety Assessments

Listings of ECOG, ECG and vital signs data will be created with change from baseline presented.

14.7. PK Data Analysis

PK data Analysis will use the PK Analysis Population. At minimum, the following PK parameters will be determined for EZM0414 based on the available blood samples collected during the dose escalation and dose expansion portions:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Terminal elimination half-life ($T_{½}$)
- AUC_{0-t}
- Area under the concentration-time curve from time zero to 24 hours post-dose (AUC_{0-24})
- Area under the concentration-time curve from time zero to 24 hours post-dose (AUC_{0-last})
- Apparent volume of distribution during the terminal (λ_z) phase (V_z/F)
- Maximum observed concentration normalized to the dose (C_{max}/D)
- AUC_{0-24} normalized to the dose (AUC_{0-24}/D)
- AUC_{last} normalized to the dose (AUC_{last}/D)
- Kel: elimination rate constant
- λ_z

Individual plasma concentrations and concentration-time data will be presented and summarized both graphically and in tabular format with descriptive statistics (n, arithmetic mean, standard deviation [SD], percent coefficient of variation [CV%], median, minimum, and maximum) according to nominal (protocol-specified) sampling times. Pharmacokinetics parameters will be calculated using noncompartmental analysis, based on actual elapsed time from dosing to each post-dose time point. Pharmacokinetics parameters will be summarized by the analysis group (see Section 14.4) using descriptive statistics (n, arithmetic mean, SD, CV%, median, minimum, maximum, and geometric mean if applicable). Individual patient level data listings of all PK parameters will be prepared.

14.8. Investigation of PK/PD Relationship

Where possible, modelling and simulation methods may be used as part of the evaluation to assess relationships between emerging safety, tolerability, PK and PD and covariates data. Clinical pharmacology department will be responsible for these analyses and, if conducted, will be reported separately from the CSR.

14.9. Efficacy Analyses

All efficacy data analyses, unless otherwise specified, will be performed on the ITT Population. The ITT Population is composed of the subjects who had received EZM0414 at MTD in the dose escalation part and rolled over to the dose expansion part, and the subjects enrolled in the Phase 1b dose expansion part of the study.

No multiplicity adjustment will be made.

14.9.1. Primary Efficacy Analyses

The primary efficacy endpoint for this study is ORR, defined as the proportion of responders in subjects with R/R MM (CR + sCR + PR + VGPR) and (CR+PR) in subjects with R/R DLBCL. The response will be determined based on IMWG 2016 Guidelines for R/R MM and on Lugano 2014 Guidelines for R/R DLBCL.

Objective response rate and the associated 95% confidence intervals (CI) will be calculated for each dose expansion cohort.

14.9.2. Secondary Efficacy Analyses

The secondary efficacy endpoints for this study include progression free survival (PFS), disease control rate (DCR), and duration of response (DOR). All of these secondary efficacy analyses will also be performed on the ITT Population.

14.9.2.1. Progression Free Survival

PFS is defined as the time from the date of the first dose of the study drug administration to the first observation of documented disease progression or death, whichever occurs first.

PFS will be summarized descriptively using the Kaplan-Meier (KM) method. The KM estimate along with the corresponding 95% CI will be computed using the Brookmeyer and Crowley method and the median will be provided. The event-free rate with corresponding 95% CI will be calculated using Greenwood's formula and will be provided at 6, 12, 18, and 24 months. Median follow-up for PFS will be estimated according to the KM estimate of potential follow-up.

KM curves will also be provided. In cases where PD or death has not been reached, censoring rules will be applied, detailed censoring rules will be pre-specified in the SAP.

14.9.2.2. Disease Control Rate

Disease control rate (DCR) in this study is defined as the proportion of subjects who have achieved confirmed CR, sCR, PR, VGPR, minimal response or stable disease (SD) per IMWG 2016 Guidelines for MM or CR, PR, or SD per Lugano 2014 Guidelines for DLBCL since administration of EZM0414 in dose expansion part (including the cycle 1 observations of the

subjects who receive EZM0414 at MTD in the dose scalation part and are rolled over to the dose expansion part). DCR will be calculated and summarized by cohort. The associated 95% confidence intervals (CI) for each cohort will be tabulated.

14.9.2.3. Duration of Response

Duration of response (DOR) is defined as the time from initial response to documented progression or death, whichever comes first, as assessed by Investigator per IMWG 2016 guidelines for MM or Lugano 2014 guidelines for DLBCL.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

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

15.1. Study Site Monitoring Visits

Before an investigational site can enter a patient into the study, a representative of Epizyme, Inc. will visit the investigational study site to:

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

During the study, a monitor(s) from Epizyme, Inc. or representative will have regular contacts with the investigational site and staff, for the following to occur:

- Ensure that each patient has been properly consented by reading and reviewing the Inform Consent Form (ICF) with them. The patient is to ask the Investigator or Nurse any questions to ensure the appropriate understanding and risks of participation in the study. Take the ICF home to discuss with family. Once this is done, document this process in the source documents accordingly.
- Regular contact visits: on site or virtual (depending on COVID-19 restrictions) will be between every 4-6 weeks as deemed appropriate, based on the workload and patient number enrolled in the study at each site.
- Provide information and support to the investigator(s) and participating site team. They will make themselves available to meet with the Site Monitor at each scheduled visit.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is ensuring patient safety is paramount, each patient is properly consented, and properly documented in the source documents, adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed regularly.
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts) at each scheduled visit. The site will enter the patient's

data regularly and on time as deemed appropriate in the corresponding Monitoring Plan.

- Record and report any protocol deviations/violations not previously sent to Epizyme, Inc.
- Confirm Adverse Events (AEs) and Serious Adverse Events (SAEs) have been properly documented on Case Report Forms (CRFs) and confirm any SAEs have been forwarded to Epizyme, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB and followed until resolved.
- The monitor will ensure all queries are resolved in a timely manner and look to identify any trends that require resolution.
- The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

15.2. Protocol Compliance

The Investigator must conduct the study in compliance with the protocol provided by the Sponsor and given approval/favorable opinion by the IRB/IEC/research ethics board (REB) and the appropriate regulatory authorities. Modifications to the protocol must not be made without required written agreement between the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC/REB and the appropriate regulatory authority(ies) approval/favorable opinion prior to implementation, except when the modification to eliminate an immediate hazard(s) to the subject. The IRB/IEC/REB may provide, if applicable regulatory authority(ies) permit, expedited review, and approval/favorable opinion for minor changes during study that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor must ensure that all protocol modifications are submitted to the regulatory authority(ies) in accordance with the governing regulations.

If other unexpected circumstances arise that require deviation from protocol-specified procedures the Investigator must consult with the Sponsor (and IRB, IEC, or REB, as required) to determine the appropriate course of action.

The site must document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site must notify the Sponsor or its designee (and IRB, IEC, or REB, as required). Significant deviations include, but not limited to, those that involve fraud or misconduct, dosing errors, increase the health risk to the subject, or confound interpretation of primary study assessments.

15.3. Audits and Inspections

Authorized representatives of Epizyme, Inc., a regulatory authority, an IEC or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an Epizyme, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on

Harmonization, and any applicable regulatory requirements. The investigator should contact Epizyme, Inc. immediately if contacted by a regulatory agency about an inspection.

15.4. Institutional Review Board (IRB)

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site timely. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trial.

16.2. Bioanalytical Data Management and Quality Control

Samples will be shipped according to the Laboratory Manual. EZM0414 will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry method. Before the analysis of study samples, the assay sensitivity, specificity, linearity, and reproducibility will be documented. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures will be included in the CSR for this protocol.

17. ETHICS

17.1. Ethics Review

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

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

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions (SUSAR) from any other study conducted with the IP. Epizyme, Inc. will provide this information to the PI.

Progress reports and notifications of Suspected Unexpected Serious Adverse Reaction(s) (SUSARs) will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by GCP as described in the ICH Tripartite Guideline E6 (R1): GCP: Consolidated Guideline. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with all applicable country and local legal and regulatory requirements.

17.3. Written Informed Consent

Informed consent will be obtained, and protocol eligibility will be established during the Screening Visit. Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. For research biopsies a separate consent form will be provided for DLBCL subjects.

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 written in the source documents, approved, used, and maintained in accordance with applicable regulations and GCP. If applicable, an ICF will be provided in a certified translation of the subject's local language.

Each Investigator will provide the Sponsor or its designee with a copy of the IRB/IEC approved ICF(s), and a copy of the IRB/IEC written approval, prior to the start of the study. Additionally, if the IRB/IEC 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.

Each subject or the subject's legally authorized representative is requested to sign the approved 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. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. 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.

Original, signed ICFs must remain in each subject's study file and must be available for inspection at any time.

The Sponsor reserves the right to delay initiation of the study at a site where the ICF(s) do not meet the standards of applicable regulations and ICH GCP.

17.3.1. 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 regularly, including but not limited to, paper or electronic 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 accordingly.

18. DATA HANDLING AND RECORD KEEPING

18.1. Electronic Case Report Form

The Sponsor or designee will provide the study sites with secure access to and training on the EDC application sufficient to permit site personnel to enter or correct information in the eCRFs on the subjects for which they are responsible.

An eCRF is required and must be completed for each randomized subject. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms. Source documentation supporting the eCRF data must indicate the subject's participation in the study and must document the dates and detail of study procedures, AEs, other observations, and subject's status.

The Investigator, or designated representative, must complete the eCRF as soon as possible after information is collected (preferably within 24 hours).

The audit trail will show the user's identified information and the date and time of any correction. The eCRFs must be signed electronically by the Investigator to attest that the data contained on the eCRFs including any changes made to the eCRFs, is correct and endorse the final submitted data for the subjects for whom the Investigator is responsible.

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

The Sponsor will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a Compact Disc or other electronic storage media will be provided to the site for placement in the Investigator's study file.

18.2. Inspection of Records

The Sponsor or designee will be allowed to conduct site visits to the Investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study treatment stocks, drug accountability records, subject paper or electronic medical charts and study source documents, and other records relative to study conduct.

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/IEC/REB for each study site.

18.3. Retention of Records

To enable evaluations and/or audits from regulatory authorities or Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records must

be retained by the Investigator according to the ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the Sponsor must be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

18.4. Disclosure and Confidentiality

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

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

18.5. Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or for valid administrative reasons at any time. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the study. The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

18.6. Subject Insurance and Indemnity

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study.

19. PUBLICATION POLICY

Clinical study results will be made publicly available in compliance with local legislation and guidelines.

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

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

20. LIST OF REFERENCES

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