TAZEMETOSTAT

EZH-1101

CELLO-1: A PHASE 1B/2 OPEN-LABEL STUDY EVALUATING TAZEMETOSTAT IN COMBINATION WITH ENZALUTAMIDE OR ABIRATERONE/PREDNISONE IN CHEMOTHERAPY NAIVE SUBJECTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER

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

Version	Date
Original Protocol (Version 1.0):	11 June 2019
Amendment 1:	29 July 2019
Amendment 2:	10 January 2020
Amendment 3:	05 June 2020
Amendment 4:	27 December 2020
Amendment 5:	14 April 2022
Amendment 6:	31 August 2022

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

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Epizyme, Inc.

Sponsor's Authorized Officer:

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PPD, MD, MPH — Date

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INVESTIGATOR'S AGREEMENT

Protocol Title: CELLO-1: A PHASE 1B/2 OPEN-LABEL STUDY EVALUATING TAZEMETOSTAT IN COMBINATION WITH ENZALUTAMIDE OR ABIRATERONE/PREDNISONE IN CHEMOTHERAPY NAIVE SUBJECTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Protocol Number: EZH-1101

I have read the EZH-1101 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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

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Printed Name of Investigator

_____

Signature of Investigator

_____

Date (dd mmm yyyy)

_____

Name/Address of Institution

EMERGENCY CONTACT INFORMATION

Protocol Title:	CELLO-1: A PHASE 1B/2 OPEN-LABEL STUDY EVALUATING TAZEMETOSTAT IN COMBINATION WITH ENZALUTAMIDE OR ABIRATERONE/PREDNISONE IN CHEMOTHERAPY NAIVE SUBJECTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER
Compound Name (Number):	Tazemetostat (EPZ-6438)
Protocol Number:	EZH-1101
IND Number:	143032
EudraCT Number:	2019-003649-14
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	**31 August 2022**
Amendment 5	14 April 2022
Amendment 4	27 December 2020
Amendment 3	05 June 2020
Amendment 2	10 January 2020
Amendment 1	29 July 2019
Original Protocol	11 June 2019

Amendment 6

Note: This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment is being made primarily for the following reasons:

1. To update background and clinical information regarding tazemetostat to align with the updated tazemetostat IB (IB v12.0).
2. To remove the requirement of scans for confirmation of progression in soft tissue at Week 9 based on RECIST 1.1 criteria.
3. To update the list of responsible personnel and emergency contact information.
4. To correct internal conflict errors introduced in Protocol Amendment #5 and clarify concomitant medication and supplement advice.

All substantial changes to the protocol are detailed in the table below:

Section # and Name	Description of Substantial Change	Brief Rationale
Section 5.4.3 Clinical Experience Section 5.6.4 Summary Section 7.5.2.1 Dose Modification for Tazemetostat Toxicity Section 12.2.1.6.1 T-Lymphoblastic Leukemia/T-Acute Lymphoblastic Leukemia Section 12.2.1.6.2 MDS/AML/MPN Section 12.2.1.7 Safety Signal Under Evaluation: B-ALL Section 12.2.6 Timeframe for Collecting AEs and SAEs	Updated clinical background, AESI, and B-ALL information with the updated tazemetostat IB (IB v12.0). Removed old Section 5.6.4 (Anticipated Safety Profile) and incorporated updated information in other background text. Corrected language for reporting primary secondary malignancies.	To make clinical experience background information, AESI information, and reporting instructions current where relevant.
Section 2 Synopsis Section 7.7 Study Design Schematic and Schedule of Assessments Section 11.3.2 Radiographic Progression-Free Survival	Removed the requirement of scans for confirmation of progression in **soft tissue** at Week 9. Corrected footnote 't' in the Study Design Schematic to match the table of Protocol-Specified Documentation for Radiographic Evidence of Disease Progression.	There is no recommendation of scans for confirmation of soft-tissue progression in RECIST 1.1.
Signature Page and Emergency Contact Information	Updated the list of responsible personnel (including signatories) and the emergency contact information where appropriate.	To make responsible personnel information and contact information current.
Section 2 Synopsis Section 8.2 Exclusion Criteria	Corrected the last bullet in exclusion criterion #3 to clarify that for phase 2 subjects who are to be randomized to one of the enzalutamide treatment groups, abiraterone (which is required for inclusion) is the only second-generation AR antagonist for which prior treatment with is **not** exclusionary.	To correct an inadvertent internal conflict error in protocol amendment #5.
Section 2 Synopsis Section 11.3.2 Radiographic Progression-Free Survival	Restored text concerning central radiology review of tumor scans as previously described in Protocol Amendment #4.	To correct an inadvertent deletion error with Protocol Amendment #5 and ensure scans are sent to the central radiology reviewer.
Section 7.7 Study Design Schematic and Schedule of Assessments	In the Schedule of Assessments, restored CTC collection to the Cycle 13+ visit column from the unscheduled visit column.	To correct an inadvertent error in Protocol Amendment #5.

Section # and Name	Description of Substantial Change	Brief Rationale
Section 9.3.2 Medications to be Used with Caution Section 9.3.3 Prohibited Medications See also the Summary of Changes in Protocol Amendment #5	Concerning medical marijuana: Rather than prohibiting all forms of medical marijuana, medical marijuana is moved to Section 9.3.2 (Medications to be Used with Caution) with the text "Medical marijuana is permitted only under physician recommendation and with the agreement of the Investigator." As before, CBD oil is still allowed.	To correct an inaccuracy in the body and Summary of Changes to Protocol Amendment #5 concerning medical marijuana.
Section 9.3.1 Permitted Medications Section 9.3.2 Medications to be Used with Caution Section 9.3.3 Prohibited Medications	Modified the following concomitant medication and supplement advice: • Over-the-counter medications, nutritional supplements, vitamins, and herbal preparations (including CBD oil), are permitted, except those to be used with caution or that are prohibited for other stated reasons, and • Other alternative therapies are to be used with caution and discussed with the *Investigator*, rather than with the Medical Monitor; also, removed this repeated bullet point in the list of prohibited medications.	To clarify the over-the-counter medications and supplements that are allowed and to add that alternative therapies are optimally discussed with Investigator, who is in the best position to assess the patient's needs and condition and is aware of substances that are prohibited or to be used with caution by protocol.

Abbreviations: AESI = adverse event of special interest; AR = androgen receptor; B-ALL = B-cell acute lymphoblastic leukemia; CBD = cannabidiol; RECIST = Response Evaluation Criteria in Solid Tumours.

In addition other non-substantial changes to the protocol are detailed in the table below. All changes, including minor editorial revisions, are visible in the tracked version.

Section # and Name	Description of Non-substantial Change	Brief Rationale
Section 2 Synopsis Section 11.3.2 Radiographic Progression-Free Survival	Restructured the statement regarding the criteria on which disease progression is determined in bone and in soft tissue. The evaluation of progression in bone will be based upon PCWG3 criteria (ie, the appearance of two or more new bone lesions on bone scan), and the evaluation of progression in soft tissue will be based on RECIST 1.1 criteria.	To add clarity concerning rPFS in this section (the intention of which criteria is to be used remains unchanged).
Section 7.5.2.1 Dose Modification for Tazemetostat Toxicity	Added the word "anemia" and moved the footnote pertaining to "anemia" in the grade 3 line in the table of Dose Modifications for Tazemetostat Treatment-Related Toxicities.	To enhance readability of table (no instructional information was changed).

Section 7.7 Study Design Schematic and Schedule of Assessments	Merged columns for "CXR or chest CT" between cycle 4 and cycle 13+ to clarify that they are done only if screening chest x-ray demonstrated metastatic chest disease, in line with the footnote 'u.'.	To enhance readability of table (no instructional information was changed).
Section 2 Synopsis Section 13.3.2.2 Analysis of Secondary Efficacy Endpoints	Removed the extraneous word "first" in the definition of PSA50	To correct a minor error.
Section 13.3.5 Health-Related Quality of Life Assessment Endpoints and Analysis	Specified that the algorithms for scoring PROs and plans for the corresponding analyses will be provided in a PRO SAP.	To clarify which SAP will address PRO analysis plans.

Abbreviations: PCWG3 = Prostate Cancer Working Group 3; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = radiographic progression-free survival; SAP = statistical analysis plan.

2. SYNOPSIS

Name of Sponsor/Company: Epizyme, Inc.		
Name of Investigational Product: Tazemetostat (EPZ-6438)		
Name of Active Ingredient: Tazemetostat		
Protocol Number: EZH-1101	**Phase:** 1b/2	**Country:** Global
Title of Study: CELLO-1: A PHASE 1B/2 OPEN-LABEL STUDY EVALUATING TAZEMETOSTAT IN COMBINATION WITH ENZALUTAMIDE OR ABIRATERONE/PREDNISONE IN CHEMOTHERAPY NAIVE SUBJECTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER		
Study centers: Approximately 20 centers globally		
Study period (years): Date first subject enrolled: November 2019 Estimated date last subject completed: February 2024		**Phase of Development:** 1b/2

Objectives:

Primary Objectives:

Phase 1b:

- To determine the safety and tolerability of each of the combinations (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone).
- To select the recommended phase 2 doses (RP2Ds) of tazemetostat for each combination treatment based on pharmacokinetic (PK) and pharmacodynamic parameters as well as efficacy and the overall tolerability of each of the combinations (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone).

Phase 2:

- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone as assessed by radiographic progression-free survival (rPFS) according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria for progression in bone or in soft tissue (the latter by Response Evaluation Criteria in Solid Tumors 1.1 [RECIST 1.1]).

Secondary Objectives:

Phase 1b and Phase 2:

- To determine the benefit of combining tazemetostat with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by:
  - Prostate-specific antigen (PSA)50 (PSA50), defined as the percentage of subjects with a ≥50% decline of PSA from baseline at any time on study for subjects with a baseline PSA ≥2.0 ug/L (ng/mL) per PCWG3 criteria.
  - Objective response rate (ORR) and best overall response (BOR) in soft tissue per RECIST 1.1 guidelines.
  - Disease control rate (DCR; no radiographic progression per PCWG3 criteria, and no unequivocal clinical progression or death) at 6 months on treatment.
  - Time to first skeletal-related event (SRE) per PCWG3.
  - Time to initiation of the next systemic treatment for prostate cancer (TTNT).
  - Time to PSA progression (TTPP), as defined as the duration from baseline to the day of PSA progression per PCWG3 criteria in months.

- Reduction in circulating tumor cells (CTC) from a state of having a detectable number of CTCs to having an undetectable number of CTCs.
- CTC response rate, defined as the percentage of subjects with a ≥30% reduction in CTC number from baseline.

- To further evaluate the safety and tolerability of the combination of tazemetostat with enzalutamide.
- To assess the PK of tazemetostat when administered in combination with enzalutamide (phases 1b and 2) and abiraterone/prednisone (phase 1b only) and the PK of enzalutamide (phases 1b and 2) and abiraterone (phase 1b only) when administered in combination with tazemetostat.

Phase 2 Only:

- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone on quality of life (QoL) as assessed by changes from baseline in FACT-P Functional Well-being Subscale (FWB) and Prostate Cancer Subscale (PCS) scores over the course of the study.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by time to definitive deterioration (TDD) in functional status and in prostate symptoms as assessed by the FACT-P FWB and PCS scores, respectively.

Exploratory Objectives:

Phase 1b only:

- To evaluate the rate of pain progression relative to the time of screening at 6 months using the Brief Pain Inventory (BPI)-Short Form (-SF) for tazemetostat in combination with enzalutamide or abiraterone/prednisone.

Phase 2 only:

- To evaluate the rate of pain progression relative to baseline at each post-baseline time point using the BPI-SF for tazemetostat in combination with enzalutamide versus enzalutamide alone.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by changes from baseline in the FACT-P domains: Emotional, Social, and Physical Well-being over the course of the study.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by changes from baseline in EQ-5D-5L visual analogue scale (VAS) and Health Utilities Index (HUI) scores over the course of the study.

Phase 1b and 2:

- To determine the benefit of tazemetostat in combination with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by PSA90.
- To determine the benefit of tazemetostat in combination with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by circulating tumor DNA (ctDNA) burden.
- To assess the pharmacodynamic modulation of EZH2 activity by tazemetostat by measuring H3K27me3 levels in paired pre- and on-treatment tumor biopsies, including biopsies taken at disease progression (in phase 2 only in responders), that may be obtained from the phase 1b and phase 2 portions of the study.
- To assess genetic and molecular characteristics of responders as compared to non-responders, including mutational status of selected genes and gene expression signatures in tumor biopsies taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders).

- To assess the genetic and molecular characteristics of responders as compared to non-responders, including the mutational status in pre- and on-treatment tumor biopsies and ctDNA in liquid biopsies. Expression profiling signatures of neuroendocrine prostate cancer (NEPC) and androgen receptor (AR) signaling in pre- and on-treatment tumor biopsies will be determined. AR-V7 and NEPC status (morphologically) and, possibly, selected neuroendocrine marker(s) will be determined in CTCs from liquid biopsies taken at baseline. Neuroendocrine status will also be determined in baseline serum samples by assessing serum biomarker neuron-specific enolase (NSE) collected pre-dosing.
- To compare concordance of genetic and molecular characteristics in tumor and liquid biopsy samples.
- To assess immunological endpoints in tumor biopsy samples, including the number and activation/exhaustion status of CD8+ and regulatory T-cell subtypes and other immune cells in tumor infiltrates from tumor biopsies taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders). Also, to investigate circulating immune cell sub-populations isolated from peripheral blood mononuclear cells (PBMCs) taken pre-treatment, on drug treatment at cycle 2 day 1, and at disease progression (only in responders) to determine the impact of drug treatment on immune cell numbers, antigen presentation, and immune cell activation status.

Methods:

This is a 2-part, global, multi-center, open-label, randomized phase 1b/2, active-controlled safety and efficacy study of oral administration of tazemetostat in combination with enzalutamide or abiraterone/prednisone (phase 1b) and of tazemetostat in combination with enzalutamide versus enzalutamide alone (phase 2) in asymptomatic or mildly symptomatic subjects with progressive, metastatic castration-resistant prostate cancer (mCRPC) who have not received chemotherapy for mCRPC and who: for phase 1b, are EITHER previously untreated with a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide) OR progressed on a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide); or for phase 2, previously progressed on abiraterone. The phase 1b portion of this study was designed to determine the RP2D of tazemetostat in combination with either enzalutamide or abiraterone/prednisone, based on safety, tolerability, pharmacokinetic, pharmacodynamic, and efficacy profiles.

In the phase 1b part of the study, there were 3 different tazemetostat dose levels planned to be tested in combination with abiraterone/prednisone and 5 different tazemetostat dose levels planned to be tested in combination with enzalutamide. A maximum of approximately 24 subjects (7 for the combination with abiraterone/prednisone, 13 for the combination with enzalutamide, and up to 4 additional subjects in the event of a dose-limiting toxicity [DLT]) were to be enrolled. Dose escalations began at 400 mg tazemetostat twice daily, followed by 600 mg tazemetostat twice daily, followed by 800 mg tazemetostat twice daily, as tolerated according to occurrence of DLTs, as defined in the protocol). For the enzalutamide combination only, dose escalation could further proceed to 1200 mg twice daily followed by 1600 mg twice daily, as tolerated. For both enzalutamide and abiraterone/prednisone, prescribed doses as recommended by the respective package inserts are to be used throughout the study. Subjects treated in the phase 1b part of the study who did not experience a DLT may continue in the study after cycle 1 on the combination regimen at the assigned dose until progression or occurrence of unacceptable toxicity.

Now that the RP2D of tazemetostat when administered in combination with enzalutamide is established as 1200 mg twice daily, the Investigator may increase the dose of tazemetostat up to the RP2D for phase 1b subjects continuing on combination therapy with enzalutamide after consulting with the Medical Monitor.

Treatment

In the phase 2 part of the study, approximately 80 chemotherapy naive, qualified subjects will be enrolled and randomized. Subjects with mCRPC previously treated with abiraterone/prednisone will be randomized 1:1 to either tazemetostat combined with enzalutamide (using the newly established tazemetostat RP2D of 1200 mg twice daily when given in combination with enzalutamide) or enzalutamide alone. Prescribed doses of enzalutamide as recommended in the package insert will be used throughout the study. Subjects will not be treated with abiraterone in the phase 2 portion of the study.

PSA increase without evidence of confirmed radiographic progression is strongly discouraged as a criterion to discontinue study therapy. Treatment should be continued for as long as the subject is tolerating the study drugs

and continues androgen deprivation therapy (ADT) (ie, surgical castration or ongoing gonadotropin releasing hormone [GnRH] analogue therapy) until confirmed radiographic disease progression by PCWG3 criteria, even if the subject continues to benefit clinically, or until unequivocal clinical progression if earlier than radiographic disease progression.

Localized, palliative radiation therapy and initiation of bisphosphonates or other approved bone targeting agents are allowed and should not result in discontinuation of study drug therapy.

The following assessments of prostate cancer status will be collected during the course of the study: overall survival, soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, SREs, health-related QoL assessments (ie, BPI-SF, FACT-P, and EQ-5D-5L), PSA, CTC enumeration, and blood biomarkers of neuroendocrine prostate cancer. The consensus guidelines of RECIST 1.1 and the PCWG3 have been taken into consideration for the determination of radiographic disease progression. The evaluation of progression in bone will be based upon PCWG3 criteria (ie, the appearance of two or more new bone lesions on bone scan), and the evaluation of progression in soft tissue will be based on RECIST 1.1 criteria. The documentation required for the determination of radiographic disease progression in both bone and soft tissue is listed below in Table S1, and a flow diagram for assessment of bone scans to declare disease progression in bone per PCWG3 after the week 9 scan is provided in Figure S1. Tumor assessments will be performed every 8 weeks for the first 6 months and then every 12 weeks thereafter, starting after cycle 7 until radiographic disease progression is seen.

Table S1. Protocol-Specified Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9 (Cycle 3 Day 1 [±7 days])	Bone lesions; 2 or more new lesions compared to **baseline** bone scan by PCWG3	Timing: at least 6 weeks after progression identified or at week 17 visit[b].	Two or more new bone lesions on bone scan (compared to week 9 scan).
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression.	n/a
Week 17 (Cycle 5 Day 1 [±7 days])	Bone lesions: Two or more new lesions on bone scan compared to week 9 bone scan.	Timing: at least 6 weeks after progression identified or at week 25 visit. Required for bone lesions observed on bone scan[b].	Persistent[c] or increase in number of bone lesions on bone scan compared to week 9 scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	n/a
Week 25 (Cycle 7 Day 1 [±7 days]) or later	Bone lesions: Two or more new lesions compared to week 9 bone scan.	Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan[b].	Persistent[c] or increase in number of lesions on bone scan compared to week 9 scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	n/a

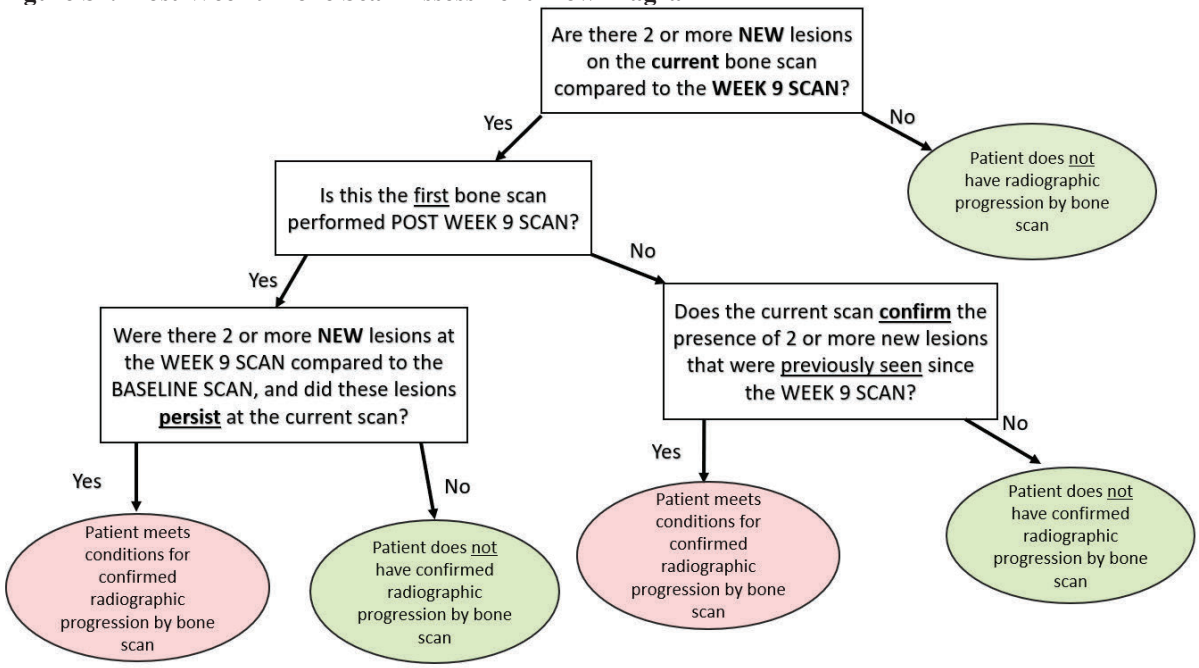
Abbreviations: CT = computed tomography; RECIST = Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; n/a = not applicable; PCWG3 = Prostate Cancer Clinical Trials Working Group 3.

[a] Progression detected by bone scan at an unscheduled visit either prior to week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.

[b] Confirmation must occur at the next available scan.

[c] For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).

Figure S1. Post Week 9 Bone Scan Assessment Flow Diagram



Note: Progression detected by bone scan at an unscheduled visit after week 9 will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the diagram.

Study films (CT/MRI and bone scan) should be read on-site using PCWG3 and RECIST 1.1 guidelines and also be submitted in a digital format for a blinded independent central radiology review. Radiographic imaging is not required after protocol-defined radiographic progressive disease is reached.

Determination of radiographic progression by central radiology review (in parallel with the Investigator's primary review) will continue until at least [redacted] rPFS events from a total of 74 subjects (37 per arm) are confirmed in phase 2, as required for primary rPFS analysis between the active (tazemetostat with enzalutamide) and control arms (enzalutamide alone).

Throughout the study, safety and tolerability will be assessed by the recording of adverse events (AEs), monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). Dosing interruptions and dose-level adjustments of tazemetostat and the combination therapy will be allowed according to protocol-defined guidelines.

In the phase 1b part of the study, a Safety Review Committee (SRC) monitored safety data on an ongoing basis, assessed DLTs, and determined the RP2D, as per charter (completed).

Subjects will have a post-treatment follow-up visit 30 (±3) days after their last dose of tazemetostat or prior to initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.

All subjects with confirmed radiographic disease progression as defined in the protocol will be discontinued from study drug and from further follow-up after the 30-day follow-up visit, even if the subject continues to benefit clinically. If the Investigator elects to continue enzalutamide treatment in the commercial setting in the case of subject who continue to benefit clinically despite confirmed radiographic progression, it will be recorded as subsequent anti-cancer therapy.

For subjects who discontinue study treatment for reasons other than confirmed radiographic disease progression (such as unequivocal clinical or chemical progression), radiographic tumor assessment scans are required every 12 weeks (±7 days) during long-term follow-up, and other study assessment will continue as scheduled, until the earlier of either: 18 months post last study drug dose; radiographic disease progression; the start of a new systemic anticancer therapy for prostate cancer; withdrawal of consent/loss to follow-up; death; or ≥[redacted] rPFS events have been observed in the study (as communicated by the Sponsor).

Study Design:

This is a 2-part, global, multi-center, open-label, randomized Phase 1b/2 study with an oral administration of tazemetostat in combination with either enzalutamide or abiraterone/prednisone (phase 1b) and tazemetostat in combination with enzalutamide versus enzalutamide alone (phase 2) in male subjects with mCRPC (refer to Figure S2). The Phase 1b dose escalation portion of this study was designed to determine the RP2D of tazemetostat in combination with either enzalutamide or abiraterone/prednisone based on safety, tolerability, PK, pharmacodynamics, and efficacy profiles.

Phase 1b

The following paragraphs describe the plan for the phase 1b dose escalation and RP2D determination portion of the study, which has been completed). The RP2D of tazemetostat when administered in combination with enzalutamide was established as 1200 mg twice daily.)

The phase 1b part of the study comprised a dose escalation to determine the RP2D for the phase 2 part and to establish the safety profile of the combination of tazemetostat with enzalutamide or abiraterone/prednisone. The selection of therapy depended on which agent the subjects were previously treated with and progressed on prior to enrollment into the study. Subjects who were previously treated with enzalutamide and/or apalutamide were to receive tazemetostat in combination with abiraterone/prednisone. Similarly, subjects who were previously treated with abiraterone/prednisone were to receive tazemetostat in combination with enzalutamide. Subjects who were previously untreated with either enzalutamide or abiraterone/prednisone were to be equally distributed in both dose escalation arms in the phase 1b part of the study.

Dose escalation was performed using a modified 3+3 design consisting of a planned maximum of approximately 24 evaluable subjects (7 for the abiraterone/prednisone combination and 13 for the enzalutamide combination, and up to 4 additional subjects in the event of a DLT). The starting dose level of tazemetostat was 400 mg orally twice daily followed by 600 mg orally twice daily followed by 800 mg twice daily, as tolerated according to occurrence of DLTs. For the enzalutamide combination only, dose escalation could further proceed to 1200 mg twice daily followed by 1600 mg twice daily, as tolerated.

For phase 1b dose escalation purposes, DLTs during the first cycle were assessed. After completion of cycle 1 of each combination (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone), all available safety data were to be reviewed jointly by the Sponsor and Investigators (the SRC), and the decision to proceed to the next dose cohort was made.

For each combination therapy, the following dose escalation procedure was followed (all dose levels of tazemetostat noted here are given twice daily):

A single subject was to be enrolled at the 400 mg dose level. If the subject did not experience a DLT, then dose escalation would proceed to the next level of 600 mg. If the subject did experience a DLT, the study would stop for this combination therapy.

At the 600 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 600 mg level, then dose escalation would proceed to the next level of 800 mg. If 1 subject experienced a DLT at 600 mg, then the 600 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 600 mg level (ie, no more than 1 DLT in 6 subjects), then dose escalation would proceed to the 800 mg level. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 600 mg experienced a DLT, then the next lower, previously tested dose of 400 mg would be expanded by 2 additional subjects for a total of 3 subjects. If no additional DLTs were observed at the 400 mg dose level, then 400 mg would be evaluated for suitability as the RP2D. If 1 DLT was observed at the 400 mg dose level, 3 additional subjects would be enrolled; 400 mg would be evaluated for suitability as the RP2D if no further DLTs occur. Otherwise, the study for this combination therapy would stop.

At the 800 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 800 mg level, then for the abiraterone/prednisone combination, 800 mg would be evaluated for suitability as the RP2D. If 1 subject experienced a DLT at 800 mg, then the 800 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 800 mg level (ie, no more than 1 DLT in 6 subjects), then for the abiraterone/prednisone combination 800 mg would be evaluated for suitability as the RP2D.

If another DLT was observed after expansion to 6 subjects at 800 mg (2 out of 6), then 600 mg would be evaluated for suitability as the RP2D.

For the enzalutamide combination only, if none of the first 3 subjects or no more than 1 of 6 subjects experienced a DLT at the 800 mg dose level, then dose escalation would proceed to the next level of 1200 mg. At the 1200 mg dose-escalated level, 3 subjects would be enrolled. If no subjects experienced a DLT at the 1200 mg level, then dose escalation would proceed to the next level of 1600 mg. If 1 subject experienced a DLT at 1200 mg, then the 1200 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 1200 mg level (ie, no more than 1 DLT in 6 subjects), then dose escalation would proceed to the 1600 mg level. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 1200 mg experienced a DLT, then the next lower, previously tested dose of 800 mg would be evaluated for suitability as the RP2D.

For the enzalutamide combination only, at the 1600 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 1600 mg level, then 1600 mg would be evaluated for suitability as the RP2D. If 1 subject experienced a DLT at 1600 mg, then the 1600 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 1600 mg level (ie, no more than 1 DLT in 6 subjects), then 1600 mg would be evaluated for suitability as the RP2D. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 1600 mg experienced a DLT, then the next lower, previously tested dose of 1200 mg would be evaluated for suitability as the RP2D.

Seven subjects were enrolled in the abiraterone/prednisone combination dose escalation arm and 14 subjects were enrolled in the enzalutamide combination dose escalation arm. Determination of the RP2D was informed by all available information, including PK parameters and the overall safety and tolerability of each combination. The RP2D of tazemetostat when administered in combination with enzalutamide was established as 1200 mg twice daily. Any available AR splice variant (ie, AR-V7) expression status and neuroendocrine (small cell NEPC) status data were also evaluated before proceeding to phase 2.

Now that the RP2D for tazemetostat in combination with enzalutamide has been established, subjects with mCRPC previously treated with abiraterone/prednisone will be enrolled and randomized 1:1 in the phase 2 part of the study to receive either tazemetostat with enzalutamide or enzalutamide alone (see below).

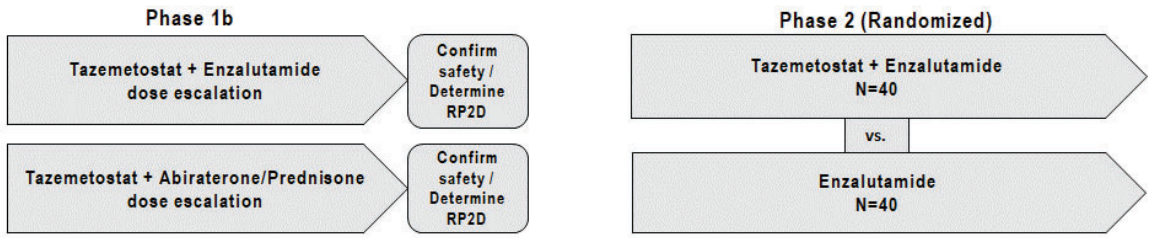
Subjects in the phase 1b part of the study who did not experience a DLT could have continued in the study after cycle 1 on the combination regimen at the assigned dose until progression or occurrence of unacceptable toxicity. For subjects who had been assigned to enzalutamide in phase 1b, the dose of tazemetostat may be increased to the RP2D after consultation with the Medical Monitor.

Phase 2

The phase 2 part of the study will include an open-label, 2-arm randomized portion. Approximately 80 chemotherapy naive, qualified subjects with mCRPC who were previously treated with abiraterone/prednisone will be enrolled and randomized 1:1 to receive either tazemetostat combined with enzalutamide (using the established RP2D of 1200 mg orally twice daily when given in combination with enzalutamide) or enzalutamide alone. All subjects will receive treatment in 28-day cycles.

Total study enrollment will be approximately 104 subjects, and the total study duration will be approximately 12 months for phase 1b and approximately [redacted] months for phase 2, for a total study duration of approximately 50 months.

Figure S2. Study Design



Key Objectives of Phase 1b and Phase 2 to Assess Combination Therapy:

- Phase 1b: Safety, pharmacokinetics, anti-tumor activity in subjects with mCRPC previously treated and untreated with second generation anti-androgens. Determine RP2D. Sample size: maximum of approximately 24 (7 for the abiraterone/prednisone combination and 13 for the enzalutamide combination, and up to 4 additional subjects in the event of a DLT).
- Phase 2 Primary Objective: rPFS. Sample size: 80
- Phase 1b/2 Secondary Objectives: PSA50, TTPP, time to first SRE, ORR and BOR, DCR, time to new treatment, CTC, CTC 30% reduction, and (for phase 2 only) FACT-P FWB and PCS subscales and TDD.
- Total sample size: approximately 104

Abbreviations: CTC = circulating tumor cells; DCR = disease control rate; DLT = dose-limiting toxicity; FACT-P = Functional Assessment of Cancer Therapy – Prostate; FWB = Functional Well-being; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; PCS = Prostate Cancer Subscale; PSA = prostate specific antigen; RP2D = recommended phase 2 dose; rPFS = radiographic progression-free survival; SRE = skeletal-related event; TDD = time to definitive deterioration; TTPP = time to PSA progression.

Sample Size Justification:

For the phase 2 randomized component of the study, to compare the combination of tazemetostat with enzalutamide to enzalutamide alone, CCI rPFS events from a total of 74 total subjects (37 per arm) will provide approximately CCI power for the analysis of rPFS, with a 2-sided total type I error of 0.05 to reject the null hypothesis that there is no difference in rPFS between the two arms. To account for the approximate CCI dropout, the sample size will increase to 80 (40 per arm). The sample size assumes that the combination of tazemetostat with enzalutamide will prolong rPFS by CCI (hazard ratio [HR] = CCI) from CCI months for enzalutamide to CCI months, with CCI of subjects lost to follow-up over an CCI-month enrollment period, an 9-month follow-up period (a total follow-up time of 18 months, tmax = 18), and a total phase 2 study duration of approximately CCI months. (The critical boundary to achieve statistical significance for the final rPFS logrank testing between two arms is HR=CCI or CCI months of improvement in rPFS.)

Number of Subjects (planned) for whole trial: Up to 104 subjects are planned for the trial to assess combination therapy (up to approximately 24 in phase 1b [enrollment completed]; 80 in phase 2).

Diagnosis and Main Criteria for Eligibility

Inclusion Criteria:

1. Age at the time of consent ≥18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (Appendix 1).
3. Life expectancy of >3 months.
4. Histologically or cytologically confirmed adenocarcinoma of the prostate. Small cell or neuroendocrine (differentiated or with neuroendocrine features) tumors of the prostate are also permitted.
5. Progressive disease in the setting of medical or surgical castration (ie, castration-resistant prostate cancer [CRPC]) by PCWG3 criteria for study entry.
   - Evidence of disease progression by rising PSA or
   - Soft tissue progression per RECIST 1.1 or
   - Evidence of disease progression by observation of 2 new bone lesions since the initiation of last systemic therapy.
6. Metastatic prostate cancer disease, as documented by the following imaging.:
   - Bone lesions on bone scan (per PCWG3) or by soft tissue disease (per RECIST 1.1) by CT/MRI imaging.
7. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue GnRH analog or antagonist (medical castration).
8. Surgically or medically castrated, with serum testosterone ≤ 50 ng/dL (≤1.73 nmol/L) at screening.
9. Prior treatment with a second-generation androgen inhibitor as follows:
   - For phase 1b, EITHER previously untreated with a second-generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide) OR progressed on a second-generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide).
   - For phase 2 randomized component (ie, enzalutamide-containing treatment groups) of the study, previously progressed on abiraterone for either castration-sensitive or castration-resistant disease; the required washout period for abiraterone is 7 days.
10. No prior treatment with cytotoxic chemotherapy for mCRPC except as follows:
    - For phase 1b, more than 6 cycles of docetaxel received for castration-sensitive disease prior to having received enzalutamide or abiraterone/prednisone is permitted.
    - For the phase 2 randomized component (ie, enzalutamide-containing treatment groups) of the study, up to 6 prior cycles of docetaxel received for castration-sensitive disease in the nonmetastic and metastatic settings prior to having received abiraterone/prednisone is permitted.
11. Demonstrate adequate organ function as defined below:
    - Absolute neutrophil count (ANC) ≥ 1,000 /μL.
    - Platelet Count ≥ 100,000 /μL.
    - Hemoglobin ≥ 9 g/dL without a transfusion within 2 weeks of screening.
    - Serum creatinine ≤ 2 × upper limit of normal (ULN) or
      – Creatinine clearance ≥ 40 mL/min as estimated by the Cockcroft and Gault formula in subjects with creatinine > 2 × ULN.
    - Bilirubin ≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 × ULN.
    - Aspartate aminotransferase (AST) ≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases.
    - Alanine aminotransferase (ALT) ≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases.

- Albumin > 3.0 g/dL (30 g/L) at screening.

12. Subjects of child-fathering potential as defined in the protocol (Section 7.4.2.1) must either practice complete abstinence or agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), or maintain medical castration during sexual contact with a pregnant female or female partner of childbearing potential (FCBP) during study treatment, for 3 weeks following the last dose of abiraterone/prednisone, and for 3 months following the last dose of enzalutamide. Male subjects with surgical castration are not required to use condoms.

    NOTE: Male subjects must not donate semen or sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months following the last dose of tazemetostat, 3 weeks following the last dose of abiraterone/prednisone, and 3 months following the last dose of enzalutamide.

Exclusion Criteria

1. Known symptomatic brain metastases.
2. Untreated or impending spinal cord compression.
3. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of starting study treatment:
    - Abiraterone within 7 days.
    - First generation: AR antagonists (eg, bicalutamide, nilutamide, flutamide) within 4 weeks.
    - 5-alpha-reductase inhibitors, ketoconazole, estrogens (including diethylstilbesterol), or progesterones within 2 weeks.
    - Chemotherapy (except as permitted in inclusion criterion #10) within 3 weeks.
    - Prior radionuclide therapy within 4 weeks.
    - Another interventional product or standard agent in a clinical study within 28 days prior to the first planned dose of tazemetostat
    - For phase 2 subjects to be randomized to one of the enzalutamide treatment groups only, prior treatment with any second-generation AR antagonist (eg, enzalutamide, apalutamide, darolutamide, proxalutamide, etc) other than abiraterone.
4. Severe concurrent disease, infection, or comorbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
5. History of another invasive cancer within 3 years of randomization, with the exception of treated non-melanoma skin cancer, treated superficial bladder cancer, or fully treated cancers with a remote probability of recurrence in the opinion of both the Medical Monitor and Investigator.
6. History of seizure or any condition that may predispose to seizure (eg, prior cortical stroke or significant brain trauma). History of sub clinical seizures manifested by loss of consciousness or transient ischemic attack within 12 months of randomization. However, subjects on medications with seizure lowering threshold will be admitted.
7. Clinically significant cardiovascular disease including the following:
    - Myocardial infarction within 6 months before screening.
    - Uncontrolled angina within 3 months before screening.
    - Congestive heart failure (New York Heart Association class 3 or 4), or a history of congestive heart failure (New York Heart Association class 3 or 4), unless a screening echocardiogram or multigated acquisition scan performed within 3 months before randomization demonstrates a left ventricular ejection fraction ≥50% (Appendix 2).
    - History of clinically significant ventricular arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes).
    - History of Mobitz 2 second-degree or third-degree heart block without a permanent pacemaker in place.

- Hypotension as indicated by systolic blood pressure <86 millimeters of mercury (mmHg) at screening.
- Bradycardia as indicated by a heart rate of <45 beats per minute on the screening ECG, and upon physical examination.
- Uncontrolled hypertension as indicated by systolic blood pressure >170 mmHg or diastolic blood pressure >105 mmHg at screening.

8. Gastrointestinal disorder affecting absorption (eg, gastrectomy, active peptic ulcer disease within 3 months before randomization).
9. Major surgery within 4 weeks of randomization.
10. For subjects taking abiraterone and prednisone, no evidence of hepatic impairment or classified as only Child-Pugh class A for hepatic impairment.
11. Hypersensitivity reaction to the active pharmaceutical ingredient of tazemetostat, abiraterone, prednisone, or enzalutamide, or any of the other components of each individual agent under study, according to the potential to be assigned to that agent(s).
12. Is unwilling to exclude grapefruit juice, Seville oranges, and grapefruit from the diet and all foods that contain those fruits from time of enrollment to while on study.
13. Is currently taking any prohibited medication(s) as described in Section 9.3.3, including live virus vaccine within 30 days before the first dose of study treatment or plans to receive a live virus vaccine during treatment.
14. Has had prior exposure to tazemetostat or other inhibitor(s) of enhancer of zeste homologue-2 (EZH2).
15. Is immunocompromised (ie, has a congenital immunodeficiency). Subjects diagnosed with human immunodeficiency virus (HIV) are eligible to participate in the study if they meet the following criteria:
    - No history of AIDS-defining opportunistic infections or have not had an opportunistic infection within the 12 months prior to enrollment.
    - No history of AIDS-defining cancers (eg, Kaposi's sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer).
    - Subjects may take prophylactic antimicrobials; however, subjects taking specific antimicrobial drugs that have a potential for drug-drug interaction or overlapping toxicities with study drugs must be excluded from study participation.
    - Subjects should be on established anti-retroviral therapy for ≥4 weeks with an HIV viral load of < 400 copies/mL and/or CD4+ T-cell (CD4+) count ≥ 350 cells/uL prior to enrollment.
16. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE] 5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Has abnormalities known to be associated with MDS (eg del 5q, chr 7 abn) and myeloproliferative neoplasms (MPN; eg, JAK2 V617F) observed in cytogenetic testing and DNA sequencing.

    NOTE: At screening, a complete peripheral blood count (CBC) with differential (manual or automated peripheral blood smear) will be performed and assessed per institutional standards to rule out myeloid malignancies, including but not limited to MDS/AML/MPN. A potential subject with a suspected or confirmed myeloid malignancy will be excluded from the study.
17. Has a prior history of T-cell lymphoblastic lymphoma/ T-cell acute lymphoblastic leukemia (T-LBL/T-ALL).
18. Is unable to take oral medications or has malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea or vomiting) that might impair the bioavailability of study treatments.

19. Subjects with hepatitis B or hepatitis C are ineligible to participate in the study unless they meet the following criteria:
    - Do not have uncontrolled hepatitis B or C infection, are not on active immunosuppressive therapy, and do not have a history of autoimmune disease requiring ongoing systemic therapy.
    - Subjects taking therapy for hepatitis where there may be a drug-drug interaction or overlapping toxicities with study drugs must be excluded from study participation.

Investigational product, dosage, and mode of administration:

In the phase 1b and 2 parts of the study:

Table S2. Phase 1b/2 Doses of Tazemetostat, Enzalutamide, Abiraterone, and Prednisone

Treatment	Dose	Frequency	Total Daily Dose
Tazemetostat	Phase 1b[a]: Per dose escalation Phase 2[c]: - 1200 mg for combination with enzalutamide	Twice daily	Phase 1b[a]: Per dose escalation Phase 2: - 2400 mg for combination with enzalutamide
Enzalutamide	160 mg	Once daily	160 mg
Abiraterone[b, d]	1000 mg	Once daily	1000 mg
Prednisone[d]	5 mg	Twice daily	10 mg

[a] The starting dose was 400 mg tazemetostat twice daily. If there were no DLTs, dose escalation would continue to 600 mg twice daily to a maximum of 800 mg twice daily, as tolerated; for the combination with enzalutamide only, dose escalation may have continued to 1200 mg twice daily and to a maximum of 1600 mg twice daily, as tolerated.
[b] Abiraterone must be taken on an empty stomach with water at least 1 hour before, or 2 hours after a meal.
[c] Orally twice daily in continuous 28-day cycles.
[d] Abiraterone and prednisone are administered in phase 1b only.

The plan for the phase 1b dose-escalation part of the study was as follows: There were 3 different tazemetostat dose levels planned to be tested in combination with abiraterone/prednisone and 5 different tazemetostat dose levels planned to be tested in combination with enzalutamide. Enzalutamide or abiraterone/prednisone was to be administered on cycle 1 day 1 and tazemetostat on day 2. Tazemetostat was to be escalated from a starting dose of 400 mg twice daily, to 600 mg twice daily, to 800 mg twice daily as tolerated, in a modified 3+3 design in combination with enzalutamide or abiraterone/prednisone. For the combination with enzalutamide only, tazemetostat could have been further escalated to 1200 mg twice daily and to a maximum of 1600 mg twice daily, as tolerated.

In the randomized phase 2 part of the study, the RP2D of 1200 mg of tazemetostat when given in combination with enzalutamide will be administered orally twice daily in continuous 28-day cycles. Enzalutamide and tazemetostat will both be administered on day 1 of each cycle.

Duration of Treatment:

Treatment administration should continue for as long as the subject is tolerating the study drugs and continues ADT (ie, surgical castration or ongoing GnRH analogue therapy) until confirmed radiographic disease progression by PCWG3 criteria as specified in Table S1 above, even if the subject continues to benefit clinically, or unequivocal clinical progression if earlier than radiographic disease progression. Enzalutamide treatment may be pursued in the commercial setting at the Investigator's discretion in this case (and will be recorded as subsequent anti-cancer therapy). Investigators are strongly discouraged from discontinuing treatment due to PSA rise alone without evidence of confirmed radiographic progression. Initiation of new therapy for prostate cancer at the time of radiographic progression will mandate discontinuation of study drug.

Criteria for Evaluation:

Efficacy Assessments:

Efficacy will be assessed through survival data, chest CT or chest X-rays, PSA levels, BPI-SF, CTC enumeration, and tumor assessments by radionuclide bone scan and CT or MRI, with disease progression defined by RECIST 1.1 for soft tissue disease or, where indicated, the appearance of two or more new bone lesions on bone scan (per PCWG3). The consensus guidelines of RECIST 1.1 and the PCWG3 are to be taken into consideration for the determination of radiographic disease progression. Study films (CT/MRI and bone scan) should be read on-site using PCWG3 and RECIST 1.1 guidelines (submitted in a digital format for a blinded independent central radiology review was removed with Amendment #5). Radiographic imaging is not required after protocol-defined radiographic progressive disease is reached.

Health-related quality-of-life assessments in the phase 2 portion of the study will also include the FACT-P and EQ-5D-5L. Every effort should be made to ensure all subjects complete as many scheduled health-related QoL assessments as possible, and assessments should be administered before other interactions in the clinic during the visit.

Pharmacokinetic Sampling:

In the phase 1b part of the study, blood samples for PK analysis were collected in cycle 1 on days 1, 2, and 21 at pre-dose (0 hours) and at 0.5, 1, 2, 4, 6, 8, and 24 hours post-dose; and in cycle 2 on day 1 at pre-dose (0 hours) and at 2 and 6 hours post-dose.

In the randomized phase 2 part of the study, blood samples for sparse PK analysis will be collected only from subjects assigned to the combination arm in cycles 2, 3, 5, and 10 on day 1 at pre-dose (0 hours) and at 2- and 6-hours post-dose. For PK assessment days, subjects will be required to take their study drug/s in the morning at the clinic after the pre-dose sample has been collected. The date and time of last dose on PK sampling days will be recorded.

Pharmacogenetics and Biomarker Assessments:

AR-V7 status and NEPC subgroups will be determined as follows: AR-V7 status will be determined by immunofluorescence (IF) detection of the splice variant in nuclei of CTCs; NEPC status will be determined in CTCs by assessing imaging of multiple small cell neuroendocrine parameters and may as well with neuroendocrine marker(s). Biomarkers, such as neuron-specific enolase (NSE), will also be determined.

Safety Assessments:

Safety will be assessed through summaries of adverse events, laboratory evaluations, vital signs, physical examinations, and ECGs. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE, version 5.0.

Statistical Methods:

Efficacy Analyses in Phase 2: The efficacy analyses will be conducted using an Intent-to-Treat population, defined as all randomized subjects. Comparisons between treatment groups for secondary endpoints will occur only if the primary endpoint (rPFS) achieves statistical significance at an alpha level of 0.05.

Primary Efficacy Endpoint Analysis:

Radiographic progression-free survival (phase 2 randomized treatment groups): The rPFS of tazemetostat in combination with enzalutamide will be compared to the rPFS of enzalutamide alone. rPFS is defined as the time from the date of randomization to the date of the first objective evidence of radiographic progression or death from any cause, whichever occurs first. In cases where PD or death has not occurred, censoring rules will be provided in the SAP. Radiographic disease progression is defined by the criteria in Table S1 (and Figure S2).

The primary analysis of rPFS for tazemetostat in combination with enzalutamide compared with enzalutamide treatment alone will be based upon at least the first [redacted] rPFS events observed. A log-rank test will be used to compare tazemetostat in combination with enzalutamide to enzalutamide treatment alone at the significance level of 0.05 (one-sided). Conventionally, HRs with corresponding 2-sided 95% confidence intervals will be estimated using the Cox proportional hazards model. Graphical methods will be used to assess the Cox proportional hazards model assumptions. rPFS will also be summarized descriptively using the Kaplan-Meier (KM) method. The KM estimate along with the corresponding 95% CI will be calculated using the Brookmeyer and Crowley method and will be provided for the median. The event-free rate with corresponding 95% CI will be calculated using Greenwood's formula and will be provided at 4 months, 8 months, 12 months, and 18 months. Median follow-up for rPFS will be estimated according to the KM estimate of potential follow-up. KM curves will also be provided.

Secondary Efficacy Endpoint Analysis:

- **PSA50:** PSA50 is defined as the percentage of subjects with a ≥50% reduction of PSA from baseline at any time on study for subjects with a baseline PSA ≥2 ug/L (2 ng/mL), per PCWG3 criteria. Confirmed PSA response is defined as a ≥50% reduction in PSA from baseline to post-baseline PSA result with ≥50% reduction from baseline, with a consecutive assessment that confirms ≥50% reduction from baseline conducted at least 3 weeks later required to confirm the PSA response. If a consecutive value meets the response criteria but is obtained within 3 weeks and the next assessment also meets response criteria and is taken after 3 weeks, then the initial response is considered as confirmed response as well. However, a subject with a missing confirmation PSA value after 3 weeks is considered as non-responder. PSA50 will be calculated by treatment group for subjects with PSA values at the baseline assessment (cycle 1 day 1 predose) and at least 1 post baseline assessment. A Cochran-Mantel- Haenszel mean score test will be used to compare the response rates between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **Time to First Skeletal-Related Event (SRE):** Time to first SRE is defined as the time from randomization to the date of the first SRE. In cases where an SRE has not occurred at the time of the analysis, the subject will be right-censored. Censoring rules will be provided in the SAP. An SRE is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. A log-rank test will be used to compare time to SREs between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **ORR and Best Overall Soft Tissue Response:** ORR is defined per RECIST 1.1 guidelines. The best overall soft tissue response as assessed by Investigators using RECIST 1.1 will be summarized. Only subjects with measurable soft tissue disease at screening (ie, at least 1 target lesion per RECIST 1.1) will be included in this analysis. Clopper-Pearson exact method will be used to compare the proportion of subjects with an objective response (complete response or partial response) per RECIST 1.1 between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **Disease Control Rate** (no radiographic progression per PCWG3, and no unequivocal clinical progression or death) at 6 months on study therapy. A Cochran-Mantel-Haenszel test will be used to compare DCR between tazemetostat in combination with enzalutamide and enzalutamide treatment alone, and the corresponding *p*-value will be provided. Also, the 95% CI will be provided for each treatment group and the difference in proportion between the two treatment groups using Clopper-Pearson exact method and Newcombe method, respectively.
- **Time to Initiation of the Next Systemic Treatment for Prostate Cancer (TTNT):** TTNT is defined as the time from the date of randomization to date of first documented administration of systemic treatment for prostate cancer. The TTNT will be right-censored at the last study assessment date if the subject did not receive subsequent treatment. A log-rank test will be used to compare time to initiation of subsequent treatment between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **Time to PSA Progression:** Time to PSA progression is defined as the duration from baseline to the date of PSA progression. PSA progression is defined as a ≥25% increase and an absolute

increase of ≥ 2 µg/L (2 ng/mL) above the nadir (or baseline value for subjects who did not have a decline in PSA value by week 17). This increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later. The date of confirmed PSA progression is the date of the initial ≥25% increase. Subjects without confirmed PSA progression at the time of analysis will be right-censored. Censoring rule will be provided in the SAP. Time from randomization to first observation of PSA progression will be assessed. A log-rank test will be used to compare TTPP between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.

- **CTCs:** In subjects who enter the study with a detectable number of CTCs, the **rate of CTC reduction to zero** is the proportion of subjects who convert to an undetectable number of CTCs. CTC response is defined as a ≥30% reduction in CTCs from baseline in subjects who enter the study with a detectable number of CTCs, and the **CTC response rate** is the proportion of subjects with a ≥30% reduction in CTCs from baseline (cycle 1 day 1 pre-dose). The rate of CTC reduction to zero and the CTC response rate for tazemetostat in combination with enzalutamide will be compared with those for enzalutamide treatment alone using the Clopper-Pearson exact method.

See also health-related quality of life (QoL) endpoints below.

Population PK Analysis:

- PK data will be combined with data from the phase 1b and phase 2 parts in a population PK model.

Safety Analysis:

Safety analyses will be based on all subjects who receive ≥1 dose or partial dose of any of the study drugs (ie, the Safety population). Safety data from the phase 1b and phase 2 portions of the study will be presented separately. In general, safety data from the phase 1b portion of the study will be tabulated by assigned dose levels and overall, and the data from the phase 2 portion of the study will be tabulated by assigned treatment group and overall. For all analyses, subjects who receive a dose modification will be retained and analyzed in the treatment group originally assigned.

Drug exposure and compliance will be summarized by descriptive statistics. Severity of all adverse events is to be evaluated by the Investigator based on the CTCAE, version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of the analysis. Tabular summaries of the number and percentage of subjects with adverse events will be presented by MedDRA system organ class and preferred term by relationship to study treatment and by severity.

Deaths will be summarized and listed and will include the categorical reason for death.

Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE, version 5.0. Separate listings and summary tables will be produced for the laboratory test groups with abnormal values flagged. Laboratory shift tables of changes from baseline to worst post-baseline values based on CTCAE toxicity grades will be produced for each parameter. Vital signs and ECG data will be listed and categorically summarized descriptively. Physical examination results will be listed.

Exploratory Analyses and Endpoints:

- **PSA90**: Defined and analyzed similarly to PSA50.
- **Changes in ctDNA burden** (defined as the proportion of ctDNA in the entire population of cell-free DNA [cfDNA]) from longitudinal samples taken throughout the period of drug treatment as compared to baseline.
- **Characterization of tazemetostat combination exposure** (possible example: C_{min}).
- **Pharmacodynamic modulation of EZH2 activity** by tazemetostat as assessed by measuring H3K27me3 levels in paired pre- and on-treatment tumor biopsies that may be obtained from the phase 1b and phase 2 portions of the study. Analyses will include change from screening to on-study values plotted at cycle 2 day 1 and at progression using a waterfall plot.
- The **mutational landscape of pre-treatment tumor biopsies and baseline ctDNA**, such as for loss of *PTEN*, *TP53*, and *RB1,* will be determined using bioinformatic analysis of whole exome next generation sequencing (NGS) and compared when possible to the mutational landscape in

biopsies taken on-treatment and at disease progression. In addition, whole transcriptome data will be obtained from tumor biopsies using RNASeq, and bioinformatics analysis of NEPC and AR signaling pathways, including AR variant AR-V7 gene expression, and other pathways involved in prostate cancer biology will be performed in matched biopsies. Finally, the state of the immune microenvironment in pre-treatment, on treatment (at cycle 2 day 1), and at disease progression (only in responders) tumor biopsies in subjects receiving tazemetostat in combination with enzalutamide will be evaluated by investigating the occurrence of various gene expression signatures of tumor inflammation and infiltrating lymphocytes available from public sources.

- **Circulating tumor DNA (ctDNA)** obtained from liquid biopsies taken minimally at baseline prior to the first dose and on the same days as CT/MRI scans to ascertain first sign of response and disease progression based on ctDNA burden will also undergo targeted whole exome sequencing (WES) to determine the mutational status of genes, such as *PTEN*, *TP53*, and *RB1*, associated with clinical outcome.
- **Concordance of genetic characteristics of disease in tumor biopsies and ctDNA** isolated from baseline liquid biopsies will be evaluated using regression analysis methods.
- **Assessment of immunological endpoints in tumor biopsies** taken at pre-treatment, on-treatment (cycle 2 day 1), and at disease progression (only in responders) in the phase 2 portion of the study will be conducted to determine the level of infiltration of various T-cell lymphocyte and other immune cell populations (cell type number and activation status) using multiplex IF staining and DNA sequence analysis. Differences in the composition of the immune microenvironment between responders and non-responders in each treatment cohort will be determined and compared to published tumor immune profiles associated with response or resistance to immunotherapy, such as checkpoint inhibitor blockade or enzalutamide therapy. In addition, circulating immune cell sub-populations isolated from PBMCs from blood taken pre-treatment, on-treatment (cycle 2 day 1), and at disease progression (only in responders) in the phase 2 portion of the study will be investigated to determine the impact of drug treatment on immune cell numbers, antigen presentation, and activation status.

Subgroup Analysis

Subgroup analysis will be performed for rPFS by AR-V7 and NEPC (negative and positive) status. A swim lane plot (time on treatment) showing AR-V7 and NEPC status will be provide for each endpoint.

Health-Related QoL Endpoints

BPI-SF (phase 1 and phase 2 exploratory objectives):

- In phase 1, the **rate of pain progression**, defined as the proportion of subjects with an increase of ≥30% from the time of screening in the average of BPI pain intensity item scores (items 3, 4, 5, and 6) at 6 months will be used to assess tazemetostat in combination with enzalutamide and tazemetostat in combination with abiraterone/prednisone. The BPI scores will be summarized descriptively at time of screening, at 3 months, and at 6 months.
- In phase 2, the **rate of pain progression**, defined as the proportion of subjects with an increase of ≥30% from baseline in the average of BPI pain intensity item scores (items 3, 4, 5, and 6) at each post-baseline time point will be used to compare tazemetostat in combination with enzalutamide to enzalutamide treatment alone. The BPI scores will be summarized descriptively at baseline and each postbaseline time point.

The BPI mean severity score will be analyzed using mixed-effects model for repeated measures (MMRM) and mixed-effects models with baseline score and treatment group as covariates, and the differences in mean scores between treatment groups will be presented with corresponding 95% CIs at each time point and overall. Changes from baseline will also be presented. The mean change from baseline will be summarized and plotted by treatment group. Continuous endpoints will be analyzed similarly as for BPI pain intensity score.

FACT-P (phase 2 secondary and exploratory objectives):

- For the **secondary objective**, the percentage of subjects with a decline from baseline in the FWB subscale score by ≥10 points and the percentage of subjects with a decline from baseline in the Prostate Cancer Subscale (PCS) score by ≥10 points at any postbaseline visit will be compared between the treatment groups.
- For the **secondary objective**, the TDD is a decline from baseline in FACT-P FWB subscale score of ≥10 points and the time from baseline to decline in FACT-P PCS subscale score of ≥10 points will be compared between the treatment groups.
- For **exploratory objectives**, scores will be summarized descriptively over the course of the study by treatment group, with emphasis on the following FACT-P domains: Emotional, Social, and Physical Well-being.

Analyses will be conducted on the intent to-treat FACT-P population, defined as all randomized subjects who have completed an evaluable FACT-P questionnaire at baseline and ≥1 post-baseline visit. An evaluable questionnaire will have sufficient items completed to allow calculation of ≥1 FACT-P subscale.

In general, to estimate longitudinal changes in FACT-P scores from baseline, the primary analysis will be carried out using an MMRM. MMRM analysis uses all available data and assumes that any missing observations are missing at random. The differences in mean scores between treatment groups will be presented with the corresponding 95% CI at each time point and overall. To address the possibility that missing data may not be at random, a second analysis will be carried out using a pattern-mixture model (PMM) with placebo-based pattern imputation. In both models, the baseline covariates may include: treatment group; time; baseline ECOG score (0–1 or 2); average baseline domain score. Due to the exploratory nature of the analyses, adjustments for multiple comparisons will not be made.

The cumulative distribution function will be presented as a continuous plot of the numerical change in FACT-P scores from baseline on the horizontal axis, with the cumulative percentage of patients experiencing up to that change on the vertical axis. One curve for each treatment group will be plotted for each visit.

EQ-5D-5L (phase 2 exploratory objective):

For the **exploratory objective**, scores will be summarized descriptively over the course of the study by treatment group, with emphasis on changes from baseline in EQ-5D-5L VAS and HUI scores over the course of the study. The analysis method is similar to those for FACT-P.

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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

Abbreviation or Specialist Term	Definition/Explanation
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AR	androgen receptor
AR-V7	androgen-receptor splice variant 7
ASIs	androgen-signaling inhibitors
ATRT	atypical teratoid rhabdoid tumor
AUC	area under the concentration versus time curves
B-ALL	B-cell acute lymphoblastic leukemia
BOR	best overall response
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
CI	confidence interval
C_{max}	peak plasma concentration
C_{min}	minimum/trough plasma concentrations
CNS	central nervous system
CR	complete response
CRF	case report form
CRPC	castration resistant prostate cancer
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cells
CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E_{max}	maximal effect
ES	epithelioid sarcoma
ESC	External Safety Committee
EQ-5D-5L	EuroQol 5-Dimension 5-Level questionnaire
EZH2	enhancer of zeste homologue-2

Abbreviation or Specialist Term	Definition/Explanation
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	United States Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FL	follicular lymphoma
FWB	functional well-being
GCP	Good Clinical Practices
GnRH	gonadotropin releasing hormone
GOF	gain-of-function
H3K27	lysine 27 of histone H3
H3K27me3	H3K27 trimethylation
HIV	human immunodeficiency virus
HMT	histone methyltransferase
HR	hazard ratio
HUI	Health Utilities Index
IB	Investigator's Brochure
IBW	ideal body weight
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IF	immunofluorescence
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INI1	integrase interactor 1
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LN	lymph nodes
LSLV	last subject's last visit
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeter of mercury
MPN	myeloproliferative neoplasm
QTcF	QT interval corrected by Fridericia's formula
RECIST	Modified Response Evaluation Criteria in Solid Tumors
MMRM	mixed-effects model for repeated measures
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
NEPC	neuroendocrine prostate cancer

Abbreviation or Specialist Term	Definition/Explanation
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NSE	neuron-specific enolase
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PCS	Prostate Cancer Subscale
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PET	positron-emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PGx	pharmacogenetic(s)
PK	pharmacokinetic(s)
PMM	pattern-mixture model
PO	oral(ly)
PR	partial response
PRC2	polycomb repressive complex 2
PSA	prostate-specific antigen
PSA50	the percentage of participants who had a PSA decline of at least 50% from baseline
PSA90	the percentage of participants who had a PSA decline of at least 90% from baseline
QoL	quality of life
QSR	Quarterly Safety Review
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 doses
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAM	S-adenosyl methionine
SD	stable disease
SET	sun(var)3-9, enhancer-of-zeste and trithorax
SMARCA4	SWItch/Sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
SRC	Safety Review Committee
SRE	skeletal-related event
SUSAR	suspected unexpected serious adverse reaction
SWI/SNF	SWItch/Sucrose Non-Fermentable
$t_{1/2}$	apparent elimination half-life
T-ALL	T-cell acute lymphoblastic leukemia
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TGI	tumor growth inhibition
T-LBL	T-cell lymphoblastic lymphoma
t_{max}	maximum plasma concentration
TSP1	thrombospondin-1

Abbreviation or Specialist Term	Definition/Explanation
TTNT	time to initiation of the next systemic treatment
TTPP	time to PSA progression
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cells
WES	whole exome sequencing
WT	wild-type

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 Practices, Food and Drug Administration (FDA) Title 21 Part 312, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines; applicable government regulations; and institutional research policies and procedures.

5.1. Background

Post-translational modifications of histones, the core proteins of chromatin, play an important role in controlling the fidelity of cellular gene transcription patterns. One of the critical transcription-controlling histone modifications is methylation of specific lysine and arginine residues, catalyzed by histone methyltransferases (HMTs) which all use S-adenosyl methionine (SAM) as a co-factor for the methylation reaction (Copeland, 2013).

Genetic alterations in a number of HMTs or associated regulatory proteins have been identified in several human cancers where they are purported to be oncogenic. Enhancer of zeste homologue 2 (EZH2) is the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono-, di-, and trimethylation of lysine 27 of histone H3 (H3K27) (Margueron, 2011).

Enhancer of zeste homologue-2 mutation and/or over-expression has been observed in several cancer types, leading to an aberrant H3K27 trimethylation (H3K27me3) state which is oncogenic (Chase, 2011).

For instance, somatic EZH2 gain-of-function (GOF) mutations at three hotspots (Y646, A682, and A692 [NM_001203247]) are found in 10% to 20% of follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). These GOF mutations result in an oncogenic dependency on EZH2 production of abnormally high H3K27me3 levels, and resultant transcriptional reprogramming of the cell (Morin, 2010).

In addition to the EZH2 GOF activation mutations described above, overexpression or amplification of EZH2 has been described in numerous tumor types, including but not limited to bladder, breast cancer, colorectal, lung, pancreatic, ovarian, prostate, mesothelioma, uveal melanoma, renal carcinoma, cholangiocarcinoma, and stomach cancer (Kuroki, 2014; LaFave, 2015; Comet, 2016).

This is partially explained by the regulation of EZH2 gene expression by the pRB-E2F pathway, which is dysregulated in many tumor types (Bracken, 2003). In many of these tumors, EZH2 has been demonstrated to function as an oncogene (Comet, 2016). For instance, EZH2 overexpression promotes anchorage-independent growth and cell invasion in breast cancer (Kleer, 2003), proliferation and epithelial-mesenchymal transition in lung cancer (Takawa, 2011; Tiwari, 2013), and tumorigenesis and metastasis in prostate cancer (Min, 2010). In addition, a gene expression profiling study shows that overexpression of EZH2 in metastatic castration-resistant prostate cancer (mCRPC) (Varambally, 2002) and decreased expression of target genes are correlated with disease stage and poor prognosis (Yu, 2007).

These data suggest that inhibition of EZH2 might also be beneficial in solid tumors that overexpress EZH2 or contain amplifications of the EZH2 gene.

5.2. Clinical Characteristics of Prostate Cancer

Worldwide, prostate cancer ranks third in cancer incidence and sixth in cancer mortality in men (Bray, 2018). Prostate cancer growth is dependent on androgens and depleting or blocking androgen action has been a mainstay of treatment for over 6 decades. Hormonal therapies include gonadotropin-releasing hormone (GnRH) analogues, anti-androgens, ketoconazole, and estrogenic compounds. Despite the early sensitivity of tumors to hormonal strategies, tumors that progress despite androgen deprivation generally represent a transition to the lethal variant of the illness, and most patients ultimately succumb to this disease (Petrylak, 2004; Pienta, 2006). Results of clinical investigations and studies on the molecular profiles of these progressing tumors show that the androgen receptor (AR) remains functional and that the tumors should respond to strategies directed at the AR signaling axis. Overexpression of the AR has been documented in upwards of 50% of such prostate cancer specimens and is believed to contribute to tumor progression (Chen, 2004; Scher, 2004). In addition, currently approved anti-androgens have the potential to act as a partial agonist and stimulate AR signaling in the setting of AR overexpression, therefore exacerbating or accelerating tumor growth. The decline in serum levels of prostate-specific antigen (PSA) seen upon discontinuation of these agents is consistent with the agonist effects ("anti-androgen withdrawal syndrome").

In clinical practice, treatment of advanced prostate cancer is therefore limited by the development of resistance to anti-androgen therapies. Enzalutamide, a potent AR antagonist, and abiraterone acetate (administered in combination with prednisone and hereafter referred to as abiraterone), a potent inhibitor of cytochrome P450 (CYP17A1) that suppresses androgen synthesis, induce declines in PSA in up to 90% of patients when administered alone to men with mCRPC. Both improve survival and are approved for the first-line treatment of chemotherapy-naive mCRPC. However, resistance develops after a median of approximately 18 months, and strategies that prolong treatment benefit are urgently required. A rise in PSA, suggesting reactivation of AR target genes, is often associated with clinical progression. Several mechanisms have been implicated in driving resistance and can be broadly divided into categories that are either dependent on or independent of ligand-binding domain-driven reactivation of AR signaling. The former can include an adaptive feedback loop of increased serum and tissue androgens and AR levels after AR antagonism with enzalutamide that in vitro modeling suggests could result in outcompeting of enzalutamide at the AR.

5.3. Rationale for Tazemetostat Treatment

Prostate cancer is the second leading cause of cancer death for men in the United States with an estimated 174,650 new cases and 31,620 deaths expected (Siegel, 2019). Prostate cancer clinically manifests at different stages with or without associated metastases. Disease development and progression are driven by elevated testosterone (and dihydrotestosterone), through induction of AR signaling (Scher, 2000).

In 1941, Charles Huggins demonstrated that androgen deprivation therapy (ADT) by means of surgical castration offered benefit to men with advanced metastatic prostate cancer (Huggins, 2002).

Current available therapies consist of medical castration by depletion of testicular androgens or by targeting AR signaling pathways. Although initial response to ADT occurs, tumors often

relapse after castration, in what is termed castration resistant prostate cancer (CRPC). This stage is defined by an increase in PSA, a target of AR signaling activation. When the disease progresses, prostate cancer metastasizes to the bone and other organs. Patients with mCRPC have poor overall survival of about 2 years from disease progression.

Two of the newer approved androgen-signaling inhibitors (ASIs) in prostate cancer target the AR signaling pathway: abiraterone acetate diminishes androgen levels derived from the adrenal glands and the tumor itself by inhibiting the enzyme CYP17A1 and thus steroidogenesis (Barrie, 1994), and enzalutamide, an AR antagonist, prevents AR translocation to the nucleus for subsequent gene activation (Tran, 2009). Even though responses are observed to these two inhibitors, most patients relapse in 1 to 2 years (Vander Ark, 2018; Einstein, 2019) with a variety of resistance mechanisms to these drugs being observed.

Leading research in prostate cancer is now focused on understanding the mechanisms of resistance to these newer ASIs. Abiraterone and enzalutamide resistance is believed to be driven by similar mechanisms found in resistance to first-line ADTs, with one of the main resistance mechanisms observed being the preservation of AR signaling. One of such mechanisms is increased expression of the AR. In several studies of mCRPC cohorts, amplification of the AR was found to be present in up to 70% of cases (Robinson, 2015; Abida, 2017; Armenia, 2018; Quigley, 2018; Wedge, 2018). In particular, there is evidence that AR amplification may be caused by an intergenic enhancer region upstream of the AR (Quigley, 2018; Takeda, 2018; Viswanathan, 2018) found present in 81% of cases (Quigley, 2018) that strongly correlates with increased AR expression and possibly drives progression to mCRPC. Another mechanism of resistance observed in certain abiraterone and enzalutamide resistant tumors is the presence of recurrent GOF mutations in the AR gene responsible for the switch of the function of these molecules from antagonist to agonist. This switch was also observed in tumors from patients that relapsed after first-line AR therapies (Azad, 2015; Robinson, 2015; Lallous, 2016). These mutations have been found in 10 to 20% of cases in mCRPC studies (Robinson, 2015; Abida, 2017; Armenia, 2018; Quigley, 2018; Wedge, 2018).

In addition, expression of AR splice variants that lack the ligand binding domain (Hu, 2009) have been recognized as a major mechanism of resistance. Studies performed in circulating tumor cells have associated androgen-receptor splice variant 7 (AR-V7) expression, the most common of the variants, with abiraterone and enzalutamide resistance (Antonarakis, 2014; Antonarakis, 2015; Scher, 2016). AR-V7 is rarely expressed in primary prostate cancer tumors but is detected in 75% of cases in CRPC and even following ADT (Sharp, 2019).

Based on the several mechanisms of resistance described above, it is clear that AR signaling is a key driver in prostate cancer even after treatment with AR-targeted therapies. Cotreatment with therapies that modulate alternative signaling pathways involved in oncogenesis in prostate cancer have been proposed as a modality to overcome resistance, including epigenetic modifiers such as EZH2.

Enhancer of zeste homologue-2 is the catalytic subunit of the multi-protein PRC2 that catalyzes the mono-, di-, and trimethylation of H3K27 (Margueron, 2011). Enhancer of zeste homologue-2 mutation and/or over-expression have been observed in several cancer types, leading to an aberrant H3K27me3 state which is oncogenic (Chase, 2011). Somatic GOF mutations within EZH2, found within subsets of non-Hodgkin lymphoma, result in an oncogenic dependency on EZH2 (Morin, 2010; Sneeringer, 2010), production of abnormally high H3K27me3 levels, and

resultant transcriptional reprogramming of the cell. In addition, genetic changes in proteins of the SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex that acts at many loci in opposition to PRC2, can lead to oncogenesis. Mutation or loss of the SWI/SNF subunit integrase interactor 1 (INI1), has been demonstrated to generate an over-activation of the PRC2 pathway and tumor cell proliferation (Wilson, 2010). Tumors in which INI1 protein is absent include tumor types such as MRT, atypical teratoid rhabdoid tumor, RTK and other rare tumors such as epithelioid sarcoma (ES), epithelioid malignant peripheral nerve sheath tumor, extra-skeletal myxoid chondrosarcoma; myoepithelial carcinoma, and renal medullary carcinoma (Margol, 2014). Inhibition of EZH2 activity by either knock-down or small molecule inhibition induces tumor cell killing and durable tumor regressions in preclinical models of rhabdoid tumors (Alimova, 2013; Knutson, 2014). Based on the strong implication of EZH2 in specific genetically-defined cancer types, efforts were undertaken by Epizyme and others to discover small molecule inhibitors of EZH2. Tazemetostat (EPZ-6438) is a selective, reversible, SAM-competitive small molecule inhibitor of the EZH2 HMT enzymatic activity (Knutson, 2013) Several other EZH2 inhibitors have been described in the literature (McCabe, 2012; Qi, 2012; Bradley, 2014).

In prostate cancer, increasing EZH2 messenger RNA and protein expression correlates with advancing disease progression. Patients with clinically localized prostate cancers with higher expression of EZH2 show a worse prognosis (Varambally, 2002). It has been proposed that EZH2 plays an oncogenic role through two different functions in androgen-driven prostate cancer. Enhancer of zeste homologue-2 plays its conventional role of transcriptional repressor that is dependent on its methyl transferase activity, and it is also proposed that it acts as a transcriptional activator targeting the AR and its downstream signaling pathway in a PRC2 and catalytic activity-independent manner (Xu, 2012; Kim, 2018). Consistent with these findings, enzymatic inhibitors of EZH2, including GSK126, GSK503, and tazemetostat, have been shown to enhance the activity of AR antagonists when tested in preclinical models of AR-dependent prostate cancer (Kim, 2018). For instance, GSK126 in combination with enzalutamide inhibited the growth of LNCaP cells in vitro and the antiproliferative effect observed with the combination treatment was greater than that of the single agents alone. Similar effect was observed when LNCaP and C4-2B (an AR-expressing, metastatic CRPC cell line) were treated with tazemetostat in combination with enzalutamide for 8 days in vitro. Moreover, the drug combination also showed synergistic suppression of LNCaP and C4-2B cell colony formation. Combination of tazemetostat and enzalutamide, reduced tumor growth in an in vivo xenograft model of C4-2B.

Additionally, neuroendocrine prostate cancer (NEPC), a subtype of CRPC characterized by independence from AR signaling, has been associated with aggressive clinical features and poor overall survival (Wang, 2014). The transition of adenocarcinoma to NEPC is recognized as one of the mechanisms of treatment resistance in prostate cancer in which the tumors undergo lineage plasticity through epigenetic reprogramming in defined genetic contexts (RB1, PTEN and TP53 loss, MYCN amplification, among others) (Beltran, 2011; Beltran, 2016) and in settings defined by other functional markers including delta-like 3 protein (Puca, 2019). In extreme cases, tumors may reprogram towards alternative pathways adopting features of neuroendocrine, neuronal, or other lineages. One of the key epigenetic factors driving the process of trans-differentiation to a neuroendocrine subtype is EZH2, which is highly expressed in this setting (Beltran, 2016; Davies, 2018; Puca, 2018).

EZH2 inhibition has been shown to reverse the reprogramming of these tumors back to a luminal state (Ku, 2017). Studies conducted in genetically-engineered mouse models demonstrated that Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis and anti-androgen therapy resistance by repressing reprogramming factors such as EZH2 and SOX2 (Ku, 2017). Dual knock-out of these tumor suppressors in vivo increased expression of SOX2 and EZH2, and treatment with EZH2 inhibitors led to re-expression of AR and sensitized the models to enzalutamide including significantly inhibited tumor growth by combination of the EZH2 inhibitor GSK503 with enzalutamide (Ku, 2017). Overexpression and copy number amplification of N-Myc are also observed in clinical NEPCs tumor samples (Beltran, 2011). N-Myc has been proposed as a driver of the NEPC phenotype that promotes tumorigenesis by abrogating AR signaling and inducing EZH2-driven transcriptional repression. Using N-Myc transgenic mouse cell lines and human cell lines overexpressing N-Myc, EZH2 inhibitors elicited anti-tumor activity preclinically both in vitro and in vivo (Dardenne, 2016). Additionally, studies conducted in neuroendocrine patient-derived organoids demonstrated dose dependent decrease in organoid formation in vitro by the EZH2 inhibitor GSK343 (Puca, 2018).

In studies conducted by Epizyme, tazemetostat dose-dependently inhibited H3K27 methylation in all prostate cancer cell lines tested after 4-day treatment. Tazemetostat also dose-dependently inhibited proliferation in vitro over the course of 14 days of treatment, especially, in cell lines that depend on AR signaling LNCaP, C4-2B and in 22Rv1, a cell line that in addition expresses the splice variant AR-V7. Furthermore, tazemetostat elicited antiproliferative activity in a cell line of the neuroendocrine subtype (NCI-H660). Combination treatment of LNCaP and C4-2B cell lines in vitro showed synergistic antiproliferative activity when tazemetostat was combined with enzalutamide or abiraterone. Enzalutamide synergistically enhanced the in vitro activity of tazemetostat in the 22Rv1 cell line, although this effect did not manifest in the in vivo xenograft setting performed in this model.

Tazemetostat (125 mg/kg oral [PO] administered twice daily) enhanced the antitumor activity of enzalutamide administered at two different doses (10mg/kg and 30 mg/kg PO once daily) in a subcutaneous LNCaP prostate cancer cell line xenograft mouse model after 14 days of dosing. respectively. The combination treatment of tazemetostat and enzalutamide at the highest dose tested achieved a tumor growth inhibition (TGI) of 72%, which was greater than the individual drug treatments alone. The combination of abiraterone and tazemetostat showed a TGI of 35%, which was greater than the antitumor activity observed for the single agent treatments.

Taken together, the studies performed at Epizyme and those reported in the literature support a combination approach of tazemetostat with second-generation ASI therapies in the second-line mCRPC setting in treatment-naive patients or following progression on abiraterone acetate or enzalutamide.

Following progression on second generation anti androgens, the last resort is currently initiation of treatment with chemotherapy such as docetaxel or cabazitaxel. At that stage, patients in the third-line setting are more difficult to treat by virtue of advanced age, aggressive nature of the disease, and depleted end organ reserves. For docetaxel, aside from the fact it is intravenously administered every 2 weeks requiring frequent clinic visits, it is also associated with a black box warning that includes toxic death, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. Furthermore, it must be administered with prednisone twice daily continuously and requires premedication with oral steroids (please refer to the current, publicly available

package insert). For cabazitaxel, it is administered intravenously every 3 weeks in combination with prednisone and requires premedication with antihistamines, corticosteroids, and H2 antagonists. Cabazitaxel has a black box warning which includes neutropenic deaths, hypersensitivities including rash, hypotension, and bronchospasm (refer to the current, publicly available package insert).

As such, the need for effective chemotherapy-free combination therapies like tazemetostat is warranted for patients in the first- and second-line setting.

5.4. Tazemetostat

5.4.1. Nonclinical Pharmacology

Tazemetostat (EPZ-6438) is a selective small molecule inhibitor of the histone-lysine methyltransferase EZH2 gene (Knutson, 2013). Tazemetostat inhibits both wild-type (WT) EZH2 and mutated EZH2 residues Y641, A677G and A687 with half maximal inhibitory concentrations (IC_{50}) ranging from 2-38 nmol/L. The compound shows a 36-fold selectivity over the most closely related HMT, EZH1, and greater than a 4500-fold selectivity over other HMTs. It selectively inhibits intracellular H3K27 methylation in a concentration- and time- dependent manner in all cell lines tested in vitro to date.

Additional details are provided in the most current version of the tazemetostat Investigator's Brochure (IB).

5.4.2. Pharmacokinetics

Tazemetostat is orally bioavailable in patients with hematological and solid tumor malignancies. The absorption is rapid with a median time to maximum plasma concentration (t_{max}) of 1 to 2 hours. The mean absolute bioavailability was approximately 33% (Study EZH-103). In dose escalation studies in patients with hematological and solid tumor malignancies, tazemetostat exhibited a more than dose-proportional increase in exposure (area under the concentration-time curve [AUC] and maximum concentration [C_{max}]). At the recommended therapeutic dose of 800 mg twice daily, the mean steady state C_{max} was 829 ng/mL and area under the concentration-time curve from 0 to 12 hours (AUC_{0-12}) was 3340 ng•hr/mL. The consistent t_{max} and apparent elimination half-life ($t_{1/2}$) across the range of doses evaluated (100 to 1600 mg twice daily) suggest overall dose-independent absorption and clearance.

There was no difference in relative bioavailability between low-fat and high-fat meal conditions. A high-fat meal exhibited a negligible effect on the extent and rate of absorption. A high-fat meal showed a 24% and 18% decrease in tazemetostat C_{max} and AUC exposures, while the geometric mean ratios for C_{max} and AUC for the major metabolite EPZ-6930 were close to 1, thereby demonstrating that a similar overall systemic exposure was seen after a high-fat meal compared to dosing in the fasted state.

There was little to no accumulation (C_{max} and AUC) of plasma tazemetostat following repeat dosing, likely due to auto-induction. The metabolite EPZ-6930 had minimal accumulation following multiple dosing. Tazemetostat is eliminated primarily via hepatic metabolism in humans, with approximately 88% bound to plasma proteins. Following administration of a single oral 800 mg dose of radiolabeled tazemetostat, the average percent recovery of the administered

dose was 15.4% in urine and 87.8% in feces. Unchanged tazemetostat accounted for 1.39% of the administered dose recovered in urine and was not detected in feces.

5.4.3. Clinical Experience

Across the clinical development program, tazemetostat has been or is being studied in clinical trials for the treatment of:

- non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).
- mantle cell lymphoma
- multiple myeloma
- mesothelioma
- integrase interactor 1 (INI1) or switch/sucrose nonfermentable (SWI/SNF)-related, matrix-associated, actin-dependent regulator of chromatin (SMARC), subfamily A, member 4 (SMARCA4)-deficient tumors in both adult and pediatric populations (including synovial sarcoma, rhabdoid tumors, renal medullary carcinoma, ES, other INI1- or SMARCA4deficient tumors).
- prostate cancer
- ovarian cancer

More than 1105 clinical study subjects have received tazemetostat as monotherapy or in combination with other drugs in Epizyme-sponsored trials. The majority of adverse events observed in these studies are consistent with known adverse reactions of the drugs under investigation and/or comorbidity, are generally mild to moderate in severity, respond to dose modification, and resolve without sequelae.

The most common (≥20%) treatment-emergent AEs, regardless of causality, observed in adult subjects across monotherapy clinical studies were nausea and fatigue. The most common TEAEs that have led to interruption of tazemetostat monotherapy dosing in ≥2% of the adult population were thrombocytopenia and neutropenia. The most common TEAEs leading to tazemetostat monotherapy dose reduction in ≥2% of the adult population were thrombocytopenia and neutropenia.

The safety profile of tazemetostat is well characterized and stable. The benefit-risk remains positive.

Adverse events of special interest include T-LBL/T-ALL, AML, MDS, and other myeloid malignancies like MPN and have been reported in patients administered tazemetostat.

Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients. The risk of myeloid neoplasia as a result of EZH2 inhibition is considered uncertain based on available literature and Epizyme clinical data.

In addition, B-cell acute lymphoblastic leukemia (B-ALL) has been reported to occur following tazemetostat exposure. Refer to the IB for further details.

Measures are in place to exclude potential subjects who may be predisposed to developing a myeloid/lymphoid neoplasia from participation as well as dose modification guidelines and laboratory monitoring for early identification of subjects who may be developing a second primary hematologic malignancy.

The degree of risk of second hematologic malignancies remains uncertain based on paradoxical preclinical literature data, and the risk may be no greater than that expected in this subject population in general. Refer to the current IB for further descriptions of adverse events, AESIs and other potential risks.

The anticipated safety profiles of abiraterone, prednisone, and enzalutamide are as stated in their respective IB, SmPC, or USPI.

- Tazemetostat is in late-stage clinical development and has shown clinical activity in subjects across the tazemetostat program, including objective responses and sustained disease stabilization. Tazemetostat has received accelerated approval in the US for ES and FL, as noted below.
- Tazemetostat is considered to be a clinically active drug that has the potential to benefit both adult and pediatric oncology subjects across different tumor types where there are unmet medical needs.

Tazemetostat (TAZVERIK®) received accelerated approvals for marketing in the US:

- On 23 January 2020, tazemetostat was approved for the treatment of adults and pediatric subjects aged 16 years and older with metastatic or locally advanced epithelioid sarcoma (ES) not eligible for complete resection.
- On 18 June 2020, tazemetostat was approved for the treatment of:
  - adult subjects with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an enhancer of zeste homolog 2 (EZH2) mutation as detected by a US Food and Drug Administration (FDA)-approved test and who have received at least 2 prior systemic therapies
  - adult subjects with R/R FL who have no satisfactory alternative treatment options.

In June 2021, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) granted approval of TAZVERIK for the treatment of subjects with R/R EZH2 gene mutation-positive FL (limited to use when difficult to treat with standard treatments) to Epizyme's development partner, Eisai.

Further details of study designs, tazemetostat exposure, and the safety profile in monotherapy and combination therapy clinical trials AEs are outlined in the current IB.

Tazemetostat has, thus far, shown clinical activity in subjects across the tazemetostat program, including objective responses and sustained disease stabilization in a number of hematologic and solid tumor malignancies in adults and children as outlined in the current tazemetostat IB. As noted above, the FDA granted accelerated approval for tazemetostat in 2020 in 2 disease states, ES and FL.

Tazemetostat is considered to be a clinically active drug that has the potential to benefit both adult and pediatric oncology subjects across different tumor types where there are unmet medical needs.

5.4.4. Pharmacodynamics

In the adult Phase I study, the pharmacodynamics of H3K27 methylation following tazemetostat dosing was measured in skin to provide evidence for on-target methylation inhibition in a surrogate tissue. In that study, IHC analysis of skin biopsies collected pre- dose and after 28 days of tazemetostat treatment revealed a post-dose decrease in H3K27me3-positive cells across all doses explored (100-1600 mg twice daily), with a maximum reduction in the percentage of H3K27me3-positive cells to 50% of baseline. Interestingly differences were observed in the tazemetostat induced reduction in H3K27me3 levels in different skin layers potentially pointing to different kinetics for H3K27me3 turnover in the cells that occupy different skin layers.

In this study, pre- and post-treatment tumor biopsies will be evaluated to enable the assessment of tazemetostat dosing on H3K27me3 levels in tumor tissue. H3K27me3 IHC data will provide mechanistic insight into the impact of EZH2 inhibition on H3K27me3 levels in cell populations within tumor. In addition, these data will be evaluated in the context of tazemetostat exposure data to explore PK-pharmacodynamics relationships.

A robust reduction in H3K27me3 by IHC staining was observed in a limited number of paired pre- and post-dose tumor biopsies collected thus far in Study EZH-202 and EZH-203. In addition to monitoring H3K27me3, expression profiles of immune markers PD-L1 and CD8 also were assessed. To date, two of six subjects from EZH-202 tested had increased tumor PD-L1 expression while undergoing treatment with tazemetostat. The increased expression of tumor PD-L1 was associated with an increased number of CD8-positive cells infiltrating the tumor stroma. These data are supportive of an observation made in the Phase 1 study E7438-G000-101 in which biopsies from a subject with ES demonstrated increased PD-L1 expression and evidence of T-cell infiltration. Given the limited number of tumor biopsies collected to date and the variability of time points assessed, it is difficult to draw conclusions regarding the immune-priming effects of tazemetostat.

5.5. Rationale

5.5.1. Rationale for Studying mCRPC

After exposure to antiandrogens, whether first or second generation, a rise in PSA, suggesting reactivation of AR target genes, is often associated with clinical progression. Several mechanisms have been implicated in driving resistance and can be broadly divided into categories that are either dependent on or independent of ligand-binding domain-driven reactivation of AR signaling. The former can include an adaptive feedback loop of increased serum and tissue androgens and AR levels after AR antagonism with enzalutamide that in vitro modeling suggests could result in outcompeting of enzalutamide at the AR.

In an attempt to overcome resistance (Attard, 2018), a study was conducted to investigate enzalutamide resistance, which is thought to be attributable to ligand-binding domain reactivation of AR signaling. It was hypothesized that cross-resistance may exist between single-agent enzalutamide and abiraterone, making their use in sequence of limited benefit, and that a

rise in androgens in patients receiving enzalutamide may result in reactivation of AR, so that disrupting this adaptive feedback loop by combining with abiraterone would re-induce enzalutamide sensitivity, resulting in prolonged patient benefit and tumor responses versus abiraterone alone.

Abiraterone effectively inhibits androgen synthesis, but it was hypothesized that raised levels of progesterone, synthetic glucocorticoids, and other potential ligands with abiraterone in the presence of high AR levels after enzalutamide treatment would result in continued AR activity and primary resistance. For that matter, in this study patients received open-label enzalutamide and at predefined PSA progression were randomly assigned to receive abiraterone plus placebo or abiraterone plus enzalutamide. Combining abiraterone with enzalutamide would not inhibit reactivation of AR independent of the ligand-binding domain, including resistance mediated by AR splice variants or glucocorticoid receptors. A total of 509 patients enrolled in period one at 51 sites worldwide and received open-label single-agent enzalutamide. Three hundred seventy (73%) of 509 patients had received a first-generation antiandrogen, 151 (30%) were receiving a stable dose of bisphosphonates or denosumab, and 421 (83%) had bone metastases on bone scan. Median duration of treatment with single-agent enzalutamide in period one was 9.1 months; 377 (74%) and 340 patients (67%) had a PSA decline of ≥30% and ≥50%, respectively, at week 21. Overall, 408 patients had stable or decreased PSA levels at weeks 13 and 21 and were therefore eligible to enter period two when they developed PSA progression. Of these, 251 patients had confirmed PSA progression, met period two eligibility criteria, and were randomly assigned to one of the two treatment groups before the cutoff date of October 7, 2016. A total of 126 were assigned to enzalutamide plus abiraterone and prednisone (combination group), and 125 were assigned to placebo plus abiraterone and prednisone. All except one patient in each treatment group received study treatment. At the data cutoff for the primary analysis, of the 258 patients who were not randomly assigned, 84 (33%) continued enzalutamide and 174 (67%) discontinued period one, primarily because of disease progression. Of the 251 patients randomly assigned, 27 (21%) of 126 patients in the combination group and 18 (14%) of 125 patients in the control group continued treatment. Median treatment duration in period two was 5.6 months for both groups. Median progression-free survival (PFS) was 5.7 and 5.6 months for the combination and control groups, respectively (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.61 to 1.12; P = .22). A predefined analysis of the PFS event by unequivocal clinical or radiographic progression or death suggested a difference in the proportion of events by treatment group, with a higher rate of clinical progression events in the combination group and a higher rate of radiologic events in the control group.

This study evaluated reinduction of sensitivity to AR antagonism by combining enzalutamide with abiraterone to treat patients with a rising PSA while receiving enzalutamide. Because the study design randomly assigned patients who had received single-agent enzalutamide until confirmed PSA progression, a primary endpoint was used that included unequivocal clinical progression. This differed from the regulatory COU-AA-302 and PREVAIL studies, which mandated radiographic progression and was considered necessary because of the ethical and pragmatic challenges of continuing AR-targeting therapy in men with a rising PSA and worsening symptoms, given the risk of patients becoming too unwell for the next proven effective line of treatment with docetaxel. In fact, approximately one fifth of patients at screening before random assignment in period two had a pain score of 3 on question three (worst pain in the previous 24 hours) of the Brief Pain Inventory (BPI)-Short Form(-SF). This study did not

meet its primary end point. Consequently, the gatekeeping procedure was not used, and secondary analyses were not adjusted for multiplicity and were considered exploratory. These included a sensitivity analysis for radiographic PFS (rPFS) that showed a nominally significant difference benefiting the combination group.

Most patients receive two or more hormonal manipulations and are then offered chemotherapy as they continue to progress and develop symptoms. (Lam, 2006). A randomized study comparing docetaxel administered every 3 weeks vs. docetaxel weekly vs. mitoxantrone has shown a modest survival benefit for docetaxel every 3 weeks, but this response is not durable (Tannock, 2004). In addition, cytotoxic chemotherapy has significant treatment-related toxicities when compared to hormonal and other non-cytotoxic therapies (see Section 5.3).

Because of resistance to second generation anti androgen therapies and due to overexpression of the AR being a common feature of progressive prostate cancer, therapies that are targeted to reverse or prevent resistance may be effective when added to second generation antiandrogens in these patients.

5.5.2. Study Rationale

The clinical benefit of tazemetostat has not yet been established in patients with progressive, mCRPC. This study will characterize the safety, efficacy, and PK in this population. There is a reasonable expectation based upon nonclinical data that clinical activity may be observed in patients with progressive, mCRPC.

Data has recently been reported to suggest that a sequencing strategy of abiraterone followed by enzalutamide may provide greater clinical benefit to subjects with mCRPC than the reverse sequence. Enzalutamide showed activity as a second-line androgen receptor pathway inhibitor, whereas abiraterone acetate did not, leading to a longer time to second PSA progression for the sequence of abiraterone followed by enzalutamide than with the opposite treatment sequence. (Khalaf, 2019) Given that PSA is a gold standard surrogate endpoint in measuring the early signals of clinical activity, the data suggest that using a sequencing strategy of abiraterone acetate followed by enzalutamide provides the greatest clinical benefit in patients with metastatic CRPC. Acquired changes in the androgen receptor signaling axis has been proposed as a mechanistic explanation as to why patients given enzalutamide had a higher second-line response. While there are known resistance mechanisms common to both drugs, enzalutamide retains androgen receptor inhibitory activity against 2 well-described mutations associated with abiraterone plus prednisone resistance. (Khalaf, 2019) The hypothesis of this optimal sequencing strategy, however, is being tested in the phase 1b component of the trial with enrollment of subjects previously treated with enzalutamide and/or apalutamide who received tazemetostat in combination with abiraterone/prednisone. Subjects are not planned to be treated with abiraterone in the phase 2 portion of this study.

This is a 2-part, global, multi-center, open-label, randomized phase 1b/2, active-controlled safety and efficacy study of oral administration of tazemetostat in combination with either enzalutamide or abiraterone/prednisone (phase 1b) and of tazemetostat in combination with enzalutamide versus enzalutamide alone (phase 2) in asymptomatic or mildly symptomatic subjects with progressive mCRPC and who: for phase 1b, are EITHER previously untreated with a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide) OR progressed on a

second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide); or for phase 2, previously progressed on abiraterone.

5.5.3. Rationale for Dose Selected

Recommended Tazemetostat Dose Determination from Previous Clinical Trial

The primary objective of a previously conducted trial, E7438-G000-101 (Phase 1 portion), was to determine the MTD and/or RP2D of tazemetostat as a single agent administered orally twice daily, continuously in 28-day cycles, in subjects with advanced solid tumors or relapsed and/or refractory B-cell lymphomas. In the dose escalation part, subjects with advanced solid tumors or B-cell lymphomas received oral tazemetostat continuously in 28-day cycles. The starting dose was 100 mg twice daily, with subsequent dose cohorts evaluated at 200 mg, 400 mg, 800 mg, and 1,600 mg twice daily. Each cohort was permitted to enroll up to 6 subjects (3+3 design), with escalation proceeding until 2 or more subjects of a cohort of 3 to 6 subjects experienced a DLT during cycle 1 of treatment. The selection of the 800 mg twice daily dose as the RP2D of tazemetostat as a single agent is supported by all available efficacy, PK/pharmacodynamics and safety data. Briefly, among subjects with advanced solid tumors, 2 (5%) of the 43 subjects achieved an objective response, including CR in 1 subject with INI1-negative malignancy at the tazemetostat 800 mg twice daily dose level and 1 PR in a subject with SMARCA4-negative malignancy at the tazemetostat 1600 mg twice daily dose. Of the 2 responders in the advanced solid tumor subgroup, the DOR was 16.1 weeks for the subject with PR and 112.1+ weeks for the subject with CR; the latter subject was ongoing in response as of the data cutoff date (Study E7438-G000-101).

In-addition, predose and postdose skin punch biopsies were successfully collected in 32 subjects enrolled in the dose escalation part of this study to determine target inhibition, as measured by downregulation of H3K27me3. A dose-dependent reduction in H3K27me3 was observed across the stratum spinosum layer of the skin, with a marked decrease in H3K27me3 as tazemetostat $AUC_{0\text{-}12}$ increased after administration of doses ranging from 100 mg to 800 mg twice daily. The reduction in H3K27me3 levels appeared to reach a plateau in the $AUC_{0\text{-}12}$ observed in the 800 mg twice daily dose cohort. An inhibitory E_{max} model–predicted decrease in H3K27me3 at the observed mean $AUC_{0\text{-}12}$ on day 15 in the 800 mg twice daily dose cohort was more than 80% of the maximum effect, indicating that target inhibition in the skin was near maximal and that doubling the dose to 1,600 mg twice daily resulted in only a modest incremental increase in the inhibition of H3K27 methylation. Furthermore, based on the safety data one subject in the dose escalation part of the study experienced a DLT (Grade 4 thrombocytopenia) while receiving tazemetostat 1,600 mg twice daily, which was the highest dose administered.

Taken together these data support the selection of the 800 mg twice daily as the recommended Phase 2 dose (RP2D) of tazemetostat as a single agent.

Current Trial Phase 1 Dose Escalation Plan for Combination RP2D Determination

In order to define the optimal dose of tazemetostat to be used in combination in the proposed multicenter, phase 1b/2, open label, randomized, active-controlled safety and efficacy study of oral tazemetostat in combination with enzalutamide or abiraterone/prednisone (phase 1b) and tazemetostat in combination with enzalutamide versus enzalutamide alone (phase 2) in asymptomatic or mildly symptomatic subjects with progressive, mCRPC who have not received

chemotherapy for mCRPC and who: for phase 1b, are EITHER previously untreated with a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide) OR progressed on a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide); or for phase 2, previously progressed on abiraterone, a phase 1b dose escalation part was included to evaluate the efficacy, safety, and PK of the tazemetostat in combination with either enzalutamide or abiraterone/prednisone. Dose escalation was performed using a modified 3+3 design consisting of a planned maximum of approximately 24 evaluable subjects (7 for the combination with abiraterone/prednisone and 13 for the combination with enzalutamide, and up to 4 additional subjects in the event of a DLT).

In the phase 1b part of the study, there were to be 3 different tazemetostat dose levels planned to be tested in combination with abiraterone/prednisone and 5 different tazemetostat dose levels planned to be tested in combination with enzalutamide. A maximum of approximately 24 subjects (7 for the combination with abiraterone/prednisone, 13 for the combination with enzalutamide, and up to 4 additional subjects in the event of a dose-limiting toxicity [DLT]) could have been enrolled. Dose escalations began at 400 mg tazemetostat twice daily, followed by 600 mg tazemetostat twice daily, followed by 800 mg tazemetostat twice daily, as tolerated according to occurrence of DLTs, as defined in this protocol. For the enzalutamide combination only, dose escalation could have further proceed to 1200 mg twice daily followed by 1600 mg twice daily, as tolerated. Enzalutamide (a strong CYP3A4 inducer) was expected to lower study drug exposure because tazemetostat is metabolized by CYP3A4; previous PK data showed that exposure lower than 800 mg twice daily could lead to substantially less target engagement. Based on emerging PK and safety data from the phase 1b portion of the study, a higher dose than 800 mg twice daily in the phase 2 portion of the study may provide for more optimal efficacy.

For both enzalutamide and abiraterone/prednisone, prescribed doses as recommended by the respective package inserts will be used throughout the study.

Intensive PK sampling was included in the dose escalation (phase 1b) of the study to explore the potential of a drug-drug interaction between tazemetostat and enzalutamide or abiraterone/prednisone. These data, for the combination with enzalutamide, was to help further guide the dose selection for the phase 2 part of the study.

Recommended Phase 2 Dose Determination for Combination with Enzalutamide (Complete)

The phase 1b dose escalation and RP2D determination of tazemetostat when given in combination with enzalutamide has been completed.

Seven subjects were enrolled in the abiraterone/prednisone combination dose escalation arm and 14 subjects were enrolled in the enzalutamide combination dose escalation arm. As described above in Section 5.5.2, subjects were not planned to be treated with abiraterone in the phase 2 portion of this study because of recently reported data suggesting that a sequencing strategy of abiraterone followed by enzalutamide may provide greater clinical benefit to subjects with mCRPC than the reverse sequence (Khalaf, 2019), a hypothesis being examined in the phase 1b component of the trial.

All available phase 1b data concerning safety, tolerability, and PK in the combination with enzalutamide were considered in making the RP2D determination.

No DLTs were observed at any dose of tazemetostat given in the planned dose escalation phase with enzalutamide. The SRC considered the totality of safety and tolerability information of the combination and endorsed doses of tazemetostat up to 1600 mg twice daily when administered in combination with enzalutamide to be considered for the RP2D.

In addition to the safety analysis, PK data were also considered in the determination of the RP2D.

As described in Section 5.6.3, tazemetostat is extensively metabolized by CYP3A4, and enzalutamide is a strong CYP3A4 inducer. As a result, it was expected that concentrations of tazemetostat in the presence of enzalutamide would be lower than concentrations of tazemetostat administered as monotherapy. Accordingly, the objective of the dose escalation phase of the study was to identify a tazemetostat dose level when used in combination with enzalutamide that delivers comparable steady-state exposure to that of the 800 mg twice daily dose of tazemetostat when administered as monotherapy.

Tazemetostat steady-state AUC was used as a metric to guide RP2D dose selection. The tazemetostat 1200 mg twice daily dosing regimen, when administered in combination with enzalutamide, produced a mean steady-state C_{max} of 568 ng/mL and $AUC_{(0-\tau)}$ of 5643 ng*h/mL, which was found to be comparable to the steady-state AUC of tazemetostat 800 mg twice daily when administered as monotherapy (6620 ng*h/mL). Therefore, because tazemetostat exposure at 1200 mg twice daily when administered in combination with enzalutamide is similar to tazemetostat exposure at 800 mg twice daily when administered as monotherapy, tazemetostat 1200 mg twice daily was endorsed as the RP2D when administered in combination with enzalutamide. This dose will be further explored in the phase 2 portion of the study.

5.6. Benefit:Risk Assessments

5.6.1. Animal Toxicology

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

Steady-state exposures (AUC_{0-24}) in rats at the lowest dose (100 mg/kg/day) at which no T-LBL occurred in the 13-week adolescent rat study were 2.5- to 8-fold greater than that observed in humans at the recommended Phase 2 dose (RP2D; 800 mg twice daily) from the ongoing Phase 1/2 Study E7438-G000-101. No incidences of abnormal bone formation have been observed in the ongoing clinical study. All subjects of child-fathering potential and their partners of childbearing potential must agree to use a reliable birth control method during the study, and for

3 months after the last tazemetostat dose, and additionally will be actively monitored for signs or symptoms of abnormal bone formation.

Additional animal toxicology is provided in the IB for tazemetostat.

5.6.2. Photo-Reactive Potential

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

5.6.3. CYP3A Metabolism

Effect of Other Drugs on Exposure to Tazemetostat

A thorough investigation for drug interaction potential was done by conducting a series of in vitro studies which included CYP phenotyping, metabolic stability, substrate, and inhibition assessment of metabolic transporters, and inhibition of major human CYP enzymes. Based on the results from the population PK analyses, the impact of concomitant drugs on tazemetostat exposure was evaluated. These results demonstrate that CYP3A4 inhibitors, CYP3A4 inducers, CYP2D6 inhibitors, CYP2D6 inducers, and pH modifiers had no clinically significant effect on tazemetostat exposure, suggesting that these drugs may be co-administered with tazemetostat (EZH-P101). With respect to potential DDI associated with drug transporters, tazemetostat is a P-glycoprotein (P-gp) substrate but not a substrate for other drug transporters studied, including breast cancer resistance protein, organic anion transporting polypeptide (OATP) 1B1 and 1B3, organic anion transporters 1 and 3, organic cation transporter 2, and multidrug and toxin extrusion 1. However, P-gp does not seem to limit tazemetostat absorption in subjects, presumably due to the relatively good passive permeability at the therapeutic dose of 800 mg twice daily. This suggests that tazemetostat is not susceptible to transporter-mediated DDI as a victim drug.

As stated above, enzalutamide (a strong CYP3A4 inducer) was expected to lower study drug exposure because tazemetostat is metabolized by CYP3A4; the previous PK data showed that exposure at a lower dose than 800 mg twice daily could lead to substantially less target engagement. Refer to Section 5.5.3 for the dose rationale for this combination to achieve a therapeutic dose level of tazemetostat.

Effect of Tazemetostat on Exposure to Other Drugs

Tazemetostat is eliminated primarily via hepatic metabolism in humans. In vitro test systems using hepatic preparations from mice, rats, dogs, rabbits, monkeys, and humans suggest that tazemetostat forms similar metabolites across species. The results of in vitro phenotyping studies indicate that CYP3A4 is the predominant enzyme responsible for tazemetostat metabolism in humans. With respect to tazemetostat as a perpetrator, although tazemetostat inhibits several CYPs in vitro, based on the inhibitory constant (Ki) and the observed tazemetostat exposure in subjects at the therapeutic dose of 800 mg twice daily, the potential clinical implications due to the inhibitory potential of tazemetostat on drugs that are substrates of CYP3A4, CYP2C8, or CYP2C19 is limited. Notably, the effect of tazemetostat on CYP3A4 is complicated with

opposing induction and time-dependent inhibition of the enzyme. The net clinical DDI outcome is a weak induction of CYP3A as indicated by an approximately 40% reduction of midazolam AUC following 800 mg twice daily dosing for 15 days (Study E7438-G000-101). While tazemetostat may potentially inhibit P-gp, OATP1B1, and OATP1B3, there is limited potential for clinically significant DDI with substrates of these transporters, based on in vitro transporter inhibition assessment and observed exposures at the recommended dose regimen of 800 mg twice daily. The 3 major metabolites are not expected to affect the activities of the major human CYPs and major drug transporters.

5.6.4. Summary

In vitro and in vivo nonclinical xenograft experiments suggest the potential for clinical antitumor activity in INI1-negative tumors, thus providing a rationale for the potential benefit of tazemetostat in the aforementioned tumors. Furthermore, in the adult phase 1 study of tazemetostat in adults, 3 subjects with MRT treated with tazemetostat 800 mg twice daily have been enrolled to the ongoing roll-over maintenance study and have demonstrated clinical activity. The nonclinical studies utilizing in vitro and in vivo prostate cancer model systems performed at Epizyme and those shown in the literature support a combination approach of tazemetostat with second generation ASI therapies in the second-line setting for patients who have not responded to or who have progressed on abiraterone acetate or enzalutamide treatment.

Given the available safety and initial activity data of tazemetostat monotherapy and combination therapy in more than 2280 adult and pediatric subjects from both clinical and post-marketing sources , there is a reasonable expectation that the safety profile observed will be substantially unchanged in patients with progressive mCRPC.

The safety profiles of the drugs to be used in combination with tazemetostat in this study (enzalutamide, abiraterone, and prednisone) are described in their respective Prescribing Information summaries.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objectives

Phase 1b:

- To determine the safety and tolerability of each of the combinations (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone).
- To select the RP2Ds of tazemetostat for each combination treatment based on PK and pharmacodynamic parameters as well as efficacy and the overall tolerability of each of the combinations (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone).

Phase 2:

- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone, as assessed by rPFS according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria for progression in bone or in soft tissue (the latter by Response Evaluation Criteria in Solid Tumors 1.1 [RECIST 1.1]).

6.2. Secondary Objectives

Phase 1b and Phase 2:

- To determine the benefit of combining tazemetostat with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by:
  - PSA50, defined as the percentage of subjects with a ≥50% decline of PSA from baseline at any time on study for subjects with a baseline PSA ≥2.0 ug/L (ng/mL) per PCWG3 criteria.
  - ORR and best overall response (BOR) in soft tissue per RECIST 1.1 guidelines.
  - DCR (no radiographic progression per PCWG3 criteria, and no unequivocal clinical progression or death) at 6 months on treatment.
  - Time to first skeletal-related event (SRE) per PCWG3.
  - Time to initiation of the next systemic treatment for prostate cancer (TTNT).
  - Time to PSA progression (TTPP), as defined as the duration from baseline to the day of PSA progression per PCWG3 criteria in months.
  - Reduction in circulating tumor cells (CTC) from a state of having a detectable number of CTCs to having an undetectable number of CTCs.
  - CTC response rate, defined as the percentage of subjects with a ≥30% reduction in CTC number from baseline.
- To further evaluate the safety and tolerability of the combination of tazemetostat with enzalutamide.

- To assess the PK of tazemetostat when administered in combination with enzalutamide (phases 1b and 2) and abiraterone/prednisone (phase 1b only) and the PK of enzalutamide (phases 1b and 2) and abiraterone (phase 1b only) when administered in combination with tazemetostat.

Phase 2 Only:

- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone on quality of life (QoL) as assessed by changes from baseline in FACT-P Functional Well-being Subscale (FWB) and Prostate Cancer Subscale (PCS) scores over the course of the study.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by time to definitive deterioration (TDD) in functional status and in prostate symptoms as assessed by the FACT-P FWB and PCS scores, respectively.

6.3. Exploratory Objectives

Phase 1b Only:

- To evaluate the rate of pain progression relative to the time of screening at 6 months using the Brief Pain Inventory (BPI)-Short Form (-SF) for tazemetostat in combination with enzalutamide or abiraterone/prednisone.

Phase 2 Only:

- To evaluate the rate of pain progression relative to baseline at each post-baseline time point using the BPI-SF for tazemetostat in combination with enzalutamide versus enzalutamide alone.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by changes from baseline in the FACT-P domains: Emotional, Social, and Physical Well-being over the course of the study.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by changes from baseline in EQ-5D-5L visual analogue scale (VAS) and Health Utilities Index (HUI) scores over the course of the study.

Phase 1b and 2:

- To determine the benefit of tazemetostat in combination with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by PSA90.
- To determine the benefit of tazemetostat in combination with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by ctDNA burden.

- To assess the pharmacodynamic modulation of EZH2 activity by tazemetostat by measuring H3K27me3 levels in paired pre- and on-treatment tumor biopsies, including biopsies taken at disease progression (in phase 2 only in responders), that may be obtained from the phase 1b and phase 2 portions of the study.
- To assess genetic and molecular characteristics of responders as compared to non-responders, including mutational status of selected genes and gene expression signatures in tumor biopsies taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders).
- To assess the genetic and molecular characteristics of responders as compared to non-responders, including the mutational status in pre- and on-treatment tumor biopsies and ctDNA in liquid biopsies. Expression profiling signatures of neuroendocrine prostate cancer (NEPC) and androgen receptor (AR) signaling in pre- and on-treatment tumor biopsies will also be determined. AR-V7 and NEPC status (morphologically) and, possibly, selected neuroendocrine marker(s) will be determined in CTCs from liquid biopsies taken at baseline. Neuroendocrine status will also be determined in baseline serum samples using serum biomarker neuron-specific enolase (NSE) collected pre-dosing.
- To compare concordance of genetic and molecular characteristics in tumor and liquid biopsy samples.
- To assess immunological endpoints in tumor biopsy samples, including the number and activation/exhaustion status of CD8+ and regulatory T-cell subtypes and other immune cells in tumor infiltrates from tumor biopsies taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders). Also, to investigate circulating immune cell sub-populations isolated from PBMCs taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders) to determine the impact of drug treatment on immune cell numbers, antigen presentation, and immune cell activation status.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 2-part, global, multi-center, open-label, randomized phase 1b/2, active-controlled safety and efficacy study of oral administration of tazemetostat in combination with enzalutamide or abiraterone/prednisone (phase 1b) and tazemetostat in combination with enzalutamide versus enzalutamide alone (phase 2) in asymptomatic or mildly symptomatic subjects with progressive, metastatic castration-resistant prostate cancer (mCRPC) who have not received chemotherapy for mCRPC and who: for phase 1b, are EITHER previously untreated with a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide) OR progressed on a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide); or for phase 2, previously progressed on abiraterone. The phase 1b portion of this study was designed to determine the RP2D of tazemetostat in combination with either enzalutamide or abiraterone/prednisone, based on safety, tolerability, pharmacokinetic, pharmacodynamic, and efficacy profiles. The study design is displayed in Figure 1.

Up to 104 subjects are planned to enroll in the trial to assess combination therapy (up to approximately 24 subjects in phase 1b; 80 subjects in randomized phase 2).

Phase 1b

The following paragraphs describe the plan for the phase 1b dose escalation and RP2D determination portion of the study, which has been completed (see Section 5.5.3). The RP2D of tazemetostat when administered in combination with enzalutamide was established as 1200 mg twice daily.

The phase 1b part of the study comprised dose escalations to determine the RP2D for the phase 2 part and to establish the safety profile of the combination of tazemetostat with enzalutamide or abiraterone/prednisone. The selection of therapy depended on which agent the subjects were previously treated with and progressed on prior to enrollment into the study. Subjects who were previously treated with enzalutamide and/or apalutamide were to receive tazemetostat in combination with abiraterone/prednisone. Similarly, subjects who were previously treated with abiraterone/prednisone were to receive tazemetostat in combination with enzalutamide. Subjects who were previously untreated with either enzalutamide or abiraterone/prednisone were to be equally distributed in both dose escalation arms of the phase 1b part of the study.

In the phase 1b part of the study, there were 3 different tazemetostat dose levels planned to be tested in combination with abiraterone/prednisone and 5 different tazemetostat dose levels planned to be tested in combination with enzalutamide. Dose escalation was performed using a modified 3+3 design consisting of a planned maximum of approximately 24 evaluable subjects (7 for the combination with abiraterone/prednisone and 13 for the combination with enzalutamide, and up to 4 additional subjects in the event of a DLT). Dose escalations began at 400 mg tazemetostat twice daily, followed by 600 mg tazemetostat twice daily, followed by 800 mg tazemetostat twice daily, as tolerated according to occurrence of DLTs, as defined in the protocol). For the enzalutamide combination only, dose escalation could further proceed to 1200 mg twice daily followed by 1600 mg twice daily, as tolerated. For both

enzalutamide and abiraterone/prednisone, prescribed doses as recommended by the respective package inserts are to be used throughout the study.

For phase 1b dose escalation purposes, DLTs (as defined in Table 2, Table 3, and Table 4) during the first cycle were assessed. After completion of cycle 1 of each combination (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone), all available safety data were reviewed jointly by the Sponsor and Investigators (the SRC) and the decision to proceed to the next dose cohort was made.

For each combination therapy, the following dose escalation procedure was followed (all dose levels of tazemetostat noted here are given twice daily):

A single subject was to be enrolled at the 400 mg dose level. If the subject did not experience a DLT, then dose escalation would proceed to the next level of 600 mg. If the subject did experience a DLT, the study would stop for this combination therapy.

At the 600 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 600 mg level, then dose escalation would proceed to the next level of 800 mg. If 1 subject experienced a DLT at 600 mg, then the 600 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 600 mg level (ie, no more than 1 DLT in 6 subjects), then dose escalation would proceed to the 800 mg level. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 600 mg experienced a DLT, then the next lower, previously tested dose of 400 mg would be expanded by 2 additional subjects for a total of 3 subjects. If no additional DLTs were observed at the 400 mg dose level, then 400 mg would be evaluated for suitability as the RP2D. If 1 DLT was observed at the 400 mg dose level, 3 additional subjects would be enrolled; 400 mg would be evaluated for suitability as the RP2D if no further DLTs occur. Otherwise, the study for this combination therapy would stop.

At the 800 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 800 mg level, then for the abiraterone/prednisone combination, 800 mg would be evaluated for suitability as the RP2D. If 1 subject experienced a DLT at 800 mg, then the 800 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 800 mg level (ie, no more than 1 DLT in 6 subjects), then for the abiraterone/prednisone combination, 800 mg would be evaluated for suitability as the RP2D.

If another DLT was observed after expansion to 6 subjects at 800 mg (2 out of 6), then 600 mg would be evaluated for suitability as the RP2D.

For the enzalutamide combination only, if none of the first 3 subjects or no more than 1 of 6 subjects experienced a DLT at the 800 mg dose level, then dose escalation would proceed to the next level of 1200 mg. At the 1200 mg dose-escalated level, 3 subjects would be enrolled. If no subjects experienced a DLT at the 1200 mg level, then dose escalation would proceed to the next level of 1600 mg. If 1 subject experienced a DLT at 1200 mg, then the 1200 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 1200 mg level (ie, no more than 1 DLT in 6 subjects), then dose escalation would proceed to the 1600 mg level. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at

1200 mg experienced a DLT, then the next lower, previously tested dose of 800 mg would be evaluated for suitability as the RP2D.

For the enzalutamide combination only, at the 1600 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 1600 mg level, then 1600 mg would be evaluated for suitability as the RP2D. If 1 subject experienced a DLT at 1600 mg, then the 1600 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 1600 mg level (ie, no more than 1 DLT in 6 subjects), then 1600 mg would be evaluated for suitability as the RP2D. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 1600 mg experienced a DLT, then the next lower, previously tested dose of 1200 mg would be evaluated for suitability as the RP2D.

Seven subjects were enrolled in the abiraterone/prednisone combination dose escalation arm and 14 subjects were enrolled in the enzalutamide combination dose escalation arm. Determination of the RP2D was informed by all available information, including PK parameters and the overall safety and tolerability of each combination. The RP2D of tazemetostat when administered in combination with enzalutamide was established as 1200 mg twice daily. Any available AR splice variant expression status (ie, AR-V7) and neuroendocrine (small cell NEPC) status data were also evaluated before proceeding to phase 2.

Now that the RP2D for tazemetostat in combination with enzalutamide has been established, subjects with mCRPC previously treated with abiraterone/prednisone will be enrolled and randomized 1:1 in the phase 2 part of the study to receive either tazemetostat with enzalutamide or enzalutamide alone.

Subjects treated in the phase 1b part of the study who did not experience a DLT may continue in the study after cycle 1 on the combination regimen at the assigned dose until progression or occurrence of unacceptable toxicity. For subjects who had been assigned to the enzalutamide combination in phase 1b, the dose of tazemetostat may be increased to the RP2D after consultation with the Medical Monitor.

Phase 2

The phase 2 part of the study will include an open-label, 2-arm randomized component. Approximately 80 chemotherapy naive, qualified subjects with mCRPC who were previously treated with abiraterone/prednisone will be enrolled and randomized 1:1 to receive either tazemetostat combined with enzalutamide (using the newly established RP2D of 1200 mg orally twice daily when given in combination with enzalutamide) as determined in phase 1b part of the study) or enzalutamide alone. All subjects will receive treatment in 28-day cycles.

Study Duration

Study duration will be approximately 12 months for phase 1b and approximately CCI months for phase 2, for a total study duration of approximately 50 months.

7.2. Number of Subjects

It is expected that approximately 104 subjects will be enrolled: a maximum of approximately 24 subjects in the phase 1b part of the study (enrollment completed); approximately 80

chemotherapy naïve, qualified subjects in the randomized phase 2 part of the study. See Section 13.2 for sample size assumptions.

7.3. Treatment Assignment

The plan for treatment assignment in the phase 1b part of the study (completed) was as follows: In the phase 1b part of the study, there were 3 different tazemetostat dose levels planned to be tested in combination with abiraterone/prednisone and 5 different tazemetostat dose levels planned to be tested in combination with enzalutamide. A maximum of approximately 24 chemotherapy naïve, qualified subjects were to be enrolled in one of the combination treatments as described above in Section 7.1. The starting dose level of tazemetostat was 400 mg orally twice daily followed by 600 mg orally twice daily followed by 800 mg twice daily, as tolerated according to occurrence of DLTs. For the enzalutamide combination only, dose escalation could further proceed to 1200 mg twice daily followed by 1600 mg twice daily, as tolerated.

For both enzalutamide and abiraterone/prednisone, prescribed doses as recommended by the respective package inserts will be used throughout the study.

In the phase 2 part of the study, approximately 80 chemotherapy naïve, qualified subjects with mCRPC who were previously treated with and progressed on abiraterone/prednisone will be randomized 1:1 to either tazemetostat combined with enzalutamide (using the newly established tazemetostat RP2D of 1200 mg twice daily when given in combination with enzalutamide) or enzalutamide alone. Prescribed doses of enzalutamide as recommended by the package insert will be used throughout the study. Subjects will not be treated with abiraterone/prednisone in the phase 2 portion of the study.

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

7.4. Restrictions During Study Treatment

7.4.1. Food and Sun Exposure

Subjects will abstain from ingesting Seville oranges, grapefruit or grapefruit juice, and foods/beverages that contain those, for 24 hours prior to the first dose of study treatment until the last dose of study treatment.

Subjects should avoid prolonged exposure to sunlight while receiving study treatment. In addition, subjects should take other measures to avoid ultraviolet exposure such as wearing sunscreen and sunglasses, wearing protective clothing, and avoiding tanning beds.

7.4.2. Pregnancy and Sperm Donation

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

7.4.2.1. Definition of Child-fathering Potential: Male Subjects

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

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

A male subject is not considered to be of child-fathering potential if he:

- Has undergone surgical castration.

7.4.2.2. Definition of Childbearing Potential: Female Partners

A female partner is considered to be a female of childbearing potential (FCBP) if she:

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

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

- Is post-menopausal (≥12 months consecutive amenorrheic)
- Is surgically sterilized (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) with surgery at least 1 month before the male partner's (subject's) first dose of study treatment, or
- Has a documented congenital or acquired disorder that is incompatible with pregnancy.

7.4.2.3. Pregnancy Prevention

Subjects must refrain from donating sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months following the last dose of tazemetostat, 3 weeks following the last dose of abiraterone/prednisone, and 3 months following the last dose of enzalutamide.

Subjects of child-fathering potential must either practice complete abstinence or agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia) or maintain medical castration during sexual contact with a pregnant female or FCBP during study treatment and for 3 months following the last dose of tazemetostat, 3 weeks following the last dose of abiraterone/prednisone, and 3 months following the last dose of enzalutamide. Male subjects with surgical castration are not required to use condoms.

Epizyme recommends that FCBP as defined in Section 7.4.2 who are partners of male study subjects also either practice complete abstinence or use a highly effective method of contraception. It is recommended that contraception begin at least 4 weeks prior to male partner's first dose of study drug, continue during study treatment (including during dose

interruptions), and continue for 3 months following the male subject's last dose of tazemetostat, 3 weeks following his last dose of abiraterone/prednisone, and 3 months following his last dose of enzalutamide. If the below contraception methods are not appropriate for the FCBP, it is recommended she be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for her. The following are examples of highly effective contraception:

- Intrauterine device (IUD)
- Bilateral tubal ligation
- 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])

NOTE: Female partners who are using hormonal contraceptives are recommended to have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to the male subject's first dose of study treatment and continue to use the same contraceptive during study treatment and for 3 months after the subject's final dose of tazemetostat, 3 weeks following his last dose of abiraterone/prednisone, and 3 months following his last dose of enzalutamide.

Female partners exempt from contraceptive recommendations are those who practice true abstinence when this is in line with their preferred and usual lifestyle (periodic abstinence [eg, calendar, ovulation, sympto-thermal, post-ovulation methods], declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception). If currently abstinent, the female partner is recommended to use a highly effective method of contraception as described above if she becomes sexually active during the subject's study treatment, and for 3 months after the subject's final dose of tazemetostat, 3 weeks following his last dose of abiraterone/prednisone, and 3 months following his last dose of enzalutamide.

7.5. Dose Adjustment Criteria

7.5.1. Dose-limiting Toxicities

Phase 1b (Dose Escalation, Cycle 1 [Completed])

Study drugs for a subject who experiences a DLT were to be stopped. Events were assessed as DLTs according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0), as shown in Table 2, Table 3, and Table 4. Refer to Section 7.1 (Overall Study Design) for a description of the dose escalation process.

Table 2: Dose-Limiting Toxicities - Tazemetostat

Toxicity Category	Toxicity/CTCAE Grade
Hematological	Grade 4 neutropenia for >5 days, or grade 3 neutropenia with fever (>38.5°C in axilla)
	Grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding or lasting ≥7 days
Other Non-hematological Toxicity	Grade 3 fatigue, or a 2-point decline in Eastern Cooperative Oncology Group (ECOG) performance status, that persists for ≥7 days
	Elevation of hepatic enzymes, including bilirubin to meet the definition of Hy's Law (per FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009)
	Grade ≥2 neurotoxicity or cardiotoxicity
	Grade 2 hypersensitivity reaction
	Nausea, vomiting, or diarrhea that persists at grade 3 or 4 despite maximal medical therapy
	Any grade 3 or higher non-hematological laboratory abnormalities that require hospitalization
	Any other grade ≥3 non-hematological toxicity not listed above that persists for ≥7 days despite best institutional standard of care.

Abbreviations: CTCAE= Common Terminology Criteria for Adverse Events.

Note: Dose-limiting toxicities resulting from the combination of tazemetostat with either enzalutamide or abiraterone/prednisone will take into account change or increase of risks known to be associated with these products in addition to any new toxicities resulting from the combination of tazemetostat with the compounds.

Table 3: Dose-Limiting Toxicities - Abiraterone/Prednisone

Toxicity Category	Toxicity/CTCAE Grade
Mineralocorticoid excess	Severe symptoms including ≥grade 3 hypokalemia and/or hypertension requiring hospitalization, lasting ≥7 days without resolution, in spite of cessation of study therapy and application of best institutional standard of care.
Adrenocortical insufficiency	≥Grade 3 severe symptoms requiring hospitalization, uncontrolled for ≥7 days, in spite of discontinuation of study therapy and best institutional standard of care.
Hepatotoxicity	• Elevation of hepatic enzymes including bilirubin to meet the definition of Hy's Law (per FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) • Isolated grade 3 elevation of ALT or AST of ≥7 days, in spite of discontinuation of study therapy, and application of best institutional standard of care. Isolated grade 3 elevation of total bilirubin without evidence of biliary obstruction that persists ≥7 days, in spite of discontinuation of study therapy, and best institutional standard of care. • Grade 4 AST or ALT of any duration. • ALT and/or AST >5x ULN or total bilirubin >3x ULN.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Note: Dose-limiting toxicities resulting from the combination of tazemetostat with abiraterone/prednisone will take into account change or increase of risks known to be associated with these products in addition to any new toxicities resulting from the combination of tazemetostat with abiraterone/prednisone.

Table 4: Dose-Limiting Toxicities - Enzalutamide

Toxicity Category	Toxicity/CTCAE Grade
Hypersensitivity	Severe symptoms ≥grade 3 allergic reaction requiring prolonged treatment (e.g. not rapidly responsive to symptomatic medication, and without resolution for ≥7 days in spite of interruption of enzalutamide and best institutional standard of care.
Ischemic Heart Disease	Rapid onset of severe, acute ≥grade 3 cardiac disorder requiring hospitalization, and unresponsive to treatment for ≥3 days, in spite of interruption of enzalutamide and best institutional standard of care.
Seizure	Grade 4 seizures, despite medical intervention, lasting ≥3 days leading to discontinuation of study therapy.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Note: Dose-limiting toxicities resulting from the combination of tazemetostat with enzalutamide will take into account change or increase of risks known to be associated with both products in addition to any new toxicities resulting from the combination of tazemetostat with enzalutamide.

7.5.2. Dose Modifications and Stopping Rules Due to Treatment-Related Toxicities

7.5.2.1. Dose Modification for Tazemetostat Toxicity

Tazemetostat dose reductions and interruptions will be allowed in phase 1b (during which tazemetostat dose reductions are allowed only after completion of cycle 1) and are allowed in phase 2; however, an interruption in the administration of tazemetostat for more than **14 days** must be discussed with the Medical Monitor before treatment can be resumed. Dose-limiting toxicities are covered in Section 7.5.1.

Dose reductions occur in a step-wise fashion and include only the previously tested doses. For examples, refer to Table 7. There can be no dose level reductions below 400 mg twice daily in the phase 1b portion of the study, and any reductions below 600 mg twice daily in the phase 2 portion of the study will be discussed with the Medical Monitor.

Toxicity will be managed by concomitant medication (as appropriate), treatment interruption, dose reduction, and treatment discontinuation, or a combination of these. During treatment with tazemetostat, dose interruption and reduction for subjects who experience tazemetostat-related toxicity will be done in accordance with the instructions in Table 5.

For any case of T-ALL/T-LBL, MDS/AML, or other myeloid malignancies like MPN, tazemetostat treatment for the subject will be discontinued. If an adult case of T-LBL/T-ALL occurs in this study, enrollment in this study will be suspended. Refer also to Section 7.5.4 concerning suspension of enrollment and Section 12.2.1.6.3 for review of these cases by the tazemetostat safety committees.

For subjects who require dose interruption due to tazemetostat-related toxicity in phase 1b or in phase 2, the treatment may re-start once the toxicity has been resolved to Grade ≤1 or baseline according to the instructions in Table 5.

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

- Platelet count must be $\geq 75 \times 10^9$/L
- Absolute neutrophil count (ANC) must be $\geq 0.75 \times 10^9$/L, and
- Any Grade 3 or higher toxicity must have resolved to Grade 1 or baseline, unless otherwise noted.

For tazemetostat, other toxicities that, in the opinion of the Investigator are possibly, probably, or definitely related to study treatment, should be managed per Table 5. Toxicities that are felt by the Investigator to be unrelated to tazemetostat but clinically significant should be discussed with the Medical Monitor. In the event of an urgent unrelated toxicity, study treatment should be interrupted as per Table 5. Dose re-escalation is not permitted.

Table 5: Dose Modifications for Tazemetostat Treatment-Related Toxicities

Toxicity[a]	During Therapy	Approximate Dose Adjustment[b]
Grade 1		
All occurrences	Continue study treatment	Maintain dose level
Grade 2[c]		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Maintain dose level
2nd occurrence (same or new toxicity)		Restart at 1 dose level below assigned dose[e]
3rd occurrence (same or new toxicity)		Discuss with Medical Monitor
Grade 3 - not including anemia[d], and not including neutropenia and thrombocytopenia (see below)		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 1 dose level below assigned dose[e]
2nd occurrence (same or new toxicity)		Discuss with Medical Monitor
3rd occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 neutropenia (ANC: <1 – 0.5 × 10^9/L)		
ANC < 0.75 × 10^9/L 1st occurrence	Interrupt tazemetostat until resolved to ANC ≥ 0.75 × 10^9/L	Restart at 1 dose level below assigned dose[e]
2nd occurrence		Discuss with Medical Monitor
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 3 thrombocytopenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 1 dose level below assigned dose[e]
2nd occurrence		Discuss with Medical Monitor
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 4		
All occurrences	Interrupt study drug until resolved to Grade 2 or less	Discuss with Medical Monitor

Abbreviations: ANC = absolute neutrophil count.

[a] Excluding alopecia and nausea, vomiting, or diarrhea not receiving adequate treatment.

[b] An interruption of tazemetostat for more than 14 days due to any toxicity must be discussed with the Medical Monitor before treatment can be resumed.

[c] Any case of Grade 2 toxicity for which the investigator deems an interruption or dose modification is warranted should be discussed with the Medical Monitor

[d] Exclude Grade 3 anemia: Subjects are allowed to continue tazemetostat at their current dose level with transfusion per Investigator discretion.

[e] Step-wise dose reduction levels for tazemetostat-related toxicities depend on the assigned dose and may include only previously tested doses; there can be no dose level reductions below 400 mg twice daily in the phase 1b portion of the study, and any reductions below 600 mg twice daily in the phase 2 portion of the study must be discussed with the Medical Monitor. If the assigned dose in phase 1b is 400 mg twice daily, only grade 1 toxicities and a first occurrence of any grade 2 toxicity will be considered tolerable.

The same set of rules of treatment interruption and resumption will be applied to the cohorts receiving combination therapy of tazemetostat and enzalutamide and tazemetostat and

abiraterone/prednisone dose modifications. Both enzalutamide and abiraterone/prednisone are considered as companion drugs to tazemetostat in this trial. There is no known overlapping toxicity between tazemetostat and the companion drugs used in this trial.

Please refer to manufacturer's latest package insert for enzalutamide and abiraterone/prednisone dose modifications for treatment-related toxicities.

A discussion with the Sponsor's medical monitor is needed if dose interruption or reduction is considered, either for both or only one of the drugs.

7.5.2.2. Dose Modification for Toxicity to Abiraterone Acetate

The suggested initial dose reduction of abiraterone, if deemed necessary by the Investigator, is 25%. If further dose reduction of abiraterone is considered necessary, the suggested step-down is an additional 25%, for a total of 50% reduction in abiraterone dosage at step 2. A discussion with the Sponsor's medical monitor is needed before the 2nd dose reduction of abiraterone. If a dose reduction is required, the Investigator will follow the guidelines in Table 6.

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (eg, thioridazine). If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug.

If the following conditions are observed, refer to the most current package insert for proper management.

- Mineralocorticoid excess characterized by hypertension, hypokalemia, low renin, and hypoaldosteronism.
- Hepatotoxicity characterized by rising transaminases and/or bilirubin.
- Adrenocortical insufficiency characterized by worsening fatigue, hyperpigmentation and symptoms of Addison's disease.

Table 6: Dose Modification for Abiraterone-Related Toxicity

	1,000 mg orally once daily with prednisone 5 mg orally twice daily
1st reduction	25% (750 mg once daily) and prednisone 5 mg twice daily
2nd reduction[a]	5% (500 mg once daily) and prednisone 5 mg twice daily
3rd reduction	Stop treatment

[a] Discussion with the medical monitor is needed before the second dose reduction.

7.5.2.3. Dose Modifications for Toxicity to Enzalutamide

There is no recommended step down for enzalutamide. Co-administration of another strong CYP2C8 inhibitor (gemfibrozil) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide in healthy volunteers (see the most current enzalutamide package insert). Co-administration of enzalutamide with other strong CYP2C8 inhibitors should be avoided if possible. If co-administration of enzalutamide with a strong CYP2C8 inhibitor cannot be avoided, refer to the most current package insert for adjustment of the dose of enzalutamide.

If the following conditions are observed:

- Hypersensitivity
- Worsening of ischemic cardiovascular disease
- Posterior reversible encephalopathy syndrome
- New onset seizures not due to metastasis

discontinue treatment and discuss with medical monitor immediately.

7.5.3. Tazemetostat Dose Modifications With Unavoidable Concomitant Moderate CYP3A Inhibitors

As described in Sections 9.3.2 and 9.3.3, after the completion of cycle 1 in the phase 1b portion of the study and at any time during the phase 2 portion of the study for subjects receiving tazemetostat, if coadministration with a **moderate CYP3A inhibitor** cannot be avoided, the recommended tazemetostat dose reductions are shown in Table 7. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the tazemetostat dose that was being taken prior to initiating the inhibitor.

Examples of **moderate CYP3A inhibitors** include, but are not limited to, those listed in Appendix 6. This list of medications is not exhaustive; refer to product information and the source websites in the appendix for the most up-to-date information.

Table 7: Recommended Dose Reductions of Tazemetostat for Moderate CYP3A Inhibitors

Current Dosage	Adjusted Dosage
1600 mg twice daily	800 mg twice daily
1200 mg twice daily	600 mg twice daily
800 mg twice daily	400 mg twice daily
600 mg twice daily	400 mg for first dose and 200 mg for second dose
400 mg twice daily	200 mg twice daily

7.5.4. Rules for Suspension of Enrollment

The Investigators, Institutional Review Boards (IRBs)/Independent Ethics Committees (ECs), regulatory agencies, and an ad hoc Quarterly Safety Review (QSR) committee will convene to

review the data and to make recommendations for potential changes in study conduct if one or more subjects develops any of the following AEs deemed to be definitely related to study treatment by the Investigator and/or Medical Monitor, based upon close temporal relationship or other factors:

- Death
- Hepatotoxicity
- T-LBL/T-ALL
- Hypersensitivity
- Posterior reversible encephalopathy syndrome
- New onset seizures not due to metastasis

In the event that study enrollment is suspended, the study will not be restarted until all parties have agreed to the course of action to be taken and the IRBs/IECs have been notified.

If a case of adult T-LBL/T-ALL occurs, study enrollment will be suspended and the benefit-risk of the drug will be assessed by the QSR Committee and the External Safety Committee (ESC). Refer also to Section 12.2.1.6.3.

7.6. Criteria for Study Suspension or Termination

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

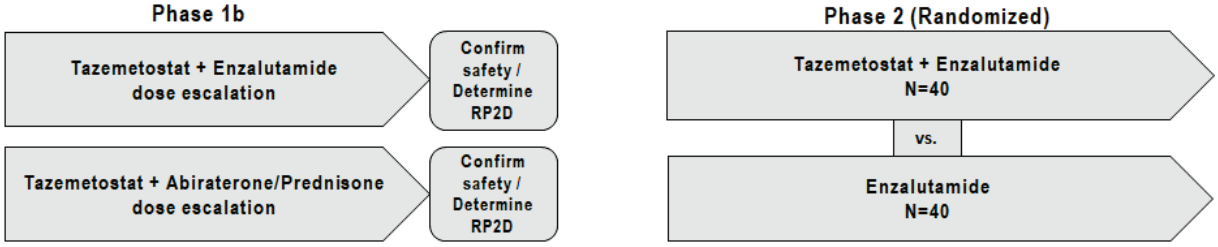
The sponsor has the right to terminate this study and remove all study material from the site at any time. Examples of where this might occur include, but are not limited to:

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

7.7. Study Design Schematic and Schedule of Assessments

The study design is displayed in Figure 1, and the Schedule of Assessments is shown in Table 8.

Figure 1: Study Design



Key Objectives of Phase 1b and Phase 2 to Assess Combination Therapy:

- Phase 1b: Safety, pharmacokinetics, anti-tumor activity in subjects with mCRPC previously treated and untreated with second generation anti-androgens. Determine RP2D. Sample size: maximum of approximately 24 (7 for the abiraterone/prednisone combination and 13 for the enzalutamide combination, and up to 4 additional subjects in the event of a DLT).
- Phase 2 Primary Objective: rPFS. Sample size: 80
- Phase 1b/2 Secondary Objectives: PSA50, TTPP, time to first SRE, ORR and BOR, DCR, time to new treatment, CTC, CTC 30% reduction, and (for phase 2 only) FACT-P FWB and PCS subscales and TDD.
- Total sample size: approximately 104

Abbreviations: CTC = circulating tumor cells; DCR = disease control rate; DLT = dose-limiting toxicity; FACT-P = Functional Assessment of Cancer Therapy – Prostate; FWB = Functional Well-being; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; PCS = Prostate Cancer Subscale; PSA = prostate specific antigen; RP2D = recommended phase 2 dose; rPFS = radiographic progression-free survival; SRE = skeletal-related event; TDD = time to definitive deterioration; TTPP = time to PSA progression.

Table 8: Schedule of Assessments

Cycle	**Screening**	**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8-9[b]**	**C10**	**C11-12[b]**	**C13+**	**Unscheduled Visits[d]**	**Post-treatment Follow-up**	**Long-term Follow Up[e]**
Study Day	-28 to -1	**1**	**2[a]**	**21[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**197[b] and 225[b]**	**253**	**281[b] and 309[b]**	**337 and every subsequent 84 days[c]**			
Week	**-4 to -1 (28 days)**	**1**	**1**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29[b] and 33[b]**	**37**	**41[b] and 45[b]**	**49 and every subsequent 12 weeks**	**As needed during study**	**30 days after last dose[f]**	**Every 12 weeks**
Window (days)					± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2		± 3	± 7
Informed consent[g]	X[g]																
Medical history	X																
Inclusion/exclusion criteria	X	X															
Randomization (IVRS/IWRS)	X[n]																
Vital signs	X	X	X[a]	X[a]	X	X	X	X	X	X		X		X	X	X	
Physical examination including weight[h]	X	X			X	X	X	X	X	X		X		X	X	X	
Height	X																
12-lead ECG[i]	X	X[i]			X		X			X		X		X	X[j]	X	
Clinical Laboratory Assessments[k]	X[k]	X[k]			X		X			X		X		X	X[j]	X	
Assess CBC with differential for myeloid malignancies[k]	X				X[k]											X	
Blood draw for NEPC markers in blood[l]	X																
Whole blood sample for ctDNA genotype analysis and PBMC isolation[m]		X				X		X		X		X		X		X	
Tumor biopsy[n]	X[n]				X[n]	X[n]											

Cycle	**Screening**	**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8-9[b]**	**C10**	**C11-12[b]**	**C13+**	**Unsched-uled Visits[d]**	**Post-treat-ment Follow-up**	**Long-term Follow Up[e]**
Study Day	-28 to -1	**1**	**2[a]**	**21[a]**	**29**	**57**	**85**	**113**	**141**	**169**	**197[b] and 225[b]**	**253**	**281[b] and 309[b]**	**337 and every subsequent 84 days[c]**			
Week	**-4 to -1 (28 days)**	**1**	**1**	**3**	**5**	**9**	**13**	**17**	**21**	**25**	**29[b] and 33[b]**	**37**	**41[b] and 45[b]**	**49 and every subsequent 12 weeks**	**As needed during study**	**30 days after last dose[f]**	**Every 12 weeks**
Window (days)					± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2		± 3	± 7
PSA[o]	X	X			X	X	X	X	X	X		X		X		X	
CTCs[o]	X	X			X	X	X	X		X		X		X		X	
PK (phase 1b; completed)[p]		X	X	X	X												
PK (phase 2)[q]					X	X		X				X					
CT/MRI and bone scan	X[r]					X[s]		X[st]		X[st]		X[st]		X[st]			X[e]
CXR or chest CT[u]	X[u]					(X)[u]											
ECOG performance status	X	X			X	X	X	X	X	X	X[b]	X	X[b]	X	X	X	
BPI-SF (phase 1b)[v]	X						X			X							
BPI-SF (phase 2)[v]		X[v]				X		X		X		X		X		X	
FACT-P[v]		X[v]				X		X		X		X		X		X	
EQ-5D-5L[v]		X[v]				X		X		X		X		X		X	
AEs/SAEs[w]	X	X	X[a]	X[a]	X	X	X	X	X	X	X[b]	X	X[b]	X	X	X	X[e]
Optional chest ultrasound[x]	X				X		X		X		X	X	X	X		X	
Concomitant medications	X	X	X[a]	X[a]	X	X	X	X	X	X	X[b]	X	X[b]	X	X	X	
Study drug dispensing		X	X[a]	X[a]	X	X	X	X	X	X		X		X			
Study drug treatment[y]		X	X[a]	X[a]	X	X	X	X	X	X		X		X			
Annual Assessments[z]		X															
Disease assessment and survival status[e]																X	X

Abbreviations: AE = adverse event; BPI-SF = Brief Pain Inventory-Short Form; CT = computed tomography; CTCs = circulating tumor cells; CXR = chest x-ray; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQol 5-Dimension 5-Level questionnaire; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; F/U = Follow-up; PD = progressive disease; NEPC =

neuroendocrine prostate cancer; NSE = neuron-specific enolase; PK = pharmacokinetic; PSA = Prostate-Specific Antigen; QoL = quality of life; SAE = serious adverse event; SRE = skeletal-related event.

[a] In cycle 1, the day 2 and day 21 visits apply only to subjects in phase 1b (completed).

[b] These visits/assessment may be completed by telephone.

[c] Starting at cycle 13, subjects will have a clinic visit every 12 weeks.

[d] **Unscheduled visits** may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, upon discontinuation of treatment, at the subject's request, or if deemed necessary by the Investigator.

[e] **Long-term follow-up** Beginning after study drug discontinuation:

- All subjects with confirmed radiographic disease progression as defined in the protocol will be discontinued from study drug and from further follow-up after the 30-day follow-up visit, even if the subject continues to benefit clinically. If the Investigator elects to continue enzalutamide treatment in the commercial setting in the case of subject who continue to benefit clinically despite confirmed radiographic progression, it will be recorded as subsequent anti-cancer therapy.
- For subjects who discontinue study treatment for reasons other than confirmed radiographic disease progression (such as unequivocal clinical or chemical progression), radiographic tumor assessment scans are required every 12 weeks (±7 days) during long-term follow-up, and other study assessment will continue as scheduled, until the earlier of either: 18 months post last study drug dose; radiographic disease progression; the start of a new systemic anticancer therapy for prostate cancer; withdrawal of consent/loss to follow-up; death; or ≥65 rPFS events have been observed in the study (as communicated by the Sponsor).

[f] **Post-treatment** follow up, or prior to initiation of an investigational agent or new anti-cancer therapy, whichever occurs first. The post-treatment/early termination assessments will be required and, in the event of a continuing AE, the subject will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely.

[g] **Informed consent** must be signed within 4 weeks before randomization; otherwise, the screening visit must be repeated.

[h] A brief **physical examination** is required at each visit, with the exception of the screening visit during which a complete physical examination will be completed.

[i] A single **ECG** will be taken at specified study visits. A single ECG will be recorded unless there is an abnormality, such as prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥480 msec, new arrhythmia, or other clinically significant finding. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart.

[j] If medically indicated.

[k] **Clinical laboratory assessments** (see Appendix 3) will include:

- **Serum chemistries, urinalysis, hematology** and **coagulation** (as well as **testosterone** at screening), and
- **CBC with differential assessment as follows**:

  During Screening and within 30 days following the end of study treatment (before initiation of subsequent antineoplastic therapy), a complete blood count (CBC) with differential (manual or automated peripheral blood smear) will be performed and assessed per institutional standards to rule out myeloid malignancies, including but not limited to MDS/AML/MPN. A potential subject with a suspected or confirmed myeloid malignancy will be excluded from the study.

  During the study treatment period, the Investigator will monitor subjects for the development of myeloid malignancies as medically indicated. Any suspected or confirmed AESIs identified during and following the study treatment period will be reported as delineated in Section 12.2.

[l] **Blood draw for NEPC markers in blood**: neuron-specific enolase (NSE; 1mL) at screening. (Note: serum chromogranin A [1 mL] was removed with Amendment

[m] **Samples for ctDNA genotype analysis** will be collected from subjects at baseline before administration of the first dose, and at all times commensurate with CT/MRI and bone scans in both the phase 1b and phase 2 parts of the study for genotype analysis. Sample collection is mandatory for both phase 1b and phase 2 part of the study. Refer to the laboratory manual for processing of the PBMC samples to be isolated from whole blood for gene expression profiling.

[n] **Tumor biopsies:** *For subjects in phase 1b*, optional tumor biopsies will be collected during baseline, disease progression, and first sign of response only from subjects who agree to provide optional tumor biopsy as documented on the informed consent form. *In the phase 2 part of the study*, tumor biopsies (primary and metastatic, including from lymph node and bone) will be collected when safe and feasible *from 12-20 subjects randomized only to the combination arm of tazemetostat plus enzalutamide* at: 1) pre-treatment, 2) cycle 2 day 1 during treatment, and 3) at the time of disease progression (only in responders); in order to ascertain which treatment group a phase 2 subject is assigned to in advance of organizing a pre-treatment tumor biopsy, randomization of phase 2 subjects who consent to provide the biopsy may occur up to 3 days before cycle 1 day 1. Randomization of phase 2 subjects not providing a pre-treatment biopsy should occur on cycle 1 day 1 but may occur up to 3 days earlier. *In both phases*, the baseline biopsy can be taken from archival tumor, provided the sample was obtained ≤1 year before enrollment. A separate laboratory manual will be provided for instructions on providing biopsy from bone. *For both phases*, Epizyme will request available archival tumor samples from all subjects (5 to 20 slides per subject) who do not provide matched biopsies from Screening (added with Amendment #5). Longitudinal biopsies should be taken whenever feasible form the same lesions.

[o] All protocol-specified **PSA** and **CTC** measurements are to be done at a central laboratory

[p] **PK (Phase 1b; completed)**: In the phase 1b part of the study blood samples for PK analysis were to be collected in cycle 1 on days 1, 2, and 21 prior to dosing (0 hours) and post-dose at 30 minutes (±5 minutes), at 1, 2, 4, 6, and 8 hours (±15 minutes), and at 24 hours (±30 minutes). In cycle 2 on day 1 samples were to be drawn pre-dose and 2- and 6- hours post-dose (±15 minutes). Subjects should have been instructed not to take their dose of study drug on these visit days before they went to the clinic and should have been instructed to take their study drug in the clinic after the PK sample is drawn. For PK assessment days, subjects were required to take their study drug/s in the morning at the clinic after the pre-dose sample has been collected. The date and time of the last dose were to be recorded.

[q] **Sparse PK (Phase 2)**: in the phase 2 part of the study in cycles 2, 3, 5, and 10 on day 1, blood samples will be drawn only from subjects assigned to the combination arm for sparse PK analysis before dosing (0 hours) and at 2 and 6 hours post-dose (±15 minutes). For PK assessment days, subjects will be required to take their study drug/s in the morning at the clinic after the pre-dose sample has been collected. The date and time of the last dose will be recorded.

[r] **Screening timeframe for CT scan or MRI, bone scan, chest X-ray, or chest CT** must occur within 4 weeks before randomization; otherwise, the screening visit must be repeated.

[s] **Visit windows for CT/MRI, bone scan, chest X-ray, or chest CT**: Window for radiological assessments is ±7 days and are performed every 8 weeks for the first 6 months and then every 12 weeks thereafter. At all visits where radiological assessment is performed, all other procedures must be completed within the ±2-day window as specified in the schedule.

[t] **CT/MRI**: Disease progression observed by CT or MRI for soft tissue disease does not require a confirmatory scan.

[u] **Chest CT** is required at all imaging time points, if screening chest x-ray demonstrated metastatic chest disease.

[v] **Health-Related Quality of Life (QoL) Assessments** (BPI-SF, FACT-P, and EQ-5D-5L) should be administered before other interactions in the clinic. In phase 2, assessments at baseline are administered on cycle 1 day 1 before other interactions in the clinic. Every effort should be made to ensure all subjects complete as many scheduled health-related QoL assessments as possible. The BPI-SF instrument should assess pain related to prostate cancer only.

[w] **AEs/SAEs** will be collected from the time the subject signs the consent form until the earlier of either screen failure, the end of the safety reporting period (30 days after the last dose of study drug), or initiation of an investigational agent or cytotoxic chemotherapy. In addition, SAEs occurring beyond 30 days post treatment that are considered to be related to study drug will be collected. All nonserious AEs will be followed to resolution or other outcome is reached until study closure and database lock. All SAEs will be followed by Epizyme to resolution or other outcome is reached, regardless of study closure/database lock. (Refer to Sections 12.2.5 and 12.2.6). Where appropriate, medical tests and examinations will be performed to document resolution or other outcome of the event(s).

[x] An **optional chest ultrasound** may be performed at screening and every 8 weeks at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL, thymus enlargement.
[y] **Study Drug Treatment**: For study visit days, subjects will self-administer study drug upon instruction from the staff.
[z] **Annual assessments** will be conducted only for subjects who remain on tazemetostat treatment to review for AEs of special interest at a clinic visit (±30 days).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Age at the time of consent ≥18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (Appendix 1).
3. Life expectancy of >3 months.
4. Histologically or cytologically confirmed adenocarcinoma of the prostate. Small cell or neuroendocrine (differentiated or with neuroendocrine features) tumors of the prostate are also permitted.
5. Progressive disease in the setting of medical or surgical castration (ie, CRPC) by PCWG3 criteria for study entry.
    - Evidence of disease progression by rising PSA or
    - Soft tissue progression per RECIST 1.1 or
    - Evidence of disease progression by observation of 2 new bone lesions since the initiation of last systemic therapy.
6. Metastatic prostate cancer disease, documented by the following imaging:
    - Bone lesions on bone scan (per PCWG3) or by soft tissue disease (per RECIST 1.1) by CT/MRI imaging.
7. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue GnRH analog or antagonist (medical castration).
8. Surgically or medically castrated, with serum testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening.
9. Prior treatment with a second-generation androgen inhibitor as follows:
    - For phase 1b, EITHER previously untreated with a second-generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide) OR progressed on a second-generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide).
    - For phase 2 randomized component (ie, enzalutamide-containing treatment groups) of the study, previously progressed on abiraterone for either castration-sensitive or castration-resistant disease; the required washout period for abiraterone is 7 days.
10. No prior treatment with cytotoxic chemotherapy for mCRPC, except as follows:
    - For phase 1b, more than 6 cycles of docetaxel received for castration-sensitive disease prior to having received enzalutamide or abiraterone/prednisone is permitted.

- For the phase 2 randomized component (ie, enzalutamide-containing treatment groups) of the study, up to 6 prior cycles of docetaxel received for castration-sensitive disease in the nonmetastic and metastatic settings prior to having received abiraterone/prednisone is permitted.

11. Demonstrate adequate organ function as defined below:
    - ANC ≥ 1,000 /µL.
    - Platelet Count ≥ 100,000 /µL.
    - Hemoglobin ≥ 9 g/dL without a transfusion within 2 weeks of screening.
    - Serum creatinine ≤ 2 × upper limit of normal (ULN) or
        - Creatinine clearance ≥ 40 mL/min as estimated by the Cockcroft and Gault formula in subjects with creatinine > 2 × ULN.
    - Bilirubin ≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 × ULN.
    - AST ≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases.
    - ALT ≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases.
    - Albumin >3.0 g/dL (30 g/L) at screening.
12. Subjects of child-fathering potential as defined in the protocol (Section 7.4.2.1) must either practice complete abstinence or agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), or maintain medical castration during sexual contact with a pregnant female or female partner of childbearing potential (FCBP) during study treatment, for 3 weeks following the last dose of abiraterone/prednisone, and for 3 months following the last dose of enzalutamide. Male subjects with surgical castration are not required to use condoms.

    NOTE: Male subjects must not donate semen or sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months following the last dose of tazemetostat, 3 weeks following the last dose of abiraterone/prednisone, and 3 months following the last dose of enzalutamide.

8.2. Subject Exclusion Criteria

1. Known symptomatic brain metastases.
2. Untreated or impending spinal cord compression.
3. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of starting study treatment:
    - Abiraterone within 7 days.

- First generation AR antagonists (eg, bicalutamide, nilutamide, flutamide) within 4 weeks.
- 5-alpha reductase inhibitors, ketoconazole, estrogens (including diethylstilbesterol), or progesterones within 2 weeks.
- Chemotherapy (except as permitted in inclusion criterion #10) within 3 weeks.
- Prior radionuclide therapy within 4 weeks.
- Another interventional product or standard agent in a clinical study within 28 days prior to the first planned dose of tazemetostat
- For phase 2 subjects to be randomized to one of the enzalutamide treatment groups only, prior treatment with any second-generation AR antagonist (eg, enzalutamide, apalutamide, darolutamide, proxalutamide, etc) other than abiraterone.

4. Severe concurrent disease, infection, or comorbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
5. History of another invasive cancer within 3 years of randomization, with the exception of treated non-melanoma skin cancer, treated superficial bladder cancer, or fully treated cancers with a remote probability of recurrence in the opinion of both the Medical Monitor and Investigator.
6. History of seizure or any condition that may predispose to seizure (eg, prior cortical stroke or significant brain trauma). History of sub clinical seizures manifested by loss of consciousness or transient ischemic attack within 12 months of randomization. However, subjects on medications with seizure lowering threshold will be admitted.
7. Clinically significant cardiovascular disease including the following:
    - Myocardial infarction within 6 months before screening.
    - Uncontrolled angina within 3 months before screening.
    - Congestive heart failure (New York Heart Association class 3 or 4), or a history of congestive heart failure (New York Heart Association class 3 or 4), unless a screening echocardiogram or multigated acquisition scan performed within 3 months before randomization demonstrates a left ventricular ejection fraction ≥50% (Appendix 2).
    - History of clinically significant ventricular arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes).
    - History of Mobitz 2 second-degree or third-degree heart block without a permanent pacemaker in place.
    - Hypotension as indicated by systolic blood pressure <86 millimeters of mercury (mmHg) at screening.
    - Bradycardia as indicated by a heart rate of <45 beats per minute on the screening electrocardiogram (ECG), and upon physical examination.

- Uncontrolled hypertension as indicated by systolic blood pressure >170 mmHg or diastolic blood pressure >105 mmHg at screening.

8. Gastrointestinal disorder affecting absorption (eg, gastrectomy, active peptic ulcer disease within 3 months before randomization).
9. Major surgery within 4 weeks of randomization.
10. For subjects taking abiraterone and prednisone, no evidence of hepatic impairment or classified as only Child-Pugh Class A.
11. Hypersensitivity reaction to the active pharmaceutical ingredient of tazemetostat, abiraterone, prednisone, or enzalutamide, or any of the other components of each individual agent under study, according to the potential to be assigned to the agent(s).
12. Is unwilling to exclude grapefruit juice, Seville oranges, and grapefruit from the diet and all foods that contain those fruits from time of enrollment to while on study.
13. Is currently taking any prohibited medication(s) as described in Section 9.3.3, including live virus vaccine within 30 days before the first dose of study treatment or plans to receive a live virus vaccine during treatment.
14. Has had prior exposure to tazemetostat or other inhibitor(s) of EZH2.
15. Is immunocompromised (ie, has a congenital immunodeficiency. Subjects diagnosed with human immunodeficiency virus (HIV) are eligible to participate in the study if they meet the following criteria:
    - No history of AIDS-defining opportunistic infections or have not had an opportunistic infection within the 12 months prior to enrollment.
    - No history of AIDS-defining cancers (eg, Kaposi's sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer).
    - Subjects may take prophylactic antimicrobials; however, subjects taking specific antimicrobial drugs that have a potential for drug-drug interaction or overlapping toxicities with study drugs must be excluded from study participation.
    - Subjects should be on established anti-retroviral therapy for ≥4 weeks with an HIV viral load of < 400 copies/mL and/or CD4+ T-cell (CD4+) count ≥350 cells/uL prior to enrollment.
16. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 5.0 criteria) or any prior history of myeloid malignancies, including MDS and AML. Has abnormalities known to be associated with MDS (eg, del 5q, chr 7 abn) and MPN (eg, JAK2 V617F) observed in cytogenetic testing and DNA sequencing.

    NOTE: At screening, a complete peripheral blood count (CBC) with differential (manual or automated peripheral blood smear) will be performed and assessed per institutional standards to rule out myeloid malignancies, including but not limited to MDS/AML/MPN. A potential subject with a suspected or confirmed myeloid malignancy will be excluded from the study.
17. Has a prior history of T-LBL/T-ALL.

18. Is unable to take oral medications or has malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea or vomiting) that might impair the bioavailability of study treatments.
19. Subjects with hepatitis B or hepatitis C are ineligible to participate in the study unless they meet the following criteria:
    - Do not have uncontrolled hepatitis B or C infection, are not on active immunosuppressive therapy, and do not have a history of autoimmune disease requiring ongoing systemic therapy.
    - Subjects taking therapy for hepatitis where there may be a drug-drug interaction or overlapping toxicities with study drugs must be excluded from study participation.

8.3. Subject Withdrawal Criteria

8.3.1. Withdrawal of Subjects from Treatment/Procedures

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to future medical care by the physician or institution.

Subjects (or legally authorized representatives) can decline to continue receiving tazemetostat 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 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.)

Reasons for removal from protocol-required treatment or procedures might include the following:

- Disease progression
- Subject request to end study treatment and/or procedures
- Safety concern (eg, AE, failure to follow contraception or pregnancy, excluded medication required)

8.3.2. Withdrawal of Subjects from Study

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

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

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

8.3.3. Replacement of Subjects

Subjects in phase 1b of the study were to be replaced if there were not a sufficient number of samples to calculate PK parameters.

Subjects in phase 2 will not be replaced in this study.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dosing

Study drug dosing is described in Table 9 below. Dose adjustment criteria are discussed in Section 7.5.

Table 9: Phase 1b/2 Doses of Tazemetostat, Enzalutamide, Abiraterone, and Prednisone

Treatment	Dose	Frequency	Total Daily Dose
Tazemetostat	Phase 1b[a]: Per dose escalation Phase 2[c]: RP2D of 1200 mg for combination with enzalutamide	Twice daily	Phase 1b[a]: Per dose escalation Phase 2: 2400 mg for combination with enzalutamide
Enzalutamide	160 mg	Once daily	160 mg
Abiraterone[b, d]	1000 mg	Once daily	1000 mg
Prednisone[d]	5 mg	Twice daily	10 mg

Abbreviations: RP2D = recommended phase 2 dose.

[a] The starting dose was 400 mg tazemetostat twice daily. If there were no DLTs, dose escalation would continue to 600 mg twice daily and to a maximum of 800 mg twice daily; for the combination with enzalutamide only, dose escalation may have continued to 1200 mg twice daily and to a maximum of 1600 mg twice daily, as tolerated.

[b] Abiraterone must be taken on an empty stomach with water at least 1 hour before, or 2 hours after a meal.

[c] Orally twice daily in continuous 28-day cycles.

[d] Abiraterone and prednisone are administered in phase 1b only

The plan for the phase 1b part of the study was as follows: There were 3 different tazemetostat dose levels planned to be tested in combination with abiraterone/prednisone and 5 different tazemetostat dose levels planned to be tested in combination with enzalutamide. Enzalutamide or abiraterone/prednisone was to be administered orally on cycle 1 day 1 and tazemetostat administered orally on day 2. Tazemetostat was to be escalated from a starting dose of 400 mg twice daily, to 600 mg twice daily, to 800 mg twice daily as tolerated, in a modified 3+3 design in combination with enzalutamide or abiraterone/prednisone. For the combination with enzalutamide only, tazemetostat could have been further escalated to 1200 mg twice daily and to a maximum of 1600 mg twice daily, as tolerated.

In the randomized phase 2 part of the study, the RP2D of 1200 mg of tazemetostat when given in combination with enzalutamide will be administered orally twice daily in continuous 28-day cycles. Enzalutamide and tazemetostat will both be administered on day 1 of each cycle.

9.2. Duration of Treatment

Prostate-specific antigen increase without evidence of confirmed radiographic progression is strongly discouraged as a criterion to discontinue study therapy. Initiation of new therapy for prostate cancer at the time of radiographic progression will mandate discontinuation of study drug.

Treatment administration should continued for as long as the subject is tolerating the study drugs and continues ADT (ie, surgical castration or ongoing GnRH analogue therapy) until confirmed radiographic disease progression by PCWG3 criteria (see Table 10 and Figure 2), even if the subject continues to benefit clinically, or until unequivocal clinical progression if earlier than radiographic disease progression.

NOTE: If the Investigator elects to continue enzalutamide treatment in the commercial setting in the case of subject who continue to benefit clinically despite confirmed radiographic disease progression, it will be recorded as subsequent anti-cancer therapy.

9.3. Concomitant Medications

Documentation of all concomitant medication administered during study treatment will be recorded in the electronic Case Report Form (eCRF) at each visit.

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

9.3.1. Permitted Medications

The following medications are permitted as specified:

- Supportive care measures and symptomatic treatment for any treatment-related toxicity, including short courses of glucocorticoids, if clinically indicated. (See also Section 9.3.2 Section 9.3.3 below.)
- Glucocorticoids may be taken by subjects with CNS tumors, under the following conditions:
  - For control of neurological symptoms that may continue at a tapering dose.
  - Intermittent use for control of nausea (not to exceed 0.3 mg/kg/dose dexamethasone, maximum of 20 mg) every 12 hours as needed.
- Non-enzyme inducing anti-epileptic drugs.
- Prophylactic use of standard anti-emetics.
- Blood and platelet transfusions, as needed per the judgment of the Investigator.
- Initiation of bisphosphonates or other approved antiresorptive medications are allowed and should not result in discontinuation of study drug therapy.
- Over-the-counter medications, nutritional supplements, vitamins, and herbal preparations (including CBD oil) are permitted, except those to be used with caution

or that are prohibited for reasons stated in Sections 9.3.2 and 9.3.3 below (for example, St. John's wort).

9.3.2. Medications to be Used with Caution

The following medications are to be used with caution in subjects receiving tazemetostat:

- **CYP3A sensitive substrates**
- **Moderate CYP3A inhibitors**. After the completion of cycle 1 in the phase 1b (completed) portion of the study or at any time during the phase 2 portion of the study for subjects receiving tazemetostat, if coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the dose of tazemetostat as shown in Section 7.5.3 (Dose Modifications With Unavoidable Concomitant CYP3A Inhibitors). After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the tazemetostat dose that was being taken prior to initiating the inhibitor.

NOTE: Examples of medications that are moderate inhibitors of CYP3A or are CYP3A sensitive substrates include, but are not limited to, those listed in Appendix 6. This list of medications is not exhaustive; refer to product information and the source websites in the appendix for the most up-to-date information.

For guidance on medications to be used with caution in subjects receiving enzalutamide, abiraterone, or prednisone, Investigators are instructed to follow the local labels.

For all subjects, the following medications may be used with caution (and are to be listed as concomitant medications in the CRF, if used):

- Over-the-counter medications, nutritional supplements, vitamins, and herbal preparations are permitted under physician recommendation and with the agreement of the Investigator only, with the exception of those that are prohibited for reasons stated in Section 9.3.3 below (for example, St. John's wort). Aspirin, nonsteroidal anti-inflammatory drugs, and low-molecular-weight heparin or prophylactic doses of heparin are permissible but should be used with caution.
- Medical marijuana is permitted only under physician recommendation and with the agreement of the Investigator.
- Any **alternative therapies** should be discussed with the Investigator prior to enrollment in the study or prior to initiating them during the study.

9.3.3. Prohibited Medications

Prohibited medications include:

- **Antineoplastic therapy** or **other investigational therapy for the treatment of cancer**, unless otherwise noted here
- Any **other experimental or unapproved drugs**.
- **Prophylactic** use of **hematopoietic colony stimulating factors**

  NOTE: Therapeutic use of hematopoietic colony stimulating factors is discouraged and should be discussed with the Medical Monitor and should be conducted

according to the 2006 American Society for Clinical Oncology Guideline for use of white blood cell (WBC) growth factors (Smith, 2006).

- **Strong inhibitors of CYP3A and strong and moderate inducers of CYP3A** within 14 days prior to first dose of study treatment and concomitantly with tazemetostat or in the absence of tazemetostat for the duration of study, except for assigned study treatment with enzalutamide (a strong inducer of CYP3A4).

  Moderate CYP3A inhibitors were prohibited during cycle 1 of the phase 1b (completed) portion of the study, starting from 14 days prior to first dose of tazemetostat.

  NOTE: Examples of medications that are moderate or strong inhibitors and moderate or strong inducers include, but are not limited to, those listed in Appendix 6 (for example, St. John's wort, which is a strong CYP3A inducer). This list of medications is not exhaustive; refer to product information and the source websites in the appendix for the most up-to-date information.

- **Enzyme inducing anti-epileptic drugs** including, but not limited to, carbamazepine, phenobarbital, phenytoin, and barbiturates, should not be taken within 14 days prior to the first dose of study treatment and for the duration of study treatment.
- Live virus vaccine within 30 days before the first dose of study treatment or during treatment.
- For guidance on **medications contraindicated with enzalutamide, abiraterone, or prednisone**, Investigators are instructed to follow the local labels.

9.3.4. Non-Drug Therapies for Disease

Radiation Therapy: Localized, palliative radiation therapy and potential concurrent dose interruptions will be permitted for pain or severe symptom control after discussion with the Medical Monitor. Radiation will be limited to non-target lesions only and documented in the eCRF.

Other Palliative Procedures: Other procedures intended for symptom control and potential concurrent dose interruptions may be permitted after discussion with the Medical Monitor. These procedures will be limited to non-target lesions only and documented in the eCRF.

9.4. Treatment Compliance

9.4.1. Treatment Compliance Procedures

For study visit days, the subject will self-administer drug upon instruction from the study staff.

The subject will be requested to maintain a medication diary of each dose of tazemetostat as well as the combination drugs (either enzalutamide or abiraterone/prednisone). The dosing diary will be returned to the site staff at each visit.

Compliance for doses taken outside of the clinic may be assessed by a count of the tablets returned to the study site by the subject and review of doses taken with the subject. This will be

recorded in the source documents, which may include the use of a subject medication diary per institutional practice.

9.4.2. 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 tazemetostat, enzalutamide, or abiraterone/prednisone.

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

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

All instances of special situations are to be reported using the paper Special Situation Form regardless of presence or absence of an associated AE. Refer to Section 12.2.1.7 for detailed instructions on how to handle the reporting of special situations.

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

9.5. Randomization

In the phase 2 part of the study, approximately 80 chemotherapy naïve, qualified subjects with mCRPC who previously progressed on abiraterone/prednisone will be randomized 1:1 to receive either tazemetostat combined with enzalutamide or enzalutamide alone.

No blinding will be used in this part of the study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Tazemetostat

Tazemetostat (EPZ-6438) is an Epizyme investigational product (IP) and is defined as an Investigational Medicinal Product (IMP) under the European Union Clinical Trials Directive (EU CT Dir). Refer to Section 10.5 for instructions on administration of tazemetostat.

	Investigational Product
Product Name:	Tazemetostat (EPZ-6438)
Formulation Description:	200-mg tablets
Dosage Form:	Tablet
Physical Description:	Round, red, biconvex, film-coated tablets
Dose[a]/Route/Schedule/Duration:	Oral/twice daily/continuous

[a] Dose is dependent on dose escalation level in phase 1b (completed) and will be the declared RP2D of 1200 mg when given in combination with enzalutamide in phase 2. See Section 9.1 for details.

Abiraterone/prednisone (tablets) and enzalutamide (capsules) will be provided by Epizyme. Please refer to the manufacturer's latest insert for further details.

10.1.2. Enzalutamide

In the phase 1b and phase 2 parts of the study, enzalutamide will be administered on day 1 of each cycle.

Subjects enrolled the study will receive enzalutamide 160 mg (four 40 mg capsules) orally once daily. The subject is to be instructed to swallow capsules whole. Enzalutamide can be taken with or without food. Please refer to the manufacturer's latest package insert for additional details.

10.1.3. Abiraterone/Prednisone

In the phase 1b part of the study, abiraterone/prednisone will be administered on day 1 of each cycle.

The recommended dose for mCRPC of abiraterone is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily in combination with prednisone 5 mg (in tablet form) administered orally twice daily (for a total daily dose of prednisone 10 mg).

Abiraterone must be taken on an empty stomach, either 1 hour before or 2 hours after a meal. The subject should be instructed that the tablets should be swallowed whole with water and not crushed or chewed.

Please refer to the manufacturer's latest package inserts for abiraterone and prednisone for additional details.

10.2. Study Drug Packaging and Labeling

Tazemetostat tablets are packaged in a white high- density polyethylene bottle with a child-resistant, tamper-evident polypropylene screw cap. The contents of the package label will be in accordance with all applicable regulatory requirements. The expiry date will be printed on the label.

For abiraterone/prednisone and enzalutamide, please refer to the manufacturer's latest package insert for further details.

10.3. Study Drug Storage

Tazemetostat must be stored in a secure area, in compliance with storage requirements listed on the label, with access limited to the Investigator and authorized site staff only.

For abiraterone/prednisone and enzalutamide, please refer to the manufacturer's latest package insert for further details.

10.4. Study Drug Preparation

No preparation for tazemetostat is needed.

For abiraterone/prednisone and enzalutamide, please refer to the manufacturer's latest package insert for further details.

10.5. Administration

Tazemetostat must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Standard institutional procedures for administering an oral agent will be followed. An adequate supply will be provided with instructions on home administration.

Tazemetostat will be taken orally twice daily with or without food. Subjects should be instructed to swallow tablets whole and not to cut, crush, or chew tablets.

Tazemetostat doses should be taken at least 8 hours apart. If a dose is missed (eg, missed morning or evening dose and did not re-dose within an appropriate amount of time), or if the subject vomits a dose, the dose should be skipped. All doses given, missed, and vomited are to be recorded.

Refer to Section 10.1.2, Section 10.1.3, as well as the prescribing information for enzalutamide, abiraterone, and prednisone for drug administration instructions.

In the phase 1b dose escalation part of the study (completed), enzalutamide or abiraterone/prednisone was administered on cycle 1 day 1 and tazemetostat on day 2. Tazemetostat was escalated from a starting dose of 400 mg twice daily to 600 mg twice daily to 800 mg twice daily as tolerated, in a modified 3+3 design in combination with enzalutamide or abiraterone/prednisone. For the enzalutamide combination only, dose escalation could further proceed to 1200 mg twice daily followed by 1600 mg twice daily, as tolerated.

In the phase 2 part of the study, the RP2D of 1200 mg of tazemetostat when given in combination with enzalutamide will be administered orally twice daily in continuous 28-day cycles. Enzalutamide and tazemetostat will both be administered on day 1 of each cycle.

10.6. Study Drug Accountability

The Investigator/designee will be responsible for taking an inventory of each shipment of tazemetostat received and comparing it with the accompanying shipment form. The Investigator/designee will verify the accuracy of the information on the form, sign and date it, and acknowledge the shipment receipt according to the instructions provided.

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

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

This will also apply to Epizyme supplied abiraterone/prednisone and enzalutamide.

10.7. Study Drug Handling and Disposal

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

This will also apply to Epizyme supplied abiraterone/prednisone and enzalutamide.

11. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and their timing are summarized in the Schedule of Assessment and Procedures (Table 8).

11.1. Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to review the informed consent form, ask questions, and make a voluntary decision. No protocol-specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB/IEC-approved informed consent form (ICF).

11.2. Screening Assessments

A signed, written informed consent must be obtained prior to any study-specific assessments or procedures being performed.

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

Procedures conducted as part of the subject's routine clinical management (eg, blood counts, chemistries, imaging studies) and obtained prior to consent may be used for screening provided the procedure meets the protocol-defined criteria and has been performed in the screening timeframe for the study (up to 28 days before enrollment).

11.2.1. Demographic/Medical History

The following demographic information will be collected: date (or year, where appropriate) of birth, race, and ethnicity. These will be documented in source documents and captured in the relevant eCRF.

The investigator or designee will obtain detailed information regarding all past medical history and surgical events. The dates and descriptions of past history and events will be documented in source documents and captured in the relevant eCRF.

11.3. Efficacy Assessments

For study assessments not included in the sections below, refer to the Schedule of Assessments (Table 8) for details.

11.3.1. Prostate Cancer Status

As described in subsequent sections, the following assessments of prostate cancer status will be collected during the course of the study: overall survival, soft tissue disease on CT scan or on MRI, bone disease on radionuclide bone scans, SREs, health-related QoL assessments (ie, BPI-SF, FACT-P, and EQ-5D-5L), PSA, CTC enumeration and blood biomarkers of neuroendocrine prostate cancer. The consensus guidelines of RECIST 1.1 and the PCWG3 (Scher, 2016) have been taken into consideration for the determination of radiographic disease progression.

11.3.2. Radiographic Progression-Free Survival

Primary efficacy will be assessed in the phase 2 part of the study by rPFS. The consensus guidelines of RECIST 1.1 and the PCWG3 have been taken into consideration for the determination of radiographic disease progression. The evaluation of progression in bone will be based upon PCWG3 criteria (ie, the appearance of two or more new bone lesions on bone scan), and the evaluation of progression in soft tissue will be based on RECIST 1.1 criteria.

The documentation required for the determination of radiographic disease progression in both bone and soft tissue is listed in Table 10, and a flow diagram for assessment of bone scans to declare disease progression in bone per PCWG3 after the week 9 scan is provided in Figure 2 . Tumor assessments will be performed every 8 weeks for the first 6 months and then every 12 weeks thereafter, starting after cycle 7 until radiographic disease progression is seen.

Table 10: Protocol-Specified Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9 (Cycle 3 Day 1 [±7 days])	Bone lesions; 2 or more new lesions compared to **baseline** bone scan by PCWG3	Timing: at least 6 weeks after progression identified or at week 17 visit[b].	Two or more new bone lesions on bone scan (compared to week 9 scan).
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression.	n/a
Week 17 (Cycle 5 Day 1 [±7 days])	Bone lesions: Two or more new lesions on bone scan compared to week 9 bone scan.	Timing: at least 6 weeks after progression identified or at week 25 visit. Required for bone lesions observed on bone scan[b].	Persistent[c] or increase in number of bone lesions on bone scan compared to week 9 scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	n/a
Week 25 (Cycle 7 Day 1 [±7 days]) or later	Bone lesions: Two or more new lesions compared to week 9 bone scan.	Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan[b].	Persistent[c] or increase in number of lesions on bone scan compared to week 9 scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	n/a

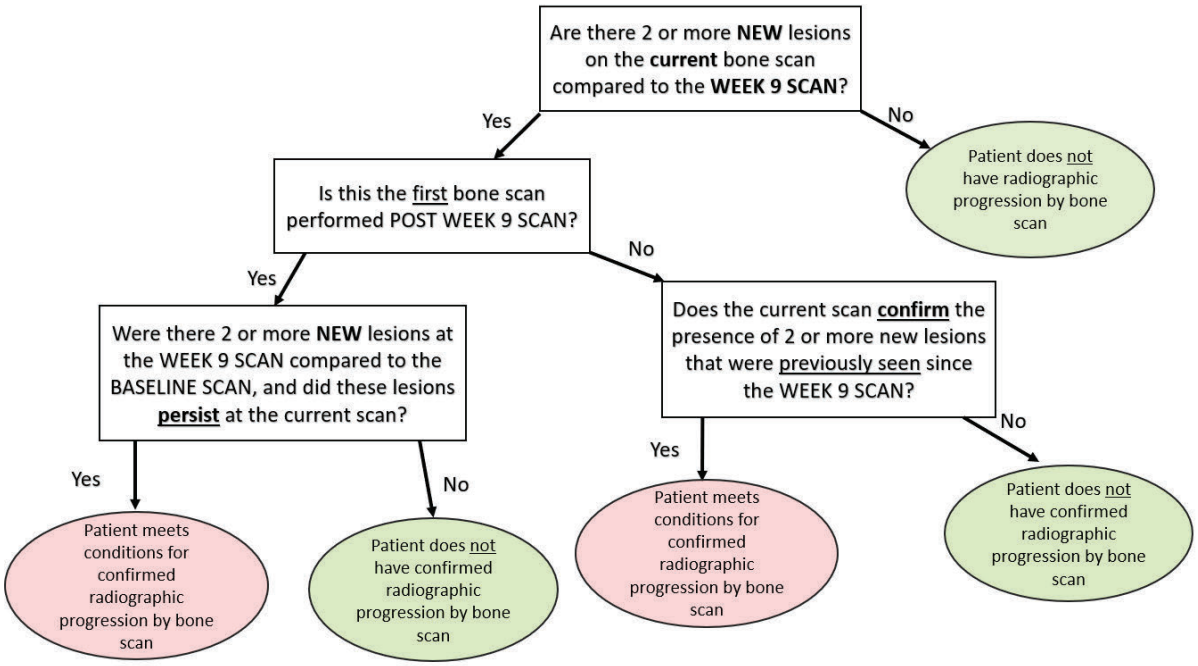
Abbreviations: CT = computed tomography; RECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; n/a = not applicable; PCWG3 = Prostate Cancer Clinical Trials Working Group 3.

[a] Progression detected by bone scan at an unscheduled visit either prior to week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.

[b] Confirmation must occur at the next available scan.

[c] For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).

Figure 2: Post Week 9 Bone Scan Assessment Flow Diagram



Note: Progression detected by bone scan at an unscheduled visit after week 9 will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the diagram.

Study films (CT/MRI and bone scan) should be read on-site using PCWG3 and RECIST 1.1 guidelines and also be submitted in a digital format for a blinded independent central radiology review.

Radiographic imaging is not required after protocol-defined radiographic progressive disease is reached.

Determination of radiographic progression by central radiology review (in parallel with the Investigator's primary review) will continue until at least [redacted] rPFS events from a total of 74 subjects (37 per arm) are confirmed in phase 2, as required for primary rPFS analysis between the active (tazemetostat with enzalutamide) and control arms (enzalutamide alone). See Section 13.2 for sample size justification.

11.3.3. Chest X-ray or Chest CT

Chest CT is required at all imaging time points, if screening chest x-ray demonstrated metastatic chest disease.

11.3.4. Prostate Specific Antigen (PSA)

All PSAs are to be done at a central laboratory. A laboratory manual detailing sample collection, preparation, storage, and shipping process will be provided.

11.3.5. Circulating Tumor Cell (CTC) Enumeration

Enumeration of CTC levels are to be done at a central laboratory. A laboratory manual detailing sample collection, preparation, storage, and shipping process will be provided.

11.3.6. Health-Related Quality of Life

The assessment of health-related QoL measures is an important aspect of this study as it will provide added information on the choice of treatment. Every effort should be made to ensure all subjects complete as many scheduled health-related QoL assessments as possible. Assessments should be administered before other interactions in the clinic during the visit.

11.3.6.1. Brief Pain Inventory-Short Form

The BPI, developed by the Pain Research Group of the World Health Organization Collaborating Centre for Symptom Evaluation in Cancer Care, is a validated patient-reported outcome instrument (Cleeland, 2009). It is a self-administered, multidimensional pain assessment questionnaire used to rapidly assess the severity of pain and its impact on functioning. The BPI-SF contains front and back body diagrams, and 4 pain severity and 7 pain interference items that are rated on an ordinal numerical scale with anchors of 0 (no pain/interference) to 10 (maximum pain/interference).

In this study, a composite of the four pain items (a mean severity score) from the BPI-SF will be used to assess the rate of pain progression as a measure of efficacy.

The BPI-SF assessment should assess pain related to prostate cancer only. Subjects in both phases of the study will complete the BPI-SF.

11.3.6.2. Functional Assessment of Cancer Therapy-Prostate (FACT-P)

The Functional Assessment of Cancer Therapy-Prostate FACT-P is a multidimensional, self-report instrument specifically designed for use with prostate cancer patients (Esper, 1997). In addition to the 27 items comprising the Functional Assessment of Cancer Therapy-General (FACT-G) that assesses 4 areas of well-being (physical well-being, social/family well-being, emotional well-being, and functional well-being), the FACT-P also contains a 12-item disease-specific prostate cancer subscale (PCS) that assesses the additional concerns specific to prostate cancer patients. The recall period is 1 week. Each question is assessed on a 5-point Likert scale: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. The FACT-G scoring guide identifies those items that must be reversed before being added to obtain subscale totals. Responses to negatively stated items are reversed by subtracting the response from “4” to obtain the item score. After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all Functional Assessment of Chronic Illness Therapy (FACIT) scales and symptom indices, higher scores represent better QoL.

Only subjects in the phase 2 portion of the study will complete the FACT-P.

11.3.6.3. EuroQoL 5-Dimension 5-Level (EQ-5D-5L)

Participant reports of general health status will be assessed using the EuroQoL Group’s 5-level EuroQoL 5-Dimension (EQ-5D-5L) questionnaire. (EuroQol, 1990; Pickard, 2007) The EQ-5D-5L has 2 components: a descriptive system and a visual analogue scale (VAS). The EQ-5D-5L

descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels, including "no," "slight," "moderate," and "severe" problems, and either "extreme" problems or "unable to" to do the activity. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Accordingly, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively, described by the EQ-5D-5L. Altogether, the instrument describes 3,125 ($=5^5$) different health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index (ie, Health Utility Index [HUI]) measuring the value to society of his or her current health. In addition, the EQ-5D-5L VAS allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health. Thresholds for meaningful change for the EQ-5D-5L utility index and VAS in cancer patients have not been conclusively defined. The EQ-5D-5L is available in more than 130 languages.

Only subjects in the phase 2 portion of the study will complete the EQ-5D-5L.

11.4. Pharmacokinetic Assessments

11.4.1. Blood Sample Collection

In the phase 1b part of the study, blood samples for PK analysis were collected in cycle 1 on days 1, 2, and 21 at pre-dose (0 hours) and at 0.5, 1, 2, 4, 6, 8, and 24 hours post-dose; and in cycle 2 on day 1 pre-dose (0 hours) and at 2 and 6 hours post-dose.

In the randomized phase 2 part of the study, blood samples for sparse PK blood samples for analysis will be collected only from subjects assigned to the combination arm in cycles 2, 3, 5, and 10 on day 1 at pre-dose (0 hours) and at 2- and 6-hours post-dose. For PK assessment days, subjects will be required to take their study drug/s in the morning at the clinic after the pre-dose sample has been collected. The date and time of last dose on PK sampling days will be recorded.

NOTE: On all days of PK blood draws, the subject must take the first tazemetostat dose at the clinic after the pre-dose (0 hour) PK blood draw.

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

11.4.2. Urine Pharmacokinetic Sample Collection

Not applicable.

11.5. Pharmacogenomics, Biomarkers, and Other Assessments

11.5.1. Tumor Biopsy

Matched biopsies will be performed or available archival biopsies will be requested to evaluate the association of genetic or molecular markers of disease, such as loss of *PTEN, TP53*, and *RB1* and gene expression signatures, including for NEPC, AR and AR splice variants, tumor inflammation and immune cell infiltration, in tumor tissue with drug response. The baseline biopsy can be taken from archival tumor, provided the sample was obtained ≤1 year before

enrollment. Epizyme will request archival tumor samples from all subjects (5 to 20 slides per subject) who do not provide matched biopsies from Screening (added with Amendment #5).

Instructions for providing biopsy from bone will be provided in a separate laboratory manual.

For subjects in phase 1b, optional tumor biopsies are obtained pre-treatment, during drug treatment at first response, and at time of disease progression.

In the phase 2 part of the study, tumor biopsies (primary and metastatic, including from lymph node and bone) will be collected when safe and feasible from 12-20 subjects randomized only to the combination arm of tazemetostat plus enzalutamide at: 1) pre-treatment, 2) on cycle 2 day 1 during treatment, and 3) at the time of disease progression only in subjects who responded to treatment. In order to ascertain which treatment group a subject is randomized to in advance of organizing a pre-treatment tumor biopsy, randomization of phase 2 subjects who consent to provide the biopsy may occur up to 3 days before cycle 1 day 1. Randomization of phase 2 subjects not providing a pre-treatment biopsy should occur on cycle 1 day 1. Longitudinal biopsies should be taken whenever feasible from the same lesions.

11.5.2. Blood Samples for Disease Markers and Pharmacogenomics (PGx)

Blood samples for disease markers and pharmacogenomics will be processed, and plasma and peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood and each fraction will be stored separately. Circulating tumor DNA (ctDNA) will be separated from plasma. PBMC isolation is done at a central laboratory, and viably frozen and standard frozen cell pellets will be collected and stored. A laboratory manual detailing the ctDNA and PBMC sample collection, preparation, storage, and shipping process will be provided.

11.5.2.1. Blood Sample for ctDNA Genotyping

Whole blood samples for ctDNA genotype analysis will be collected as detailed in Table 8.

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

11.5.2.2. AR-V7 and NEPC Status in Circulating Tumor Cells

AR-V7 and NEPC status (morphologically) will be determined in CTCs from liquid biopsies taken at baseline. AR-V7 status will be determined by IF detection of the splice variant in nuclei of CTCs; NEPC status will be determined morphologically in CTCs by assessing imaging of multiple small cell neuroendocrine parameters. Neuroendocrine status will also be determined in baseline serum samples by assessing serum biomarker neuron-specific enolase (NSE) collected pre-dosing.

Enumeration of CTC levels are to be done at a central laboratory. A laboratory manual detailing sample collection, preparation, storage, and shipping process will be provided.

11.5.2.3. Blood Biomarkers of Neuroendocrine Prostate Cancer

A blood sample will be drawn at screening in phase 2 to assess for the NEPC biomarker NSE (serum chromogranin A was removed with Amendment #5).

11.5.3. Future Use of Biosamples

Not all the tissue 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 to 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 both 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 the FDA guidance. The Sponsor will notify the Investigator in writing that the samples have been destroyed. The Sponsor reserves the right to destroy biosamples for any reason during the storage period without further notice.

11.6. Follow-up

11.6.1. Post-treatment Follow-up Visit

Subjects will have a post-treatment follow-up visit 30 (±3) days after their last dose of tazemetostat or prior to initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.

11.6.2. Long-Term Follow-up

Beginning after study drug discontinuation:

- For subjects who discontinue study treatment for reasons other than confirmed radiographic disease progression (such as unequivocal clinical or chemical progression), radiographic tumor assessment scans are required every 12 weeks (±7 days) during long-term follow-up, and other study assessment will continue as scheduled, until the earlier of either: 18 months post last study drug dose; radiographic disease progression; the start of a new systemic anticancer therapy for prostate cancer; withdrawal of consent/loss to follow-up; death; or ≥65 rPFS events have been observed in the study (as communicated by the Sponsor).s communicated by the Sponsor).

11.6.3. Subsequent Therapy After Discontinuation of Study Treatment

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

11.6.4. Evaluation of Response to Subsequent Anti-Cancer Therapy

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

Refer to the Schedule of Assessment and Procedures (Table 8) for additional details.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Vital Signs

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

- Systolic blood pressure
- Diastolic blood pressure
- Heart rate
- Temperature

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.

12.1.2. Weight and Height

Weight is required to be measured at screening, on Day 1 of each cycle, and at the post-treatment visit.

Height measurement is required at screening only.

12.1.3. Physical Examination

A brief physical examination is required at each visit, with the exception of the screening visit during which a complete physical examination will be completed.

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 tazemetostat administration until the end of the study, an AE must be documented. In addition, resolution of any abnormal findings during the study will be noted in source document and the eCRF if clinically significant.

These assessments will be completed as indicated in the Schedule of Assessments and Procedures, refer to Table 8.

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

12.1.4. Electrocardiogram (ECG)

A standard 12-lead ECG will be performed. ECG collection will occur after a 10-minute rest and with the subject in a supine position. ECGs will be collected prior to any blood collection.

The ECGs will be performed as indicated in the Schedule of Assessments and Procedures (Table 8). A single ECG will be recorded unless there is an abnormality, such as prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥480 msec, new arrhythmia, or other clinically significant finding. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart.

Machine read ECGs should be reviewed by the Investigator at the time of assessment. ECGs will be read locally within 72 business hours and data from the Central Reader should be entered in the clinical database.

If cardiotoxicity is suspected, the investigator may conduct additional testing per institutional standard of care (eg, cardiac biomarkers, including B-type natriuretic peptide and cardiac troponin I or cardiac troponin T).

12.1.5. Laboratory Assessments

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

Specific laboratory tests for hematology, serum chemistry, urinalysis, and coagulation profile are detailed in Appendix 3.

During Screening and within 30 days following the end of study treatment (before initiation of subsequent antineoplastic therapy), a complete blood count (CBC) with differential (manual or automated peripheral blood smear) will be performed and assessed per institutional practice to rule out myeloid malignancies, including but not limited to MDS/AML/MPN.

During the study treatment period, the Investigator will monitor subjects for the development of myeloid malignancies as medically indicated.

Any suspected or confirmed AESIs identified during and following the study treatment period will be reported as delineated in Section 12.2.

12.1.6. Creatinine Clearance

Creatinine clearance is required only if serum creatinine is >1.5 × ULN. Creatinine clearance should be calculated by Cockcroft-Gault formula (Appendix 4) or by institutional standard and must be >50 mL/min.

12.1.7. ECOG Performance Status

See Appendix 1.

12.1.8. Optional Chest Ultrasound

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

12.2. Adverse Events

12.2.1. Definitions of Adverse Events

12.2.1.1. Adverse Event (AE)

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

Worsening of a pre-treatment event, after initiation of any study drugs, must be recorded as a new AE. For example, mild intermittent dyspepsia prior to dosing of study drug, but becoming severe or more frequent after the first dose of study drug, requires that a new AE of severe worsening dyspepsia (with the appropriate date of onset) be recorded as an AE in the eCRF.

"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, if they fulfill the definition.

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

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

All AEs that occur after any subject has signed informed consent, before treatment, during treatment, or within 30 days following the cessation of study treatment or prior to initiation of another investigational agent or cytotoxic chemotherapy, whichever occurs first, whether or not they are related to the study, must be recorded in the eCRF forms.

12.2.1.2. Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (ie, baseline, treatment, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered adverse or as meeting seriousness criteria of hospitalization.

- Results in disability or incapacity

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, and accidental trauma (eg, sprained ankle) which do not constitute a substantial disruption.

- Is a congenital abnormality or birth defect as a result of intra-uterine exposure.
- Is an important medical event.

NOTE: Events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions (in subjects without pre-existing seizure disorder) that do not result in hospitalization, or development of drug dependency or drug abuse.

Serious AEs will be collected from the time a subject has signed informed consent until screen failure, 30 days following the cessation of treatment, or upon initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first, whether or not the events are related to the study. Any SAEs that occur beyond 30 days following cessation of treatment that are considered related to study treatment will also be reported.

12.2.1.3. Laboratory Abnormalities

Any laboratory value that is considered clinically significant by the investigator and/or has caused a medical intervention or is accompanied by clinical symptoms should be reported as an AE. All laboratory AEs should be repeated until the values return to normal limits, to baseline, or until a plausible explanation (ie, concomitant disease) is found for the pathological laboratory values.

Laboratory abnormalities are recorded in the lab eCRF, but those that have not required medical intervention should not be recorded as AEs. 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).

12.2.1.4. Other Safety Assessment Abnormalities

Other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline and events considered to be clinically significant by the investigator, are to be recorded as an AE in accordance with the definitions provided in Section 12.2.1.1 and Section 12.2.1.2, respectively.

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

12.2.1.5. Disease-Related Events

Events that meet the criteria for seriousness but are thought to be associated with progression of the disease under study should not be reported as SAEs **unless** they are untoward for that subject and/or disease under investigation.

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

12.2.1.6. Adverse Events of Special Interest (AESIs)

The following AESIs have been identified as requiring mitigation steps and monitoring to minimize the risk for the occurrence of these events. All potential and identified AESIs must also be discussed with the Medical Monitor and reported using an SAE form (Section 12.2.1.2). All instances of AESI will undergo review by the tazemetostat safety committees (Section 12.2.1.6.3).

Refer to the most current version of the tazemetostat IB for additional information about AESIs.

12.2.1.6.1. T-Lymphoblastic Leukemia/T-Acute Lymphoblastic Leukemia

Lymphoblastic lymphomas are considered thymus derived malignancies that have not yet completed T-cell maturations. Approximately 90% of lymphoblastic lymphomas are the T-cell phenotype and typically occur in young adults and adolescents, accounting for 29% of pediatric and 2% of adult non-Hodgkin lymphoma with a median age at diagnosis of 25 years (Lones, 2007; Lai, 2013; Cortelazzo, 2017). T-LBL is morphologically and immunophenotypically indistinct from T-ALL, with both diseases arising from precursor lymphoid cells of the T-cell lineage (Portell, 2012; Patel, 2014). Despite the similarities of the two diseases, significant yet unknown characteristics lead to differences in clinical presentations (Burkhardt, 2009). Initial

clinical manifestation of both adult and pediatric T-LBL includes a mediastinal mass or lymphadenopathy with <25% bone marrow blasts. Adult T-LBL patients tend to have less thymic disease and greater lymph node disease and bone marrow involvement (Baleydier, 2008; Swerdlow, 2008; Campo, 2011). In contrast, T-ALL cases predominantly present with bone marrow and peripheral blood disease, and >25% bone marrow blasts (Swerdlow, 2008; Campo, 2011).

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

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

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

Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of T-LBL/T-ALL so that tazemetostat may be discontinued in the subject and treatment can be initiated for these malignancies. Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric subjects. Two events of T-LBL have occurred in approximately 160 pediatric subjects. Total exposure to tazemetostat includes more than 1105 subjects (adults and pediatrics) in clinical trials and over 2,280 subjects from both clinical and post-marketing sources.

The risk of T-LBL/T-ALL in adults is not known; however, the incidence of treatment-related T-LBL/T-ALL in adults is expected to be uncommon.

If an adult case of T-LBL/T-ALL occurs in this study, enrollment in this study will be suspended. Refer also to Section 12.2.1.6.3 below.

12.2.1.6.2. MDS/AML/MPN

As of 2022, less than 1% of cases of myeloid malignancies have been reported in an estimated cumulative exposure of >2280 patients from both clinical and post-marketing sources. All myeloid malignancy events were reported in adult clinical trial subjects. Brief textual summaries of each myeloid malignancy are provided in the IB.

In the event of suspicion of these malignancies or related concerns, please contact the Medical Monitor for evaluation and consideration of dose adjustments. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any case of MDS/AML and other myeloid malignancies like MPN. For any case of MDS/AML or other myeloid malignancies like MPN that occurs in the study, tazemetostat treatment will be discontinued in the subject. Refer also to Section 12.2.1.6.3 below.

12.2.1.6.3. Tazemetostat Safety Committees

The QSR and the ESC will review all AESI cases per charter, including T-LBL/T-ALL, MDS/AML and other myeloid malignancies like MPN (both related and unrelated), and other solid tumor malignancies.

If a case of T-LBL/T-ALL occurs in the study, the subject will be permanently discontinued from the study. Enrollment of new subjects and dosing of subjects on study will be paused while the QSR/ESC assesses the case; new enrollment and continued dosing will resume pending a decision by the QSR/ESC and communication with health authorities.

If a case of MDS/AML or other myeloid malignancies like MPN occurs in the study, tazemetostat treatment will be discontinued for the subject.

Recommendations for next steps in the event of an AESI will be communicated, per charter, by the Epizyme Chief Medical Officer.

The ESC is composed of independent oncology medical consultants, one of whom serves as the Chair. The ESC meets quarterly to review new data, or it may meet ad hoc.

The purpose of the ESC is to provide independent review of clinical data for the purposes of identifying and evaluating secondary malignancy safety signals from Epizyme sponsored clinical trials. The ESC also monitors the data of those study subjects who have experienced the tazemetostat AESIs, namely T-LBL/T-ALL, MDS, AML, and other myeloproliferative malignancies such as MPN.

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

12.2.1.7. Safety Signal Under Evaluation: B-cell acute lymphoblastic leukemia (B-ALL)

A 73-year-old female patient experienced an SAE of B-ALL while enrolled in Study EZH-501. The patient was diagnosed with Grade 2 follicular lymphoma (FL) in Oct 2016 following an initial diagnosis of diffuse large B-cell lymphoma (DLBCL) on 14 Aug 2006.

The patient was enrolled in the FL EZH2 mutant-type cohort of the phase 2 E7438-G000-101 study and began treatment with tazemetostat 800 mg twice daily on 04 Jan 2017.

Prior to enrollment in the E7438-G000-101 study, the patient had received 2 prior systemic therapeutic regimens as follows: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (22 Sep 2006 to 21 Mar 2007) with the addition of methotrexate and dexamethasone 04 Oct 2006 to 18 Jan 2007. Under an investigational protocol (ROMULUS), the subject received treatment with MabThera (rituximab) with pinatuzumab vedotin (11 Jun 2013 to 17 Sep 2013 and 15 Oct 2013 to 17 Dec 2013).

On the E7438-G000-101 study, the patient received tazemetostat for 26 cycles and achieved an objective PR at week 16 that was maintained through week 104.

The subject was subsequently enrolled onto the EZH-501 maintenance study and received the first dose on 21 Jan 2019. Molecular characterization of the B-ALL clone found in the bone marrow biopsy from November 2020 was conducted for comparison to the primary FL tumor sample isolated in the October 2016 lymph node biopsy. The molecular analysis of the B-ALL and FL clones indicates that they are not related, and that the B-ALL clone is not derived from the FL clone through a clonal evolution mechanism. Based upon medical review of the biology, nonclinical data, and literature with regard to this sentinel case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure.

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

Based upon medical review of the biology, nonclinical data and literature of this case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure. Refer to the tazemetostat IB for case detail. However, Epizyme will continue to monitor patient safety with regard to secondary malignancy and all hematological secondary malignancies will be assessed by the tazemetostat QSR and ESC (Section 12.2.1.6.3).

12.2.2. Reporting of Special Situations

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

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

- Report to Sponsor or designee using a paper Special Situations Form following the procedures for reporting SAE (Section 12.2.8).

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

- Enter the non-serious event on the AE eCRF and mark the SAE field, “no”. The eCRF SAE-related fields should not be completed.
- Report to Sponsor or designee using a paper Special Situations Form following the procedures for reporting SAEs (Section 12.2.8).

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 Sponsor or designee using both a paper Special Situations Form and a paper Serious Adverse Event Form following the procedures for reporting SAEs (Section 12.2.8).

12.2.3. Grading and Severity

The severity of all AEs and SAEs, including appropriate laboratory values, will be graded utilizing the CTCAE v5.0. The link to the CTCAE version 5.0 is:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

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

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

ADL = activities of daily living; AE = adverse event.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care 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'); both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre- defined outcomes as described in Section 12.2.1.2 which are based on patient/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

12.2.4. Relationship to Study Drug

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

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 drugs
- 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 study drugs using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the study drug):

- **Probable**: A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, 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 study drug.
- **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.

12.2.5. Outcome and Follow-Up

Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved, or fatal. All AEs/SAEs will be followed by the Investigator to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal), or until an outcome is reached, stabilization occurs (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained through the study closure and database lock. All SAEs (including all AESIs) will be followed by Epizyme to resolution or other outcome is reached, regardless of study closure/database lock. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

12.2.6. Timeframe for Collecting AEs and SAEs

AEs: Adverse events will be collected from the time when the subject signs the informed consent form until the earlier of either screen failure, 30 days after the discontinuation of study treatment, or until the initiation of subsequent anti-cancer therapy.

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

Beyond the 30-day follow-up or until the initiation of subsequent anti-cancer therapy, the Investigator will report any new SAE that they consider to be possibly related to study treatment.

Note that any incidence of a primary secondary malignancy, even if occurring more than 30 days after the last dose of study drug, will be reported to the Sponsor as an SAE.

12.2.7. Recording Adverse Events and Pregnancy

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 recorded during the study at the investigational site. Clinically significant changes, per Investigator assessment, in laboratory values, blood pressure, and pulse should be recorded as AEs.

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.

Should a pregnancy occur in the partner of a subject after starting treatment with tazemetostat, it must be recorded on the study pregnancy form and reported to Epizyme using the SAE reporting timeframes and contact information on the form. Pregnancy in itself is not regarded as an AE.

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 not be handled as AEs.

12.2.8. Reporting of SAEs and AESIs

All SAEs and all potential and identified AESIs (regardless of seriousness or relationship to study drug) will be reported within 24 hours of the investigator becoming aware of the event using the contact information printed on the SAE form. The investigator must promptly notify the sponsor or its designee of all SAEs in order that the legal obligations and ethical responsibilities of the sponsor or its designee are met.

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

An investigator who receives an investigator safety report describing a Suspected, Unexpected Serious Adverse Reaction (SUSAR) or other specific safety information from the sponsor will file it with the IB and will notify the IRB/EC/CEC, if appropriate according to local requirements.

12.3. Safety Review Committee (SRC)

During the phase 1b (complete) part of the study, an SRC composed of investigators, medical monitors, and Epizyme study members reviewed safety data, available PK data, treatment delays, study agent dosing records, treatment reductions, and treatment discontinuations from each cohort. The SRC assessed DLTs and endorsed acceptable doses of tazemetostat to be considered as the RP2D for the combination with enzalutamide. Its membership, and procedures are outlined in an SRC charter.

The SRC reviewed safety data from cycle 1 (days 1 through 28) from each dose escalation cohort. The SRC reviewed the following safety data:

- AEs/SAEs, including DLTs and any actions taken with the study treatment (eg, dose reduction, dose interruption, dose withdrawal)
- Clinical laboratory values
- ECGs
- Vital signs
- Concomitant medications

Based on the review of data, the Epizyme SRC could have recommended that the study continue as planned or may alternatively recommend that the study be placed on hold or terminated. A recommendation of study hold, study treatment dose de-escalation, or study termination would be made in the event of the discovery of an unexpected, serious, or unacceptable risk to the subjects in the study and implemented via QSR and/or ESC review (Section 12.2.1.6.3).

The Epizyme Medical Monitor along with the Principal Investigator will also review safety data on an ongoing basis during the dose expansion (phase 2) part of the study.

12.4. Quarterly Safety Review (QSR) Committee

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

13. STATISTICS

The statistical analysis plan will be developed and finalized before database lock.

13.1. Analysis Sets

13.1.1. Phase 1b Analysis Sets

Enrolled Population: The enrolled population consists of all subjects in the phase 1b part who signed the inform consent form and were not screen failures. The enrolled population will be used in summaries of disposition of subjects, protocol deviations, demographics and other baseline characteristics, as well as efficacy analyses.

Safety Population: The Safety population is defined as all subjects who received ≥1 dose or partial dose of any of the study drugs. The safety population will be used for all safety analysis. Subjects will be analyzed according to the assigned dose level for the respective dose escalation cohort.

Dose-Limiting Toxicity (DLT) Population (Phase 1b only): The DLT Population set will consist of dose escalation cohort subjects in the Safety Population who received at least 80% of planned study drug during cycle 1. Subjects will be analyzed according to the assigned dose level for the respective dose escalation cohort.

Pharmacokinetic (PK) Population: The PK population will include all subjects in the Safety population who have ≥1 post-dose sample collected to allow estimation of the PK parameters. The PK population will be used for population-based analysis.

13.1.2. Phase 2 Analysis Sets

I**ntent-to-treat (ITT) Population**: The ITT population is defined as all subjects who are randomized into the trial. The ITT population will be used for summaries of disposition of subjects, protocol deviations, demographics and other baseline characteristics as well as efficacy analysis. Subjects will be analyzed according to the treatment arm to which they are randomized.

Safety Population: The safety population is defined as all subjects in the ITT population who have received at least one dose or partial dose of study medication. The safety population will be used for all safety analysis. Subjects will be analyzed according to the treatment which they actually received.

Pharmacokinetic (PK) Population: The PK population will include all subjects in the ITT population who have ≥1 post-dose sample collected to allow estimation of the PK parameters. The PK population will be used for population-based analysis.

FACT-P Population: The FACT-P population will include all subjects in the ITT population who complete an evaluable FACT-P questionnaire at baseline and ≥1 post-baseline visit. An evaluable questionnaire will have sufficient items completed to allow calculation of ≥1 FACT-P subscale.

13.2. Sample Size Justification

For the Phase 2 randomized component of the study: The sample size calculation was performed based on the primary endpoint of rPFS. To compare the combination of tazemetostat

with enzalutamide to enzalutamide alone, [redacted] rPFS events from a total of 74 total subjects (37 per arm) will provide approximately [redacted] power for the analysis of rPFS, with a 2-sided total type I error of 0.05 to reject the null hypothesis that there is no difference in rPFS between the two arms. To account for the approximate [redacted] dropout, the sample size will increase to 80 (40 per arm).

The sample size assumes that the combination of tazemetostat with enzalutamide will prolong rPFS by [redacted] (hazard ratio [HR] = [redacted]) from [redacted] months for enzalutamide to [redacted] months, with [redacted] of subjects lost to follow-up over a [redacted]-month enrollment period, a 9-month follow-up period (a total follow-up time of 18 months, tmax = 18), and a total phase 2 study duration of approximately [redacted] months. (The critical boundary to achieve statistical significance for the final rPFS logrank testing between two arms is HR=[redacted] or [redacted] months of improvement in rPFS.)

13.3. Analyses

13.3.1. Disposition, Demographics, Baseline Characteristics, and Prior Cancer Treatments

Subject disposition, including reasons for treatment and study withdrawal, will be summarized descriptively for each population described in Section 13.1 and provided in a listing.

Demographics and other baseline characteristics, including medical history, cancer-related history, prior cancer treatments, and performance status, will be listed and summarized descriptively.

Medical history and prior surgical terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary in use at the time of the analysis and presented by system organ class (SOC) and preferred term (PT). Surgical history will be summarized by the MedDRA high-level group term (HLGT) and PT.

Reported terms for prior cancer treatments will be coded using the World Health Organization (WHO) Drug Dictionary in effect at the of the analysis and will be listed for each subject, and the numbers of subjects who received each treatment will summarized according to generic name.

13.3.2. Efficacy Analyses

All efficacy analysis will be performed by dose level using the enrolled population for the phase 1b part and by treatment using the ITT population for the phase 2 part.

13.3.2.1. Primary Efficacy Endpoint Analysis

- **Radiographic progression-free survival (phase 2 randomized treatment groups)**: The rPFS of tazemetostat in combination with enzalutamide will be compared to the rPFS of enzalutamide alone. rPFS is defined as the time from the date of randomization to the date of the first objective evidence of radiographic progression or death from any cause, whichever occurs first. In cases where PD or death has not occurred, censoring rules will be applied as provided in the SAP. Radiographic disease progression is defined by the criteria in Table 10 and Figure 2. The primary analysis of rPFS for tazemetostat in combination with enzalutamide compared with enzalutamide treatment alone will be

based upon at least the first [redacted] rPFS events observed. A log-rank test will be used to compare tazemetostat in combination with enzalutamide to enzalutamide treatment alone at the significance level of 0.05 (one-sided). Conventionally, HRs with corresponding 2-sided 95% CI will be estimated using the Cox proportional hazards model. Graphical methods will be used to assess the Cox proportional hazards model assumptions. rPFS will also be summarized descriptively using the Kaplan-Meier (KM) method. The KM estimate along with the corresponding 95% CI will be calculated using the Brookmeyer and Crowley method and will be provided for the median. The event-free rate with corresponding 95% CI will be calculated using Greenwood's formula and will be provided at 4 months, 8 months, 12 months, and 18 months. Median follow-up for rPFS will be estimated according to the KM estimate of potential follow-up (Schemper, 1996). KM curves will also be provided.

In the phase 2 portion of the study, comparisons between treatment groups for the secondary endpoints will occur only if the primary endpoint (rPFS) achieves statistical significance at an alpha level of 0.05.

13.3.2.2. Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoint analyses will include.

- **PSA50**: PSA50 is defined as the percentage of subjects with a ≥50% reduction of PSA from baseline at any time on study for subjects with a baseline PSA ≥2 ug/L (2 ng/mL) per PCWG3 criteria. Confirmed PSA response is defined as a ≥50% reduction in PSA from baseline to the post-baseline PSA result with ≥50% reduction from baseline, with a consecutive assessment also with ≥50% reduction from baseline conducted at least 3 weeks later required to confirm the PSA response. If a consecutive value meets the response criteria but is obtained within 3 weeks and the next assessment also meets response criteria and is taken after 3 weeks, then the initial response is considered as confirmed response as well. However, a subject with a missing confirmation PSA value after 3 weeks is considered as non-responder. PSA50 will be calculated by treatment group for subjects with PSA values at the baseline assessment (cycle 1 day 1 predose) and at least 1 post baseline assessment. A Cochran-Mantel-Haenszel mean score test will be used to compare the response rates between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **ORR and Best Overall Soft Tissue Response**: ORR is defined per RECIST 1.1 guidelines. The best overall soft tissue response as assessed by Investigators using RECIST 1.1 will be summarized. Only subjects with measurable soft tissue disease at screening (ie, at least 1 target lesion per RECIST 1.1; see Appendix 5) will be included in this analysis. The Clopper-Pearson exact method will be used to compare the proportion of subjects with an objective response (complete response or partial response) per RECIST 1.1 between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **Disease Control Rate** (no radiographic progression per PCWG3, and no unequivocal clinical progression or death) at 6 months on study therapy. A Cochran-Mantel-Haenszel test will be used to compare DCR between tazemetostat in combination with enzalutamide and enzalutamide treatment alone, and the corresponding *p*-value will be

provided. Also, the 95% CI will be provided for each treatment group and for the difference in proportion between the two treatment groups, using Clopper-Pearson exact method and Newcombe method, respectively.

- **Time to First SRE**: Time to first SRE is defined as the time from randomization to the date of first SRE. In cases where a SRE has not occurred at the time of the analysis, the subject will be right-censored. Censoring rules will be provided in the SAP. An SRE is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. A log-rank test will be used to compare time to first SREs between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **Time to Initiation of the Next Systemic Treatment for Prostate Cancer (TTNT)**: TTNT is defined as the time from the date of randomization to date of first documented administration of the next systemic treatment for prostate cancer. The TTNT will be right-censored at the last study assessment date if the subject did not receive a subsequent treatment. A log-rank test will be used to compare time to initiation of subsequent treatment between tazemetostat in combination with enzalutamide and enzalutamide alone.
- **Time to PSA Progression**: Time to PSA progression (TTPP) is defined as the duration from baseline to the date of PSA progression. PSA progression is defined as a ≥25% increase and an absolute increase of ≥ 2 μg/L (2 ng/mL) above the nadir (or baseline value for subjects who did not have a decline in PSA value by week 17). This increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later. The date of confirmed PSA progression is the date of the initial ≥25% increase. Subjects without confirmed PSA progression at the time of analysis will be right-censored. Censoring rules will be provided in the SAP. Time from randomization to first observation of PSA progression will be assessed. A log-rank test will be used to compare TTPP between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.
- **CTCs**: In subjects who enter the study with a detectable number of CTCs, the **rate of CTC reduction to zero** is the proportion of subjects who convert to an undetectable number of CTCs. CTC response is defined as a ≥30% reduction in CTCs from baseline in subjects who enter the study with a detectable number of CTCs, and the **CTC response rate** is the proportion of subjects with a ≥30% reduction in CTCs from baseline (cycle 1 day 1 pre-dose). The rate of CTC reduction to zero and CTC response rate for tazemetostat in combination with enzalutamide will be compared with those for enzalutamide treatment alone using the Clopper-Pearson exact method.

Refer also to secondary QoL endpoint analysis described in Section 13.3.5.

13.3.2.3. Subgroup Analysis

Subgroup analysis will be performed for rPFS by AR-V7 and NEPC (negative and positive) status. A swim lane plot (time on treatment) showing AR-V7 and NEPC status will be provide for each endpoint.

13.3.3. Pharmacokinetic and Population Pharmacokinetic Analysis

In-order to assess the effect of tazemetostat on abiraterone/prednisone and enzalutamide PK and, vice-versa, the effect of enzalutamide and abiraterone/prednisone treatment alone on tazemetostat PK, the following PK parameters were assessed during the dose-escalation portion of the study (phase 1b) on Days 1, 2, and 21 in cycle 1:

- $AUC_{0\text{-last}}$: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration.
- $AUC_{0\text{-}24}$: area under the plasma concentration-time curve from time 0 to the time of 24 hours.
- C_{max}: maximum plasma concentration.

Plasma concentrations will be summarized using descriptive statistics (n, mean, SD, coefficient of variation [CV%], standard error [SE] of the mean, median, maximum, and minimum) at each scheduled evaluation time point. The mean PK concentrations will be plotted over time since last dose and time since first dose.

Population PK analyses will also be performed. Population PK modeling will be conducted combining data from the phase 1b and phase 2 portions of the study to quantitatively describe the PK profile of tazemetostat, explore the PK variability, and identify any covariate effects.

In addition, exposure relationship for efficacy and safety endpoints will be investigated based on phase 2 data where appropriate. The objective of exposure-response analysis is to characterize the relationships between exposure and efficacy, and exposure and safety.

- Key efficacy variables include (but are not limited to) the following:
  - Radiographic rPFS
  - Additional efficacy endpoints as appropriate (eg, PSA50, TTPP, DCR, ORR)
- Key safety variables include (but are not limited to) the following:
  - AE of interest identified based on the data

Key exposure variables will be based on measured or population PK model predicted concentrations and will include peak concentration (C_{max}), steady-state concentration at the end of a dosing interval (C_{min}), and AUC at steady-state for tazemetostat. Effect of clinically relevant covariates will be evaluated.

Exploratory PK analysis is discussed below in Section 13.3.4.

13.3.4. Exploratory Analyses and Endpoints

As data warrant, exploratory analysis may be performed on each exploratory endpoint listed below.

In addition, exploratory analyses may be performed to examine the relationship between exposure to tazemetostat and clinical and safety endpoints (including tumor size or change in tumor size from baseline). Also, through aggregate analysis of tumor biomarker data, exploration of whether a subset of subjects might benefit from tazemetostat with enzalutamide will be performed.

Additional details of the analysis of exploratory endpoints will be described in a separate PK/pharmacodynamic/biomarker SAP, and the results of these analyses may be reported separately from the CSR. Refer also to Section 11.5.3 for future use of tissue samples.

Exploratory endpoints include:

- **PSA90**: Defined and analyzed similarly to PSA50.
- **Changes in ctDNA burden** (defined as the proportion of ctDNA in the entire population of cell-free DNA [cfDNA]) from longitudinal samples taken throughout the period of drug treatment as compared to baseline.
- **Characterization of tazemetostat combination exposure** (possible example: C_{min}).
- **Pharmacodynamic modulation of EZH2 activity** by tazemetostat as assessed by measuring H3K27me3 levels in paired pre- and on-treatment tumor biopsies that may be obtained from the phase 1b and phase 2 portions of the study. Analyses will include change from screening to on-study values plotted at cycle 2 day 1 and at progression using a waterfall plot.
- The **mutational landscape of pre-treatment tumor biopsies and baseline ctDNA**, such as for loss of *PTEN, TP53*, and *RB1*, will be determined using bioinformatic analysis of whole exome next generation sequencing (NGS) and compared when possible to the mutational landscape in biopsies taken on-treatment and at disease progression. In addition, whole transcriptome data will be obtained from tumor biopsies using RNASeq, and bioinformatics analysis of NEPC and AR signaling pathways, including AR variant AR-V7 gene expression, and other pathways involved in prostate cancer biology will be performed in matched biopsies. Finally, the state of the immune microenvironment in pre-treatment, on treatment (at cycle 2 day 1), and at disease progression (only in responders) tumor biopsies in subjects receiving tazemetostat in combination with enzalutamide will be evaluated by investigating the occurrence of various gene expression signatures of tumor inflammation and infiltrating lymphocytes available from public sources.
- **Circulating tumor DNA (ctDNA)** obtained from liquid biopsies taken minimally at baseline prior to the first dose and on the same days as CT/MRI scans to ascertain first sign of response and disease progression based on ctDNA burden will also undergo targeted whole exome sequencing (WES) to determine the mutational status of genes, such as *PTEN*, *TP53*, and *RB1*, associated with clinical outcome.
- **Concordance of genetic characteristics of disease in tumor biopsies and ctDNA** isolated from baseline liquid biopsies will be evaluated using regression analysis methods.
- **Assessment of immunological endpoints in tumor biopsies** taken at pre-treatment, on-treatment (at cycle 2 day 1), and at disease progression (only in responders) in the phase 2 portion of the study will be conducted to determine the level of infiltration of various T-cell lymphocyte and other immune cell populations (cell type number and activation status) using multiplex IF staining and DNA sequence analysis. Differences in the composition of the immune microenvironment between responders and non-responders in each treatment cohort will be determined and compared to published tumor

immune profiles associated with response or resistance to immunotherapy, such as checkpoint inhibitor blockade or enzalutamide therapy. In addition, circulating immune cell sub-populations isolated from PBMCs from blood taken pre-treatment, on-treatment (cycle 2 day 1), and at disease progression (only in responders) in the phase 2 portion of the study will be investigated to determine the impact of drug treatment on immune cell numbers, antigen presentation, and activation status.

Refer also to Section 13.3.5 for information about analysis of exploratory QoL endpoints.

13.3.5. Health-Related Quality of Life Assessment Endpoints and Analysis

The following are key health-related QoL endpoints for each instrument; other endpoints from these instruments may also be assessed. The algorithms for scoring patient reported outcomes (PROs) and plans for the corresponding analyses will be provided in a PRO SAP.

BPI-SF (phase 1 and phase 2 exploratory objectives):

In phase 1, the **rate of pain progression**, defined as the proportion of subjects with an increase of ≥30% from the time of screening in the average of BPI pain intensity item scores (items 3, 4, 5, and 6) at 6 months will be used to assess tazemetostat in combination with enzalutamide and tazemetostat in combination with abiraterone/prednisone. The BPI scores will be summarized descriptively at time of screening, at 3 months, and at 6 months.

In phase 2, the **rate of pain progression**, defined as the proportion of subjects with an increase of ≥30% from baseline in the average of BPI pain intensity item scores (items 3, 4, 5, and 6) at each post-baseline time point will be used to compare tazemetostat in combination with enzalutamide to enzalutamide treatment alone. The BPI scores will be summarized descriptively at baseline and each postbaseline time point.

The BPI mean severity score will be analyzed using mixed-effects model for repeated measures (MMRM) and mixed-effects models with baseline score and treatment group as covariates, and the differences in mean scores between treatment groups will be presented with corresponding 95% CIs at each time point and overall. Changes from baseline will also be presented. The mean change from baseline will be summarized and plotted by treatment group. Continuous endpoints will be analyzed similarly as for BPI pain intensity score.

FACT-P (phase 2 secondary and exploratory objectives):

For the **secondary objective**, the percentage of subjects with a decline from baseline in the FWB subscale score by ≥10 points and the percentage of subjects with a decline from baseline in the Prostate Cancer Subscale (PCS) score by ≥10 points at any postbaseline visit will be compared between the treatment groups.

For the **secondary objective**, the TDD is a decline from baseline in FACT-P FWB subscale score of ≥10 points and the time from baseline to decline in FACT-P PCS subscale score of ≥10 points will be compared between the treatment groups.

For **exploratory objectives**, scores will be summarized descriptively over the course of the study by treatment group, with emphasis on the following FACT-P domains: Emotional, Social, and Physical Well-being.

The analyses will be conducted on the intent to-treat FACT-P population, defined as all randomized subjects who have completed an evaluable FACT-P questionnaire at baseline and ≥1 post-baseline visit. An evaluable questionnaire will have sufficient items completed to allow calculation of ≥1 FACT-P subscale.

In general, to estimate longitudinal changes in FACT-P scores from baseline, the primary analysis will be carried out using an MMRM. MMRM analysis uses all available data and assumes that any missing observations are missing at random. The differences in mean scores between treatment groups will be presented with the corresponding 95% CI at each time point and overall. To address the possibility that missing data may not be at random, a second analysis will be carried out using a pattern-mixture model (PMM) with placebo-based pattern imputation. In both models, the baseline covariates may include: treatment group; time; baseline ECOG score (0–1 or 2); average baseline domain score. Due to the exploratory nature of the analyses, adjustments for multiple comparisons will not be made.

The cumulative distribution function will be presented as a continuous plot of the numerical change in FACT-P scores from baseline on the horizontal axis, with the cumulative percentage of patients experiencing up to that change on the vertical axis. One curve for each treatment group will be plotted for each visit.

EQ-5D-5L (phase 2 exploratory objective):

For the **exploratory objective**, scores will be summarized descriptively over the course of the study by treatment group, with emphasis on changes from baseline in EQ-5D-5L VAS and HUI scores over the course of the study. The analysis method is similar to those for FACT-P.

13.3.6. Safety Analyses

13.3.6.1. General Considerations

Safety analyses will be based on all subjects who receive ≥1 dose or partial dose of any of the study drugs (ie, the Safety population). Safety data from the phase 1b and phase 2 portions of the study will be presented separately. In general, safety data from the phase 1b portion of the study will be tabulated by assigned dose levels and overall, and the data from the phase 2 portion of the study will be tabulated by assigned treatment group and overall. For all analyses, subjects who receive a dose modification will be retained and analyzed in the treatment group originally assigned.

13.3.6.2. Study Drug Exposure and Compliance

Study drug exposure and compliance (including for example, duration, cycles, total amount, dose intensity, dose modifications, and percentage of assigned study drug taken) for each of the study drugs will be listed and summarized using descriptive statistics. Exposure will be summarized separately by treatment group and overall.

13.3.6.3. Adverse Events and Deaths

Summary tables will be provided for all reported TEAEs, defined as AEs that started or worsened in severity on or after the date of the first dose of study drug (study day 1) through

30 days after the end of treatment. Handling of missing or partially missing start and end dates for AEs and SAEs will be provided in the SAP. For cases in which it is not possible to ascertain treatment emergence, the event will be classified as treatment emergent.

Severity of all AEs is to be evaluated by the Investigator based on the CTCAE version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of the analysis. . Laboratory values also will be classified by toxicity grade based on the CTCAE version 5.0.

Tabular summaries of the number and percentage of subjects with adverse events will be presented by MedDRA system organ class and preferred term by relationship to study treatment and by severity as listed below. If a subject experiences repeat episodes of the same AE (as defined by the MedDRA system organ class and preferred term), then the event with the highest reported severity grade and the strongest causal relationship to study drug will be used for purposes of incidence tabulations.

- All TEAEs
- TEAEs with ≥10% incidence overall based on preferred term
- TEAEs of Grade 3 or 4
- Treatment-related TEAEs
- Treatment-related TEAEs of Grade 3 or 4
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to discontinuation of study drug
- Treatment-emergent SAEs
- Treatment-related treatment-emergent SAEs
- TEAEs of special interest

Separate listings of all AEs, SAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to dose modifications (interruption and dose reduction) will be provided. A listing of the AESIs described in this protocol will also be provided.

Deaths will be summarized and listed as follows:

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

The summaries and listing of deaths will include the categorical reason for death.

13.3.6.4. Clinical Laboratory Values

All clinical laboratory values will be standardized according to the International System of Units prior to summarization. Laboratory values also will be classified by toxicity grade based on the CTCAE version 5.0.

Separate listings and summary tables will be produced for the laboratory test groups (eg, hematology, coagulation, chemistry, urinalysis). Laboratory values outside the normal ranges will be flagged as "L" (Low) or "H" (High) in the data listing. Laboratory shift tables of the changes from baseline values to the worst post-baseline values based on CTCAE toxicity grades will be produced for each parameter.

13.3.6.5. Other Safety Measures

Vital sign values will be listed and summarized descriptively. In addition, descriptive summaries based on the predefined markedly abnormal criteria shown below will be produced.

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

Electrocardiogram data will be listed. Categorical analyses of absolute QTcF values and changes from baseline in QTcF values by the predefined threshold levels shown below will be produced.

QTcF Value	**Threshold Levels**
Absolute value	>450 msec >480 msec >500 msec
Increases from baseline	>30 msec >60 msec

Physical examination results will be listed by subject.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of **Epizyme** 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** or its representatives. This will be documented in a Clinical Study Agreement between **Epizyme** and the investigator.

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

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

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

14.2. Audits and Inspections

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

14.3. Institutional Review Boards/Independent Ethics Committees

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, **Epizyme** may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements, and **Epizyme**'s policy on Bioethics.

16.3. Written Informed Consent

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

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

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

No protocol-specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB/IEC-approved ICF.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

17.2. 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. PUBLICATION POLICY

A summary of the study results will be made publicly available within 12 months of reaching the end of the study, defined as the date of the last subject's last visit (LSLV).

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 Epizyme, Inc. 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.

19. LIST OF REFERENCES

Abida W, Armenia J, Gopalan A, et al. Prospective Genomic Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. *JCO Precis Oncol.* 2017;2017.

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

Antonarakis ES. Predicting treatment response in castration-resistant prostate cancer: could androgen receptor variant-7 hold the key? *Expert review of anticancer therapy.* 2015;15(2):143-145.

Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med.* 2014;371(11):1028-1038.

Armenia J, Wankowicz SAM, Liu D, et al. The long tail of oncogenic drivers in prostate cancer. *Nat Genet.* 2018;50(5):645-651.

Attard G, Borre M, Gurney H, et al. Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment. *J Clin Oncol.* 2018;36(25):2639-2646.

Azad AA, Volik SV, Wyatt AW, et al. Androgen Receptor Gene Aberrations in Circulating Cell-Free DNA: Biomarkers of Therapeutic Resistance in Castration-Resistant Prostate Cancer. *Clin Cancer Res.* 2015;21(10):2315-2324.

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

Barrie SE, Potter GA, Goddard PM, et al. Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase). *The Journal of steroid biochemistry and molecular biology.* 1994;50(5-6):267-273.

Beltran H, Prandi D, Mosquera JM, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. *Nat Med.* 2016;22(3):298-305.

Beltran H, Rickman DS, Park K, et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. *Cancer Discov.* 2011;1(6):487-495.

Bracken AP, Pasini D, Capra M, et al. EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *The EMBO journal.* 2003;22(20):5323-5335.

Bradley WD, Arora S, Busby J, et al. EZH2 inhibitor efficacy in non-Hodgkin's lymphoma does not require suppression of H3K27 monomethylation. *Chemistry & biology.* 2014;21(11):1463-1475.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.

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

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

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

Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. *Nat Med.* 2004;10(1):33-39.

Cleeland CS. The brief pain inventory user guide. 2009; https://www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf. Accessed 6/1/2019.
Comet I, Riising EM, Leblanc B, et al. Maintaining cell identity: PRC2-mediated regulation of transcription and cancer. *Nat Rev Cancer.* 2016;16(12):803-810.
Copeland RA. Molecular pathways: protein methyltransferases in cancer. *Clin Cancer Res.* 2013;19(23):6344-6350.
Cortelazzo S, Ferreri A, Hoelzer D, et al. Lymphoblastic lymphoma. *Crit Rev Oncol Hematol.* 2017;113:304-317.
Dardenne E, Beltran H, Benelli M, et al. N-Myc Induces an EZH2-Mediated Transcriptional Program Driving Neuroendocrine Prostate Cancer. *Cancer Cell.* 2016;30(4):563-577.
Davies AH, Beltran H, Zoubeidi A. Cellular plasticity and the neuroendocrine phenotype in prostate cancer. *Nat Rev Urol.* 2018;15(5):271-286.
Devine BJ, McCarron MM. Clinical Pharmacy: Case Studies:Case Number 25 Gentamicin Therapy. *Drug Intelligence & Clinical Pharmacy.* 1974;8(11):650-655.
Einstein DJ, Arai S, Balk SP. Targeting the androgen receptor and overcoming resistance in prostate cancer. *Curr Opin Oncol.* 2019;31(3):175-182.
Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer (Oxford, England : 1990).* 2009;45(2):228-247.
Esper P, Mo F, Chodak G, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997;50(6):920-928.
EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. 2020; https://drug-interactions.medicine.iu.edu/MainTable.aspx.
Hu R, Dunn TA, Wei S, et al. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. *Cancer Res.* 2009;69(1):16-22.
Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *J Urol.* 2002;167(2 Pt 2):948-951; discussion 952.
Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol.* 2019;20(12):1730-1739.
Kim J, Lee Y, Lu X, et al. Polycomb- and Methylation-Independent Roles of EZH2 as a Transcription Activator. *Cell Rep.* 2018;25(10):2808-2820 e2804.
Kleer CG, Cao Q, Varambally S, et al. EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. *Proc Natl Acad Sci U S A.* 2003;100(20):11606-11611.
Knutson SK, Warholic NM, Johnston LD, et al. Synergistic Anti-Tumor Activity of EZH2 Inhibitors and Glucocorticoid Receptor Agonists in Models of Germinal Center Non-Hodgkin Lymphomas. *PLoS One.* 2014;9(12):e111840.
Knutson SK, Warholic NM, Wigle TJ, et al. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *Proc Natl Acad Sci U S A.* 2013;110(19):7922-7927.

Ku SY, Rosario S, Wang Y, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. *Science.* 2017;355(6320):78-83.
Kuroki H, Hayashi H, Okabe H, et al. EZH2 is associated with malignant behavior in pancreatic IPMN via p27Kip1 downregulation. *PLoS One.* 2014;9(8):e100904.
LaFave LM, Beguelin W, Koche R, et al. Loss of BAP1 function leads to EZH2-dependent transformation. *Nat Med.* 2015;21(11):1344-1349.
Lai C, Dunleavy K. NK/T-cell lymphomas in children. *Best Pract Res Clin Haematol.* 2013;26(1):33-41.
Lallous N, Volik SV, Awrey S, et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. *Genome Biol.* 2016;17:10.
Lam JS, Leppert JT, Vemulapalli SN, et al. Secondary hormonal therapy for advanced prostate cancer. *J Urol.* 2006;175(1):27-34.
Lones MA, Heerema NA, Le Beau MM, et al. Chromosome abnormalities in advanced stage lymphoblastic lymphoma of children and adolescents: a report from CCG-E08. *Cancer Genet Cytogenet.* 2007;172(1):1-11.
Margol AS, Judkins AR. Pathology and diagnosis of SMARCB1-deficient tumors. *Cancer genetics.* 2014;207(9):358-364.
Margueron R, Reinberg D. The Polycomb complex PRC2 and its mark in life. *Nature.* 2011;469(7330):343-349.
McCabe MT, Ott HM, Ganji G, et al. EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations. *Nature.* 2012;492(7427):108-112.
Min J, Zaslavsky A, Fedele G, et al. An oncogene-tumor suppressor cascade drives metastatic prostate cancer by coordinately activating Ras and nuclear factor-kappaB. *Nat Med.* 2010;16(3):286-294.
Morin RD, Johnson NA, Severson TM, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet.* 2010;42(2):181-185.
Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.
Patel B, Kang Y, Cui K, et al. Aberrant TAL1 activation is mediated by an interchromosomal interaction in human T-cell acute lymphoblastic leukemia. *Leukemia.* 2014;28(2):349-361.
Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351(15):1513-1520.
Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes.* 2007;5:70.
Pienta KJ, Bradley D. Mechanisms underlying the development of androgen-independent prostate cancer. *Clin Cancer Res.* 2006;12(6):1665-1671.
Portell CA, Sweetenham JW. Adult lymphoblastic lymphoma. *Cancer J.* 2012;18(5):432-438.
Puca L, Bareja R, Prandi D, et al. Patient derived organoids to model rare prostate cancer phenotypes. *Nat Commun.* 2018;9(1):2404.
Puca L, Gavyert K, Sailer V, et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. *Sci Transl Med.* 2019;11(484).
Qi W, Chan H, Teng L, et al. Selective inhibition of Ezh2 by a small molecule inhibitor blocks tumor cells proliferation. *Proc Natl Acad Sci U S A.* 2012;109(52):21360-21365.

Quigley DA, Dang HX, Zhao SG, et al. Genomic Hallmarks and Structural Variation in Metastatic Prostate Cancer. *Cell.* 2018;175(3):889.
Robinson D, Van Allen EM, Wu YM, et al. Integrative Clinical Genomics of Advanced Prostate Cancer. *Cell.* 2015;162(2):454.
Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials.* 1996;17(4):343-346.
Scher HI, Buchanan G, Gerald W, et al. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. *Endocr Relat Cancer.* 2004;11(3):459-476.
Scher HI, Heller G. Clinical states in prostate cancer: toward a dynamic model of disease progression. *Urology.* 2000;55(3):323-327.
Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer. *JAMA Oncol.* 2016;2(11):1441-1449.
Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016;34(12):1402-1418.
Sharp A, Coleman I, Yuan W, et al. Androgen receptor splice variant-7 expression emerges with castration resistance in prostate cancer. *J Clin Invest.* 2019;129(1):192-208.
Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34.
Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006;24(19):3187-3205.
Sneeringer CJ, Scott MP, Kuntz KW, et al. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas. *Proc Natl Acad Sci U S A.* 2010;107(49):20980-20985.
Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* International Agency for Research on Cancer; 2008.
Takawa M, Masuda K, Kunizaki M, et al. Validation of the histone methyltransferase EZH2 as a therapeutic target for various types of human cancer and as a prognostic marker. *Cancer Science.* 2011;102(7):1298-1305.
Takeda DY, Spisak S, Seo JH, et al. A Somatically Acquired Enhancer of the Androgen Receptor Is a Noncoding Driver in Advanced Prostate Cancer. *Cell.* 2018;174(2):422-432 e413.
Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351(15):1502-1512.
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. In: 9th ed. Boston, MA: Little, Brown & Co.; 1994:253-256.
Tiwari N, Tiwari VK, Waldmeier L, et al. Sox4 is a master regulator of epithelial-mesenchymal transition by controlling Ezh2 expression and epigenetic reprogramming. *Cancer Cell.* 2013;23(6):768-783.
Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science.* 2009;324(5928):787-790.
U. S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. March 2020; https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Vander Ark A, Cao J, Li X. Mechanisms and Approaches for Overcoming Enzalutamide Resistance in Prostate Cancer. *Frontiers in oncology.* 2018;8:180.
Varambally S, Dhanasekaran SM, Zhou M, et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature.* 2002;419(6907):624-629.
Viswanathan SR, Ha G, Hoff AM, et al. Structural Alterations Driving Castration-Resistant Prostate Cancer Revealed by Linked-Read Genome Sequencing. *Cell.* 2018;174(2):433-447 e419.
Wang HT, Yao YH, Li BG, et al. Neuroendocrine Prostate Cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from NEPC diagnosis-a systematic review and pooled analysis. *J Clin Oncol.* 2014;32(30):3383-3390.
Wedge DC, Gundem G, Mitchell T, et al. Sequencing of prostate cancers identifies new cancer genes, routes of progression and drug targets. *Nat Genet.* 2018;50(5):682-692.
Wilson BG, Wang X, Shen X, et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell.* 2010;18(4):316-328.
Xu K, Wu ZJ, Groner AC, et al. EZH2 oncogenic activity in castration-resistant prostate cancer cells is Polycomb-independent. *Science.* 2012;338(6113):1465-1469.
Yu J, Yu J, Rhodes DR, et al. A polycomb repression signature in metastatic prostate cancer predicts cancer outcome. *Cancer Res.* 2007;67(22):10657-10663.